Measuring Moisture Content of Pharmaceutical Products Using Water Activity

Introduction

The terms moisture content and water content are often used interchangeably and represent a measure of the quantity of water in a product. Moisture content provides valuable information about yield and quantity, making it important from a financial standpoint. In addition, moisture content provides information about texture since increasing levels of moisture provide water mobility and lower the glass transition temperature.

Water activity represents the energy status of the water in the system. It is equal to the relative humidity of the air in equilibrium with a sample in a sealed chamber. It is defined as the vapor pressure of water in a sample divided by the vapor pressure of pure water at the sample temperature. Water activity provides valuable information about microbial spoilage, chemical stability, and physical stability. Water activity and moisture content together provide a complete moisture analysis.

Moisture content and water activity are currently measured using separate techniques or instruments. Water activity is measured using either a capacitance or chilled mirror water activity instrument while moisture content is measured using any one of the 35 different methods listed in Official Methods of the AOAC (AOAC, 1995). Combining the two analyses in one instrument saves time and labor. Decagon's new AquaLab Series 4TE DUO and AquaSorp Isotherm Generator now make it possible to measure both water activity and moisture content using Decagon's proven water activity measurement technology.

To measure moisture content using water activity requires an understanding of the relationship between the two parameters. This relationship, referred to as the moisture sorption isotherm, is complex and unique to each product type. It must be determined experimentally by measuring water content at several water activity values. This only needs to be done once for a given product. Isotherm analysis can be done manually with saturated salt slurries and desiccators or automatically using an isotherm generator instrument. Decagon's AquaSorp isotherm generator can rapidly generate robust isotherms with unmatched data resolution (Figure 1).

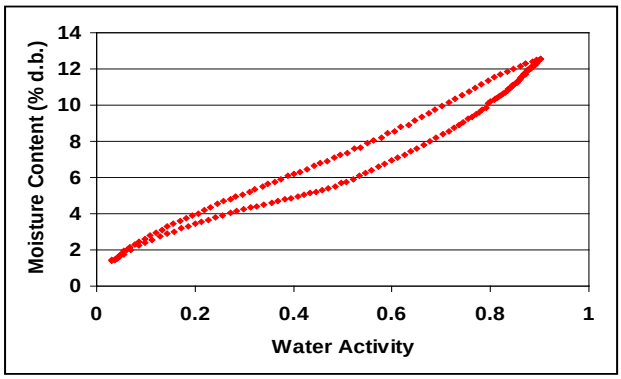

Figure 1. Moisture sorption isotherm for microcrystalline cellulose generated using the AquaSorp Isotherm Generator at 25 °C.

Once an isotherm has been generated, it can be used to indirectly determine moisture content based on a water activity measurement. This is most easily accomplished using a model that characterizes the isotherm. Many different isotherm models have been proposed, but the most commonly used models are the GAB and BET. Decagon has developed another model, called the Double Log Polynomial (DLP) that is superior to the others for modeling complex isotherms. The models are determined empirically using the data collected during isotherm generation and the resulting equation can be used to calculate moisture content using water activity.

Decagon's new AquaLab Series 4TE(V) DUO, a chilled mirror water activity instrument, has been designed to accept isotherm equations. Using the isotherm equation for a specific product, the Series 4 can determine moisture content from the water activity values it generates. Each product to be analyzed for moisture content will have a unique isotherm model that must be selected using the Series 4 menu commands prior to testing. A Series 4TE(V) DUO is required because the test must be conducted at the same temperature as the original isotherm to be valid.

Clearly, the accuracy of this moisture content method relies on the quality of the isotherm and the repeatability of the water activity measurement. To further investigate the feasibility of measuring moisture content by water activity, Decagon Devices investigated the process using several different product types.

Materials and Methods

Six products were selected for testing that represent a wide variety of types from homogeneous ingredients to complex final products. The products included: fiber powder, flu powder, gel caps, microcrystalline cellulose, corn starch, and solid dosage tablets. Working isotherms were obtained for each product in duplicate using the AquaSorp Isotherm Generator. Settings for the AquaSorp were: 25°C temperature, 100 ml/min flow rate, min a_w 0.03 and max a_w 0.85. The "as is" moisture content in triplicate was determined for all of the products using convection oven loss on drying. Time and temperature settings for loss on drying were based on AOAC recommendations when available. All moisture measurements are expressed as percent dry basis.

To create samples varying in moisture content, 10 sub-samples were taken for each product, 5 of which were wetted by exposure to 100% relative humidity in a sealed desiccator while the other 5 were dried by exposure to desiccated air inside another sealed desiccator. Sub-samples were removed from the desiccators at different times to create samples varying in moisture content. As the sub-samples were removed, they were sealed in jars and set aside until all sub-samples had been removed from the desiccator. The time in the wet and dry desiccators for the sub-samples of each product was adjusted based on the diffusion properties of the product. All sub-samples for a product were then analyzed in triplicate for moisture content and water activity. Moisture content was measured as before and water activity was measured using Decagon's AquaLab Series 4TE.

The isotherm testing results were characterized using DLP models. Duplicate isotherms were analyzed as one isotherm to average across both isotherm data sets. Shortened intervals better representing the natural moisture content variation range of the product were used for fiber powder, flu powder, and corn starch. Moisture contents predicted using average water activity values were compared to average moisture contents from oven loss on drying. Standard Error of Prediction (SEP), which is interpreted as the 95% confidence interval for the predicted value around the actual value (smaller value is better), and R2 value (closer to 1 is better) were used to measure the strength of the DUO method. The relative strength of a secondary method is measured by how well it matches the reference method. For this study, the SEP value can be considered a measure of the ability of the moisture content by water activity method to correctly match reference data.

Since there is no standard for measuring moisture content, a true accuracy cannot be calculated (Isengard, 2001). Accuracy and precision are used interchangeably in moisture content literature, but in reality, only a precision can be determined. Consequently, the best way to compare moisture content methods is by comparing their repeatability. The precision values of the oven loss on drying and moisture content by water activity methods were calculated as the average standard deviation of triplicate analyses across all samples for a given product.

Results and Discussion

Moisture content values calculated from water activity agreed well with oven loss-on-drying values for all products as evidenced by the low SEP and high R2 values (Table 1). The worst SEP value occurred when moisture content was predicted by water activity for tablets (0.17%) and the best was for flu powder (0.01%). Most secondary methods consider an SEP of 0.60% or lower to be acceptable and all SEP values were well below that range indicating that moisture content by water activity can be considered a viable secondary method. Figure 2 illustrates the excellent level of agreement between the moisture content values predicted from water activity and the moisture contents determined using oven loss on drying. The unusually low R2 value for tablets and gel caps resulted from the small variation in moisture content across samples (very flat isotherm).

Table 1. Isotherm curve and model combinations that provided the lowest SEP values for each product type.

Product	*SEP	R^2
Fiber Powder	0.160	0.945
Flu Powder	0.011	0.906
Gel Caps	0.121	0.093
MCC	0.160	0.958
Corn Starch	0.163	0.989
Tablets	0.170	0.563

* SEP values are in % moisture (d.b.)

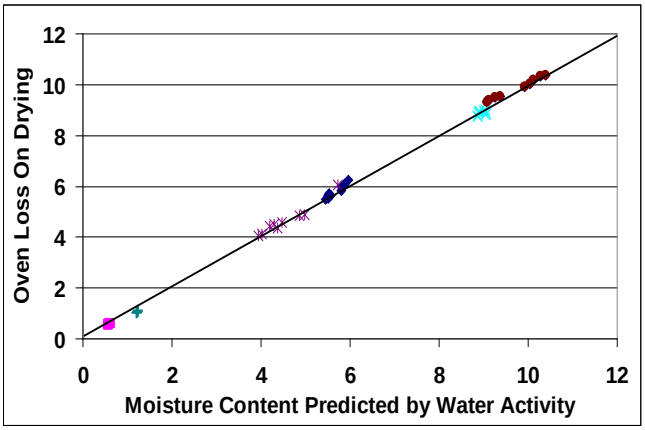

Figure 2. A comparison of moisture contents predicted by water activity (y-axis) to moisture contents determined using oven loss on drying (x-axis) for fiber powder (♦), flu powder (■), gel caps (X), MCC (*), corn starch (●), tablets (+). The solid line represents the 1:1 complete agreement line.

Table 2 shows a comparison between the precision of the oven loss on drying method and the moisture content by water activity method. For every product investigated, moisture content by water activity gave better precision even though loss on drying is considered the reference method. Table 3 shows that in comparison to reported precision values for other methods, moisture content by water activity has the highest level of precision.

Table 2. Average precision values for oven loss on drying and moisture content by water activity for all of the products analyzed. The values represent an average of standard deviations of triplicate moisture analyses across 10 samples for each product.

Product	Oven LOD Precision (% Moisture d.b)	Moisture by a_w Precision (% Moisture d.b)
Fiber Powder	0.075	0.004
Flu Powder	0.016	0.0001
Gel Caps	0.021	0.003
MCC	0.094	0.006
Corn Starch	0.047	0.002
Tablets	0.048	0.0001

Table 3. Commonly reported precision (also reported as accuracy) values for most frequently used moisture content determination methods.

Method	Precision (Accuracy) (% Moisture)
Moisture content by Water Activity	0.0001-0.003
Drying Oven	0.1-0.5
Infrared Drying	0.1-0.5
Halogen Drying	0.1-0.5
Microwave Drying	0.1-0.5
Distillation	1
Karl Fischer	0.05-0.5
Infrared Spec	0.3-1
Microwave Spec	0.3-1
NMR Spec	0.1
Gas Chromotagraphy	0.01-0.1

Conclusion

Moisture content by water activity is an excellent moisture content measuring option and is especially attractive when both water content and water activity measurements are needed on the same sample. A product specific isotherm is needed, which can be obtained manually or using an isotherm generator. The precision of this method is the best of any of the secondary methods, and exceeds that for loss on drying. The accuracy can not be assessed because there is, to date, no absolute method for measuring moisture content.

Reference List

AOAC. 1995. Official Methods of Analysis of AOAC International. p. 42-1-42-2. *In* T.R.Mulvaney (ed.) AOAC International, Arlington, VA.

Isengard,H.D. 2001. Water content, one of the most important properties of food. Food Control 12:395-400.

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