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A Study on Moisture Isotherms of Formulations: the Use of Polynomial Equations to Predict the Moisture Isotherms of Tablet Products

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ABSTRACT

The objectives of this study were to investigate the effects of manufacturing parameters on the moisture sorption isotherms of some tablet formulations and to predict the moisture isotherms of the final formulations using polynomial equations. Three tablet formulations including a placebo and 2 drug products were prepared through wet granulation, drying, compression, and coating processes. Equilibrium moisture content of excipients and granules at 25°C with different relative humidities were determined using a dynamic moisture sorption microbalance, while such data for tablets were determined using desiccators. Moisture sorption isotherms were expressed in polynomial equations. Excipient isotherms were used to predict the moisture sorption isotherms of the 3 tablet products. Results showed that different physical properties of granules and tablets, such as particle size distribution, density, and porosity resulting from different granulation and compression conditions did not have significant effect on the moisture isotherms of the materials. Changing coating materials from a powder mixture to a film also did not change the moisture sorption characteristics significantly. The predicted moisture sorption isotherms of the formulations agreed well with the experimental results. These results show that moisture isotherms of solid pharmaceutical products manufactured with conventional processes may be predicted using the isotherms of excipients, and polynomial equations may be used as a tool for the prediction of moisture isotherms.

KEYWORDS: prediction, moisture sorption isotherm, excipients, formulations

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INTRODUCTION

Water in pharmaceutical products either as the residual water from processing or as the result of exposure to high relative humidity (RH) may affect the chemical or physical stability of moisture-sensitive products. Moisture transfer from gelatin capsule shells to the hygroscopic fill contents or to low RH environment may result in brittle capsule products.[1,2] Sorption of moisture from the manufacturing environment by hygroscopic granules can lead to a sticking problem during compression. Equilibrium moisture sorption isotherm of a product is a key factor governing the rate of moisture uptake by the packaged product during shelf life, besides the environmental conditions and container permeability.[3,4] Therefore, it will be beneficial if the moisture sorption isotherm of a formulation can be predicted at the early stage of formulation development. Such a prediction can guide the excipient selection in formulation design to increase the efficiency of product development.

Much effort has been focused on moisture sorption studies. A sorption-desorption moisture transfer (SDMT) model has been developed by Zografi et al[5] to predict the moisture transfer among pharmaceutical excipients in closed systems using a vapor transfer theory and the Guggenheim-Anderson-de Boer (GAB) equation. This model shows that the equilibrium moisture content of a multicomponent pharmaceutical mixture can be calculated using the moisture isotherms of the components. The model has been successfully used to balance the moisture content and the brittleness of capsule products[1,2] and to study the stability of a moisture-sensitive product.[6] Based on the vapor transfer theory and Fick's first law, a new model using polynomial isotherm has also been developed for the prediction of moisture uptake by packaged products during shelf life.[4] Considering the effects of processing, Dalton and Hancock have demonstrated the feasibility of predicting the water content of some model formulations by adding the contribution of water from each excipient.[7] It will be useful for a product development purpose to extend the scope of the previous work to study the effects of different processing conditions, such as the percentage of granulation fluid, massing time, compression forces, and the coat-

Table 1. Quantitative Compositions and Granulation Time of Tablet Formulations

Ingredients	Formulation (% wt/wt)		
	Placebo	A	B
Avicel PH-102	46.0	-	33.0
Avicel PH-101	-	17.2	24.8
Lactose, anhydrous	46.0	-	-
Lactose, monohydrate	-	-	14.7
Hydroxypropyl cellulose (Klucel EXF)	5.0	2.9	2.3
Crospovidone	2.0	3.9	-
Sodium dodecyl sulfate	-	1.9	-
Magnesium stearate	1.0	0.5	0.5
Croscarmellose sodium	-	17.2	4.8
Silicon dioxide	-	-	0.5
Opadry II, blue, 32K10887		3.2	-
Opadry II, green, 85F11651	-	-	4.0
Drug A	-	53.2	-
Drug B	-	-	15.4
Water*	35	90	40
Granulation massing time (min)	5	6	6

*The percentage of water was calculated based the quantity of water/quantity of dry blend for granulation.

ing process for tablets, on the moisture sorption of different products.

The purpose of this work was to evaluate the effects of processing parameters on the moisture sorption isotherms of several tablet products in development. Polynomial equations were used to represent the moisture sorption isotherms of excipients for predicting the isotherms of the final tablet formulations.

MATERIALS AND METHODS

Materials

The quantitative compositions of 1 placebo and 2 active drug formulations are listed in **Table 1**.

Preparation of Powder Mixture, Granules, and Tablets

Powder mixtures of 1 kg batch size were prepared by blending all ingredients in a 4-quart V-blender (Patterson-Kelley, East Stroudsburg, PA) for 20 minutes. Granules were prepared at 15 kg batch size with a wet granulation process using a 75 L Gral high shear granulator (Machines Collette, Wommelgem, Belgium). Intragranular components were premixed at low speed for 5 minutes in the granulator. Water was then added to activate granulation while mixing, followed by massing at high speed. The amount of water and high shear massing time used for granulation of different formulations are listed in **Table 1**. The wet granules were dried in a fluid bed dryer (Model S3, Aeromatic AG, Muttenz, Switzerland) and milled using a Fitzmill (Model DAS06, The Fitzpatrick Co., Elmhurst, IL) at low speed. The dry granules were mixed with disintegrant and magnesium stearate for 5 minutes using a 2 ft^3 V-blender (Patterson-Kelley). The lubricated granules were compressed into tablets using a 16-station rotary compression machine (Betapress, Manesty, Merseyside, UK) at 40 rpm. The active drug tablets, A and B, were color coated with a 20% suspension of the coating materials in water using a 24-in perforated coating pan system (Compu-Lab, Thomas Engineering Inc., Hoffman Estate, IL).

In addition to the conditions listed in **Table 1**, a second granulation run was conducted to examine the effect of different granulation conditions on moisture sorption of the

placebo formulation by increasing the amount of water from 35% to 42% and the massing time from 5 minutes to 6.5 minutes.

Determination of Moisture Sorption Isotherms

Equilibrium moisture contents of powder and granules were determined using a dynamic moisture sorption microbalance (DMSM) (MB 300W, VTI Corp, Hialeah, FL). Approximately 25 to 50 mg of sample was placed into a sample pan and dried at 60°C with 0% humidity until the weight change was less than 0.02% over 10 minutes. Then, the sample was equilibrated under controlled RH ranging from 5% RH to 95% RH at 25°C. The criterion used for the drying step was also used for judging the equilibrium at each RH.

Equilibrium moisture contents of tablets were determined using a desiccator method with saturated salt solutions to provide desired RHs.[8,9] Tablets were placed in petri dishes and allowed to equilibrate in the desiccators stored in a temperature control chamber (SB11-160, Weiss, Reiskirchen-Lindenstruth, Germany) at 25°C for 2 weeks. At the end of 2 weeks, the equilibrium moisture content of the tablets was measured using a loss on drying (LOD) method by heating the samples at 110°C for 7 hours, followed by determining the weight differences of the samples before and after drying. The equilibrium moisture content of the placebo granules was also determined by this method for comparison with the DMSM method.

Moisture sorption isotherms were obtained by fitting the equilibrium moisture content into polynomial equations with respect to RH using a SigmaPlot software (Version 7, SPSS Inc, Chicago, IL).

Determination of Particle Size

Particle size distribution of granules was measured by sieve analysis using a series of US standard testing sieves. Approximately 100 g of the granules were shaken on a sieve shaker (SS-8R, Gilson Company, Worthington, OH) for 5 minutes. The amount of particles retained on each screen after shaking was determined by weight measurement and used to calculate the cumulative mass on each screen. Mass mean particle size was calculated by interpolation using the following equation:

$$Mass\ Mean\ Particle\ Size = X_1 + \frac{Y_1 - 50}{Y_1 - Y_2}(X_2 - X_1) \qquad (1)$$

where X_1 is the nearest sieve opening size of screen for cumulative particle mass greater than 50% on the screen, and Y_1 is the cumulative mass of particles on the corresponding screen. X_2 is the nearest sieve opening size of screen for cumulative particle mass smaller than 50% on the screen, and Y_2 is the cumulative mass of particles on the corresponding screen for X_2.

Determination of Granulation Density

Bulk and tapped densities of the placebo formulation that was granulated using different conditions were measured using a 100 mL graduated cylinder according to a *United States Pharmacopeia (USP)* method.[10] Tapped density was determined by method II with a total of 5000 taps. True density of granules was determined using a helium pycnometer (AccuPyc 1300, Micromeritics, Norcross, GA) according to a *USP* method.[11]

Porosity Analysis

Porosity of granules and tablets were studied by mercury porosimetry using a Poremaster 60 GT (Quantachrome Corp, Boynton Beach, FL). The apparent volume of tablets was calculated from the tablet weight and the true density of granules by helium pycnometry, plus the total volume intruded into the tablets by mercury porosimetry. Porosity of tablets was then calculated by dividing the intruded volume by the apparent volume of tablets.

Intragranular porosity of the granules was determined using the intruded volume that corresponded to the intragranular region on the volume-pressure curve.

Prediction of Moisture Isotherm of Tablet Products

Assuming that there is no significant interaction and solid phase transition of ingredients during the manufacturing process, the moisture isotherm of a solid formulation was calculated using the following equation:

$$f_{prod}(RH) = \sum_{i=1}^{i=n} x_i f_i(RH) \qquad (2)$$

where $f_{prod}(RH)$ and $f_i(RH)$ represent the moisture sorption isotherms of the product and the *i*th ingredient in the product, respectively; x_i is the weight fraction of *i*th ingredient, and *RH* represents the percentage relative humidity.

RESULTS AND DISCUSSION

Methods for Moisture Equilibrium Study

The utility and the limitation of the DMSM method, previously called an moisture balance (MB) method, have

been discussed in detail by Dalton and Hancock.[7] This method is automated and is flexible for controlling humidity and temperature. Moisture equilibrium for powders and granules at any given humidity by this method can usually be achieved within a few hours. It is convenient to use for screening purposes. However, the rate of moisture equilibrium of compressed tablets may be substantially lower than that of powders. Results in **Figure 1** show that the time needed for the tablets to reach equilibrium at a given humidity in a desiccator is approximately 1 week. Since different desiccators can provide different humidities at the same time, the desiccator method with LOD measurement is a convenient method for studying the moisture equilibrium of tablets.

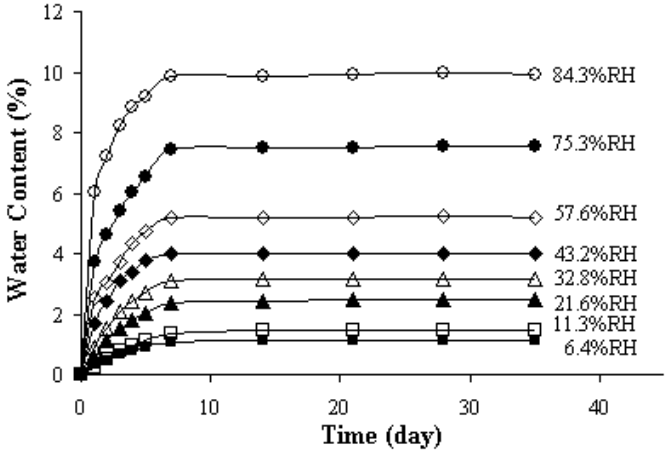

Figure 1. Moisture uptake by tablets of formulation A as a function of time at different relative humidities at 25°C.

Results of the DMSM and the desiccator methods showing the moisture content of the placebo blend as a function of RH are similar, with the DMSM results being slightly lower at low RH (**Figure 2**). In the DMSM method, there is a drying step at 60°C at the beginning, and the subsequent equilibrium data can be considered as sorption data.[7] The desiccator method in this study did not have this pretreatment step, and equilibrium could be reached either by sorption or desorption mechanism, depending on the initial water content of the samples. The slight difference shown in **Figure 2** represents the combined effects of the lower drying temperature of the DMSM method (60°C) compared with that of the regular LOD method (110°C) and the potentially different mechanism of moisture sorption or desorption because of the different treatment of samples for the 2 methods discussed above. Nevertheless, the 2 methods appear to be equivalent based on the data shown in **Figure 2**. Therefore, the DMSM method can be used to provide a reasonable estimate of equilibrium water contents, unless the materials contain a significant amount of tightly bonded hydration water.

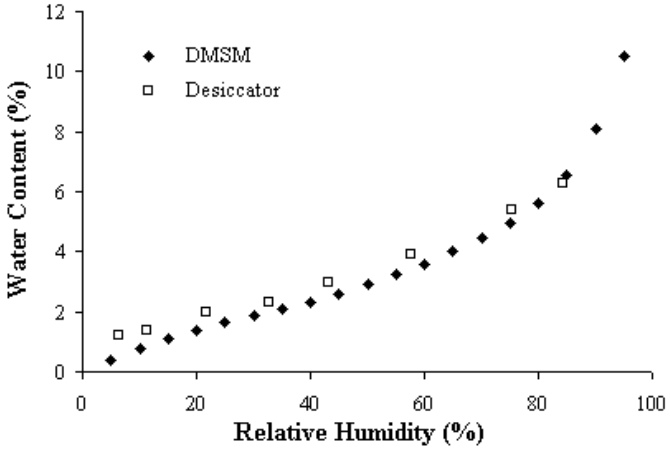

Figure 2. Comparison of moisture sorption isotherms of placebo blend determined using DMSM and desiccator methods at 25°C.

Moisture Sorption Isotherms

Any equations that would give a good fit over the entire range of humidity could be used to represent the moisture isotherms of pharmaceutical excipients and products.[5] In general, an empirical polynomial equation is more versatile for curve fitting than a theoretical equation such as the GAB equation, although the polynomial equation has no physical meaning. In addition, the polynomial equation permits simple differentiation and integration in applying the isotherms to predict the moisture uptake by packaged products through a diffusion-controlled process during storage.[4] In this study, the moisture isotherms determined by the DMSM method for excipients and drug substances were determined by curve fitting into polynomial equations in a general format of the following equation:

$$f_i(RH) = y_0 + aRH^{0.5} + bRH + cRH^2 + dRH^3 + eRH^4 + gRH^5 + hRH^6 \quad (3)$$

where the symbol $f_i(RH)$ indicates the equilibrium moisture content as a function of the percentage of relative humidity, *RH*. The symbol of % was omitted from the equation for a simplification purpose.

Not all the terms in Equation 3 were used for every ingredient. Only the significant terms were selected for individual material based on *t* test. The selected terms and the coefficients for each excipient and drug substance used in this study are listed in **Table 2**. The experimental data and

Table 2. Coefficients of Equation 3 for Moisture Sorption Isotherms Determined by DMSM at 25°C*

Sample	y_0	a	b	c	d ($\times 10^{-4}$)	e ($\times 10^{-6}$)	g ($\times 10^{-8}$)	h ($\times 10^{-10}$)
Avicel 102	−2.4104	2.3493	−0.5225	0.0227	−7.4823	13.905	−12.902	4.7253
Avicel 101	−3.2397	3.2412	−0.7588	0.0290	−8.8282	15.562	−13.950	4.9873
Lactose, anhydrous	0	0	0	0.0004	−0.3410	1.0117	−1.3094	0.6214
Hydroxypropyl cellulose	0	0	0	0.0096	−5.4397	14.442	−17.1420	7.6473
Crospovidone	−12.833	12.547	−3.0926	0.0987	−23.013	32.502	−24.856	8.2355
Magnesium stearate	0	0	0	0.0037	−1.7721	3.9205	−4.0570	−1.5881
Croscarmellose sodium	−5.9531	7.0457	−2.3219	0.1239	−40.910	73.107	−66.100	24.083
Sodium dodecyl sulfate	0	0	0	0	−0.0036	0.0226	−0.0446	0.0278
Lactose monohydrate	0	0	−0.0033	0.0004	−0.1758	0.3924	−0.4209	0.1735
Silicon dioxide	−74.418	72.736	−20.801	0.6922	−190.00	306.48	−259.76	89.015
Opadry II, blue, 32K10887	−17.389	17.385	−5.0205	0.1661	−44.692	70.943	−59.074	19.925
Opadry II, green, 85F11651	0	0	0	0	0	2.6799	−6.6364	4.3914
Drug A	0.0152	−0.0004	0	1.2×10^{-6}	0	0	0	0
Drug B	0	0	0	0	0	0.0099	−0.0223	0.0140

*DMSM indicates dynamic moisture sorption microbalance.

the fitted isotherms are shown in **Figure 3**. These results show that the materials have a wide range of hygroscopicity. Crospovidone is the most hygroscopic, while lactose monohydrate, sodium dodecyl sulfate, and the 2 new drug substances A and B can be considered nonhygroscopic. The equilibrium water contents of all materials are fitted well by polynomial equations, showing that the polynomial equations are versatile, and can be used for predicting the moisture isotherms of formulations.

Effect of Granulation

The placebo formulation was used to study the effect of granulation conditions on the equilibrium moisture content of the resulting granules. The formulation contained a significant portion of anhydrous lactose to represent the potential polymorph transition of ingredients during wet granulation. Different amounts of water and massing time were used for granulation. Results show that the moisture sorption isotherms of the 2 granules were practically identical (**Figure 4**) even though the bulk and tapped densities, pore size distributions, porosities, and particle size distributions of the 2 granules were significantly different (**Table 3**). The 2 granules also have a similar moisture sorption isotherm as the dry blend except at the high humidity, indicating that the granulation process under different conditions has a negligible effect on moisture sorption of raw materials. The slightly higher moisture content of the granules compared with the blend at high humidity was probably due to moisture condensation in the micropores, which were detected by mercury porosimetry for these 2 granules, or due to the formation of amorphous region and the partial disruption of the crystallinity of ingredients during the manufacturing process.[12]

Effects of Compression and Film Coating of Tablets

Formulation A was compressed with different compression forces into 0.364 g ovaloid tablets with substantially different hardness and porosity (**Table 4**). The tablet hardness for this formulation covered the desired hardness for the intended commercial product. Pore size distributions measured by mercury porosimetry for all the tablets are in the macropore range, with pore size distribution ranging from 0.05 to 3 μm. No pores below 0.05 μm were detected for these tablets. As expected, the softer tablets have larger pores and a significantly higher porosity then the harder tablets. However, moisture isotherms of these tablets are identical (**Figure 5A**). In addition, the moisture isotherms of the tablets were similar to the dry blend of ingredients. Therefore, it can be concluded that compression within a reasonable range of compression forces does not signifi-

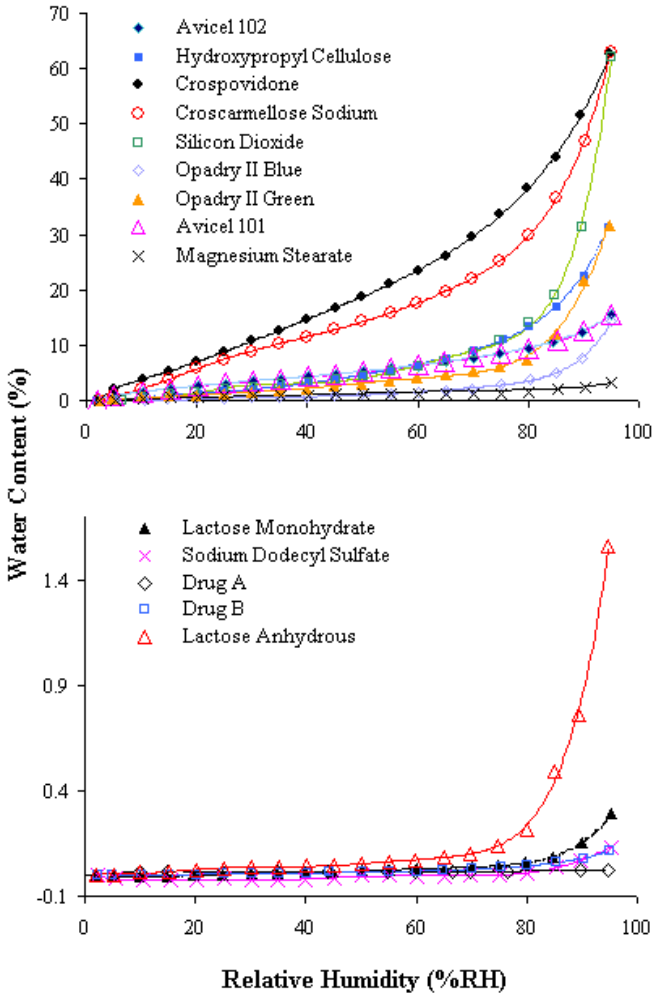

Figure 3. Equilibrium water content of ingredients determined at 25°C using DMSM method. Lines are fitted curves.

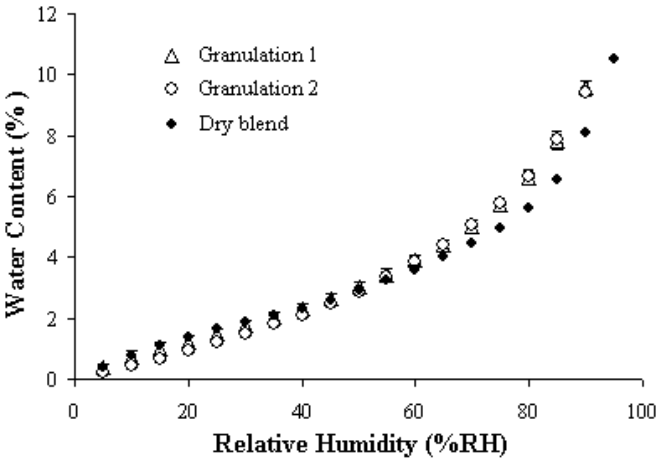

Figure 4. Effect of wet granulation on moisture sorption isotherm of placebo formulation determined by DMSM at 25°C. Granulation 1, 35% water and 5 minutes massing; Granulation 2, 42% water and 6.5 minutes massing.

cantly alter the moisture sorption capacity of the formulation components.

Film coating materials for tablets are commercially available in the form of powder mixtures. The powders are changed into films covering tablets, through a liquid coating process. When the coating liquid of Opadry II, green, 85F11651, was cast into a film, the moisture sorption isotherm of the dry film remained similar to the powder except at the high RH (**Figure 5B**). This similarity suggested that moisture sorption by the material was achieved mainly by partition other than adsorption. The reduction of surface area by the film forming process had little effect on moisture sorption by the material. Therefore, the isotherm of the film coating powder can be used to calculate the moisture isotherm of the coated tablets.

Prediction of Moisture Sorption Isotherms of Formulations

As discussed previously, DMSM method may underestimate the water content of hydrous materials. Overgranulation of highly soluble components and polymorph conversion during the processes may still be the potential causes of changes in the moisture sorption characteristics of raw materials.

Dalton and Hancock have shown that it is possible to predict the moisture content of processed formulations using the water content of excipients.[7] This study widened the scope of the previous study to include complex formulations including drug products, and to study the effects of different manufacturing conditions, such as the percentage of granulation fluid, massing time, compression forces, and the coating process, on the prediction of moisture sorption isotherms of products. The experimental and the predicted moisture isotherms of the 3 tablet formulations with polynomial equations are shown in **Figure 6**. The placebo formulation contained anhydrous lactose. The slightly higher LOD results of the placebo tablets compared with the excipient blend (**Figure 6A**) were probably due to the formation of hydrous lactose during wet granulation and to the detection of the hydrous water by the LOD method rather than by the DMSM method. Formulation A did not contain lactose. The predicted results for formulation A agreed very well with experimental data even though 2 different methods were used for water detection of raw materials and tablet products (**Figure 6B**). Formulation B contained lactose monohydrate. The hydration water was detected by LOD but not by DMSM. Therefore, the LOD results of tablets at low RH were slightly higher than the DMSM results of the blend (**Figure 6C**). Overall, the moisture isotherms of dry blends, granules, and tablets are similar for a given formulation, showing that the common manufactur-

Table 3. Physical Properties of Placebo Granules*

Test	Granulation 1	Granulation 2
Bulk density (g/mL)	0.50	0.69
Tapped density (g/mL)	0.61	0.80
Max pore size (μm)	4.3	1.0
Porosity (%)	29.5	12.3
Mass mean particle size (μm)	233	600

*Granulation 1: 35% water and 5 minutes massing. Granulation 2: 42% water and 6.5 minutes massing.

Table 4. Compression Force, Tablet Hardness, and Porosity of Formulation A*

Compression Force (KN)	Tablet Hardness (SCU)	Porosity (%)	Max Pore Size (μm)
12.0	20.2	14	1.5
7.5	14.9	18	2.0
7.0	13.0	21	3.0

*KN indicates kilonewton; and SCU represents Strong Cobb Unit. Formulation A consisted of 0.278 × 0.52-inch ovaloid tablets, 0.364 g per tablet.

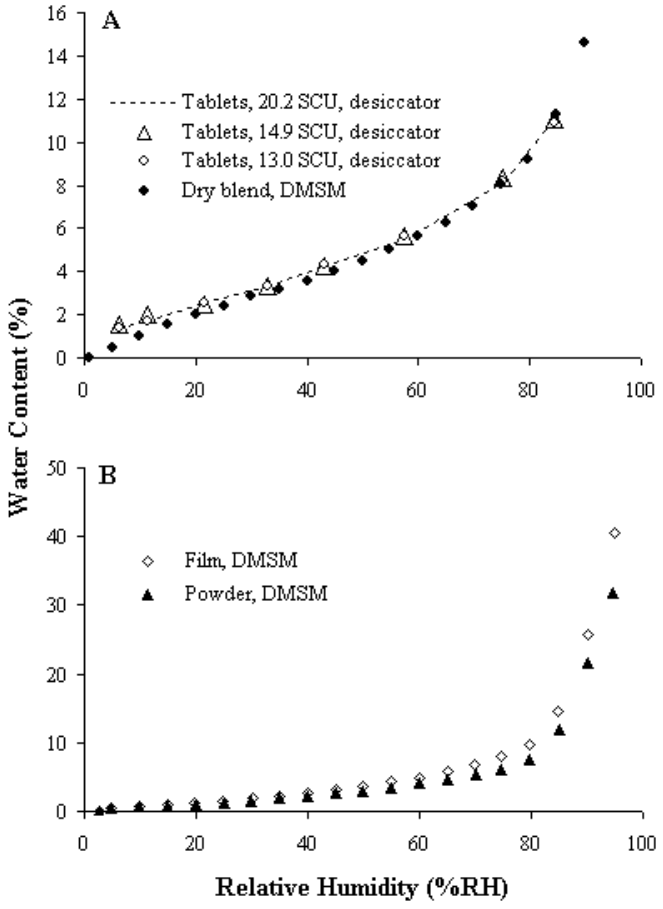

Figure 5. Effects of tablet hardness of formulation A (A) and changing Opadry II, green, 85F11651 from powder to a film (B) on moisture sorption isotherms of the materials.

ing processes such as wet granulation, tablet compression, and film coating do not alter the moisture sorption properties significantly. Therefore, the moisture isotherms of solid formulations may be reliably predicted using the isotherms of excipients, and polynomial equations may be used to represent the moisture isotherms of ingredients and formulations for this prediction purpose.

CONCLUSION

Different parameters of conventional manufacturing processes including wet granulation, compression, and film coating did not significantly alter the moisture sorption property of raw materials in the current study. Moisture sorption isotherms of the final solid formulations were successfully predicted using polynomial equations to represent the isotherms of all ingredients and formulations. This predictive approach may be used as a convenient tool for excipient selection and formulation design to protect moisture-sensitive compounds, provided that there is no substantial polymorphic conversion during process.

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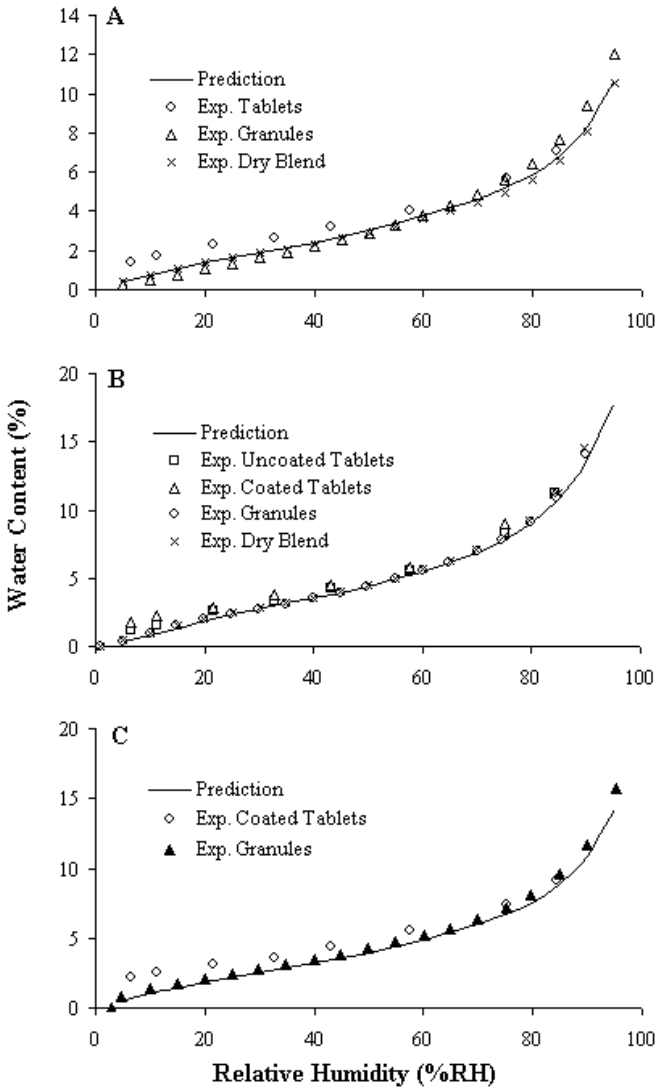

Figure 6. Predicted and experimental isotherms of placebo (A), formulation A (B), and formulation B (C) at 25°C.

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