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Granulation Moisture Content Analysis: An Evaluation of Two Instruments

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ABSTRACT

Reliable methods of determining moisture content of granulations are essential to develop products that are readily and consistently manufactured. This study evaluated two instruments for loss on drying (LOD) measurement, the Computrac model MA-5 and the Mark-I. Both instruments were evaluated using the USP oven method for LOD determination as a standard. All of these instruments/methods involved thermogravimetric analysis (TGA). Computrac MA-5 utilizes a heating coil as heat source and Mark-I uses four parallel quartz infrared heaters as heat source. Results showed that the Mark-I moisture analyzer and the oven method gave values much closer to those predicted for the compounds tested, while the Computrac seems to be inconsistent in determining the LOD of materials which are in equilibrium with their bound water of hydration and their evolved volatile compounds.

INTRODUCTION

In the production of tablets, it is often necessary to produce a granulation mixture before compression (i) to increase the particle size, (ii) to decrease the amount of dust generated, (iii) to increase the product's content uniformity, (iv) to increase flowability into the compression die, and (v) to improve compression characteristics. Wet granulation is the most widely used granulation method (1,2). After the liquid has been added and the particles have been allowed to coalesce, it is necessary to dry the mixture before compression. A critical phase in the drying process is the determination of the moisture content of the granulation at any time and definition of the drying end point. If the formulation is too wet, the tablet may be too hard and will not have the proper dissolution characteristics. If the formulation is too dry, the tablet may possess poor compressibility. Thus, reliable methods of determining moisture content are essential in development of products that are readily and consistently manufactured.

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This project's goals were to evaluate the accuracy and reproducibility of two instruments of determining the moisture content of granulations and to determine the optimal temperature at which to perform such analysis. The Mark-I moisture analyzer, the Computrac model MA-5 moisture analyzer, and the oven method use a technique known as thermogravimetric analysis, or TGA. TGA involves the volatilization of some component of the test mixture through the application of thermal energy. As the volatile component leaves the test preparation, the samples's mass will change, resulting in a corresponding change in the sample's gravimetric representation or weight. The researcher or instrument then measures the difference in the sample's weight with respect to its initial weight.

When performing TGA on materials which contain volatile components as part of their molecular structures (known as "bound moisture," moisture possessing a vapor pressure lower than that of the pure liquid at the same temperature), it is important that consideration be given to the point at which the volatile component is lost. If this temperature is exceeded, the volatile component may be lost and therefore the test will give higher values for unbound moisture percentage than would be expected from residual moisture content alone. The common pharmaceutical excipient lactose monohydrate, for example, loses its water of hydration at about 100°C and becomes anhydrous at 120°C (3).

Two of the methods evaluated (Mark-I and Computrac) use as their end point the determination in the change in slope of the weight versus time of drying curve over a predetermined length of time (see Fig. 1). The loss of weight within the specified time frame is mathematically monitored during the drying procedure. When the slope conditions are met, the instruments terminate the analysis and display the results (4,5).

Low moisture content samples (final loss on drying less than 1%) present unique problems in formulation and manufacturing. With very low moisture content materials, the accuracy of the final granulation moisture content analysis (GMCA) is more critical than it is for a formulation with higher tolerances. For example, if two granulation mixtures with actual moisture contents of 5.0% and 1.0% were evaluated and found to have moisture contents of 4.5% and 0.5%, respectively, each would have a moisture content 0.5% lower than its actual value. The resulting percent error, however, was less for the 5.0% granulation than for the 1.0% granulation (with the former having only a 10% error and the latter having a 50% error).

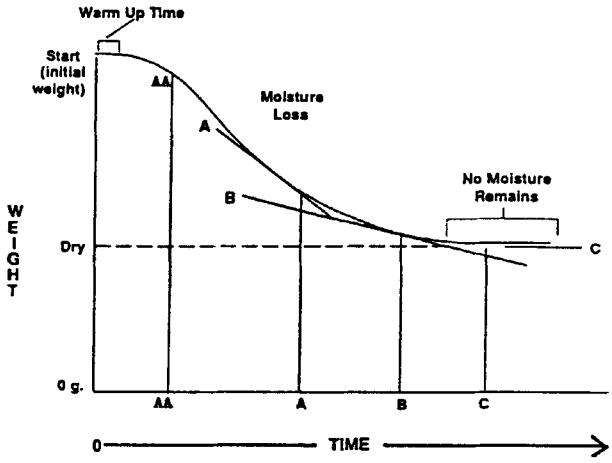

Figure 1. Typical drying curve. The typical drying curve consists of three portions: heating, evaporation, and diffusion. From the starting time to point AA, the sample increases in temperature to that of the test run. The portion of the curve from AA to A represents the loss of residual moisture as well as loss of some moisture from the particles. At point A, most of the residual moisture has been volatilized and diffusion out of the particles continues until point B. At point B, the rate of diffusion out of the particles slows and continues until point C. From point C on, the sample is considered completely dry. This last portion of the curve is often the longest of the drying curve and can last up to 24 hr, depending on the sample and the system.

Finally, we planned to establish a model that would accurately demonstrate the moisture content of materials containing less than 1.0% moisture. We also wanted to avoid a compound that contained a bound moisture of hydration which would complicate our loss on drying (LOD) determinations. To this end, we established a model that used dried sand with added moisture of a known percentage. This model worked exceedingly well and provided useful data.

EXPERIMENTAL

Equipment

Mark-I

A Mark-I Moisture Analyzer (Denver Instrument Company) was purchased from Omnimark Instrument Corporation. The Mark-I heats the sample to a specified temperature (from 30°C to 210°C, programmable in up to two temperature steps) using four parallel quartz infrared elements, and then maintains the temperature

throughout the test run. One advantage of this instrument is that it continually displays the actual temperature within the drying chamber and will print these temperatures at specified intervals. The researcher can program the Mark-I to set the end-point slope to be from 0.01% to 9.99% of initial weight over 0.5 to 60 min using its internally programmed actual slope or using a formula of the researcher's choice.

Computrac MA-5

The Computrac model MA-5 heats the sample to a predetermined temperature utilizing a heating coil (its heating range is from 75° to 165°C. The MA-5, though, unlike the Mark-I, does not display the actual temperature inside the drying chamber. The MA-5 calculates both a predicted value and a current actual value of moisture content. It waits until four predicted values agree to within 0.1% and the prediction is within 0.3% of the final moisture before terminating the test and displaying the results (5).

Oven Method

An American Scientific Products model DP-31 vacuum oven was used. In order for drying to occur, the vapor pressure of the liquid in the mixture must exceed the atmospheric vapor pressure. By introducing a vacuum with this oven, we expected to increase the drying rate at any given temperature by decreasing the partial pressures of all atmospheric gasses. The oven was used only as a check for the absolute accuracy of the Mark-I and the Computrac since the drying time in the oven often approaches 24 hr, a time far longer than permissible in an actual production setting.

Materials

Two lots of placebo granulation containing 90% lactose monohydrate (wet massing was performed and the granulation was then dried in oven at 49°C overnight), two lots of lactose monohydrate powder, and two lots of wet granulation containing A-50711 were used in this study. One lot of sand (washed and dried) was obtained from Mallinckrodt Specialty Chemicals (Paris, KY).

Lactose monohydrate loses 75% of its water of crystallization at 103°–105°C, and 100% at 120°C. Drying at 80°C removes the residual, unbound moisture only (7). Erroneous results could occur if analysis is conducted at temperatures exceeding the heat of dissociation. We therefore wanted to characterize the LOD tendencies of lactose at various temperatures to determine the optimal temperature at which to conduct LOD studies with each instrument.

A-50711 presents substantial difficulties in moisture content determinations because of its thermodynamic instability. The melting point of A-50711 is approximately 80°C. Therefore, since the drug may become volatilized at temperatures where LOD studies take place, the reading acquired may be inaccurate. We therefore also wished to characterize the LOD tendencies of this formulation and determine the optimal temperature at which to conduct its LOD studies.

Sand was chosen as a low moisture content model based on two assumptions. First, the consistency of sand fairly accurately represented that of a typical granulation. Secondly, as mentioned above, we were interested in a model which would not have any bound moisture and therefore would not lose moisture of hydration at any temperature.

Procedures

Analyses on the Mark-I and the Computrac MA-5 were performed in accordance with the operating instructions of each instrument (4,5). All tests were performed on a minimum of three different samples. The ideal sample weight with the Mark-I was set at 5.0 g and care was taken to vary by not more than 0.1 g (2%) from this amount. The Computrac is preprogrammed from the manufacturer to accept samples weighing between 3 and 5 g. The temperatures on each instrument were set before running the sets of lots. The runs were allowed to continue until the instruments reached their predetermined end points and terminated the analysis. In Computrac MA-5, the predetermined end-point slope is preset at the factory and the operator cannot change this preset value, whereas in the Mark-I, the operator can program the instrument to set the end-point slope to be from 0.01% to 9.99% of initial weight over 0.5 to 60 min. In this study, 0.01%/min and 0.05/min were tested. Care was taken to ensure the uniform distribution of materials around the sample pans as disparities in sample thickness could produce false results. Three minutes elapsed between each sample run on both of the above instruments since the Computrac's operation manual indicated that a smaller waiting time may result in erroneous results.

Analyses using the oven method were performed using the guidelines established in the United States Pharmacopeia (6). We analyzed 1.5 g of material placed

in glass vials. The vials were dried for 2 hr using the same conditions under which we would conduct the test. Care was taken to provide for uniform sample thickness among all the vials (sample thickness ranged from 5 to 7.5 mm). Sample weights were taken at both 20 and 24 hr and the weights compared to ensure complete dryness. The difference in weight was then taken and calculated as a percentage of the original weight of the sample, and the percent volatile was computed.

The sand was prepared by drying overnight in an oven at 100°C at a vacuum of 20 cm Hg. Baseline LODs were then established on the Mark-I at 100°C with an end-point slope 0.05%/min and found to range between 0.04% and 0.06% moisture. The same baseline studies were conducted with the Computrac at 100°C and found to contain moisture between 0.00% and 0.02%. We tested the sand at temperatures up to 160°C to ensure that no bound moisture was released during testing, and found that none was. This assured that the only moisture to be released during an LOD study of the sand samples would be the residual moisture.

The sand was evaluated only with the Mark-I and the Computrac. For analysis in the Mark-I, 4.950 ± .0100 g was added to a pretared aluminum sample pan. One drop of water weighing .050 ± .003 g was placed on the sand with a micropipette. Placement of the drop within the sample varied from pan to pan. The samples were analyzed and the values recorded. Since the Computrac cannot accept weights greater than 5 g, 3.5665 ± 0.049 g of sand and one drop of water weighing .035 ± 0.002 g was used, with the rest of the procedure identical to that used with the Mark-I. The water added in the amounts given above produced samples with percent moisture (w/w) between 0.64% and 1.50%, with a mean of 0.79% and a standard deviation of 0.00227.

RESULTS AND DISCUSSION

Of all three methods evaluated, we consider the oven method to be the most accurate because the extent of time spent in the oven allows the materials to reach a true state of dryness. However, because the residual moisture in the materials can take up to 24 hr to dry, this method is impractical from the production standpoint where turn-around time must be as short as possible.

Figures 2 through 7 are average percent moisture versus temperature curves for each lot of material evaluated with each instrument. The Mark-I and the oven produce similar results in most cases. The Computrac's

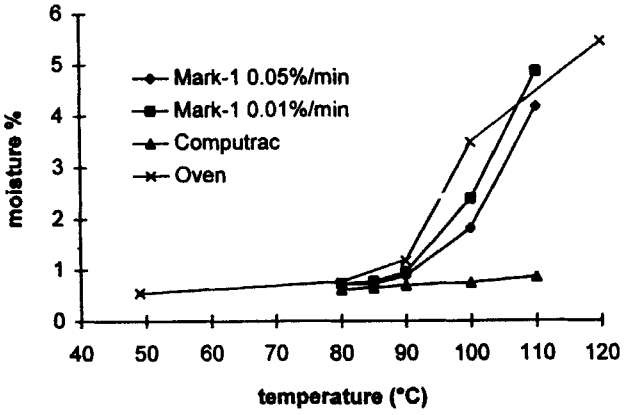

Figure 2. Placebo granulation containing lactose monohydrate, lot A.

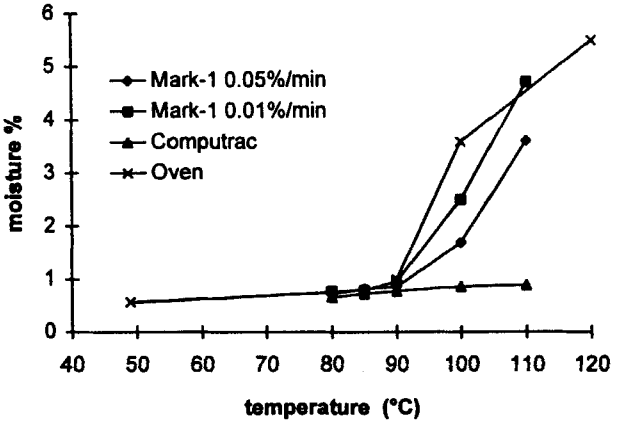

Figure 3. Placebo granulation containing lactose monohydrate, lot B.

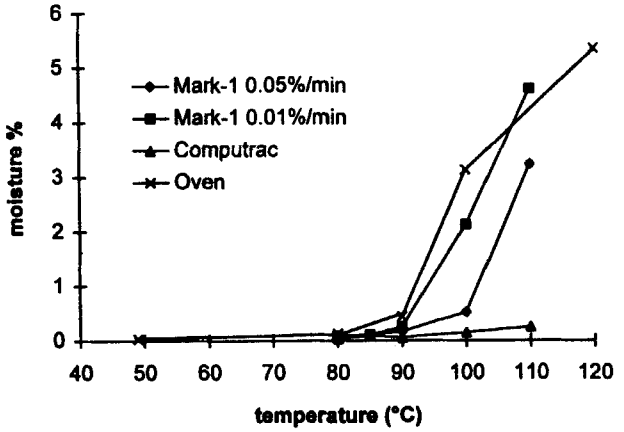

Figure 4. Lactose monohydrate, lot A.

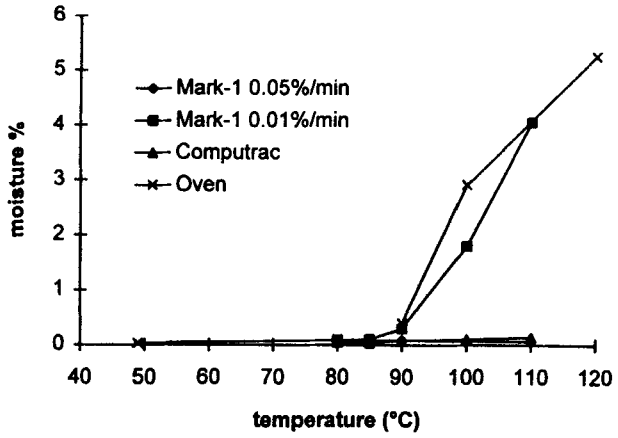

Figure 5. Lactose monohydrate, lot B.

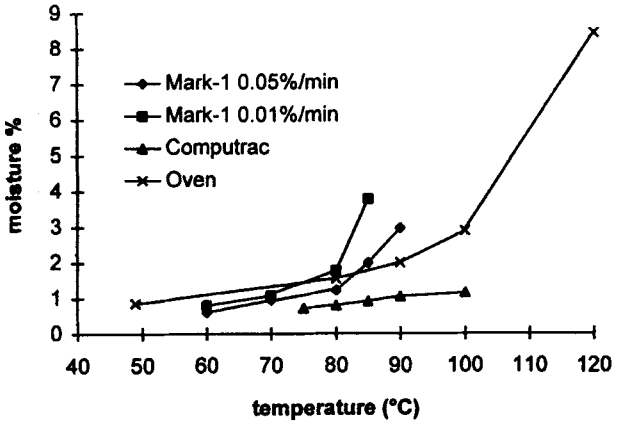

Figure 6. A-50711 granulation, lot A.

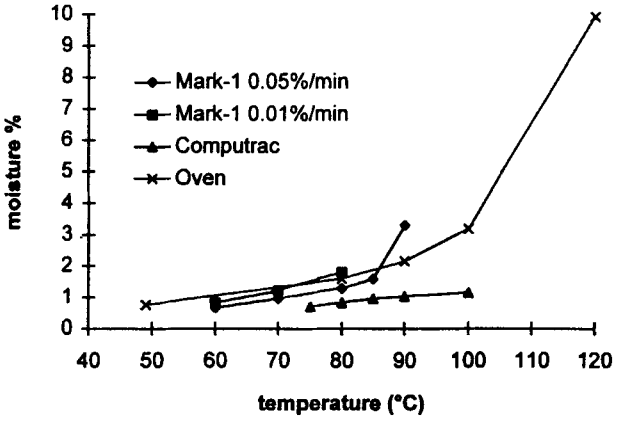

Figure 7. A-50711 granulation, lot B.

moisture determinations, however, are often much lower than those of the Mark-I and oven, especially at temperatures of 100°C and above for the placebo granulations and lactose monohydrate, and at 85°C or above for A-50711 granulation. This would suggest that the Computrac underdries the samples. This becomes especially apparent with the two lots of lactose monohydrate powder which are expected to contain approximately 5.1% total moisture (5% water of crystallization and approximately 0.1% adsorbed water) One expects the moisture content of lactose or granulations containing lactose to rise dramatically at temperatures greater than 100°C. With the Computrac at 110°C, however, the percent moisture never exceeds 0.25%, while the Mark-I and oven give results up to 4.61 and 5.35%, respectively.

The following are possible explanations for the underdrying phenomena in the Computrac. First, there may be an inherent programming problem in the Computrac MA-5's software that terminates the program before the test is complete. The second explanation is the different heating rates among the three instruments. The Mark-I heats samples with incident infrared radiation, allowing the samples to heat less quickly and creating a more gentle heating environment. The oven also reaches a gentle plateau of temperature as it approaches the set temperature, thus avoiding the sudden spikes in temperature observed with the Computrac. As shown in Fig. 8, Nagase et al. (8) have shown that the water of hydration molecules leave the compound more slowly at higher heating rates than those subjected to slower heating rates. At slower heating rates, the kinetic component decreases and the equilibrium component increases. From Fig. 8, it is apparent that as the heating rate increases, the moisture loss decreases. Thus, the software of the Computrac would prematurely terminate the test as it detected a rate of moisture loss lower than the default value.

In order to obtain an accurate measurement of residual moisture content in granulations containing lactose monohydrate, a set temperature should be chosen, below 100°C, at which water of hydration starts to dissociate from lactose monohydrate.

Figures 4 and 5 showed that Mark-I analysis of lactose lot A with end-point slope set at 0.05%/min produced lower than expected results of extensively repeated testing. One explanation is that the lag time required for the heating chamber to warm to its set temperature of 100°C and 110°C was greater than the time required to reach its set end point. It is possible that lactose lot B contained enough residual moisture to pre-

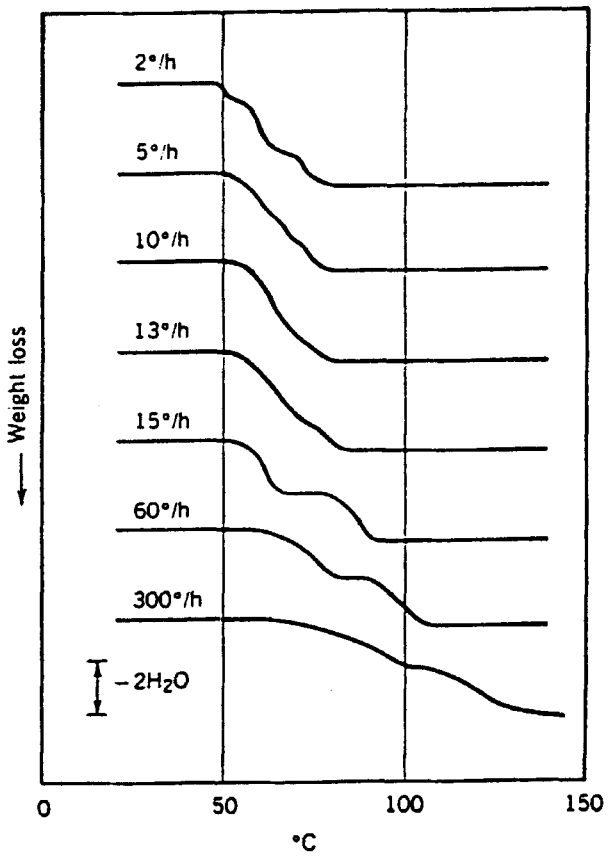

Figure 8. Thermogravimetric curves of $CuSO_4 \cdot 5H_2O$ (Nagase et al., Ref. 8). At slower heating rates, the kinetic component decreases and the equilibrium component increases. At higher heating rates, the two water of hydration molecules leave the compound more slowly than those subjected to slower heating rates.

vent meeting the end-point slope before the temperature in the heating chamber had stabilized. The 0.01%/min slope setting, however, produced the expected results for both lots. Thus, for samples with an expected LOD of 0.1% or lower, the 0.01%/min slope should be used.

Furthermore, experiments were done to determine the time required to complete a test at each temperature. Figure 9 demonstrated this time dependency for the two lots of lactose monohydrate evaluated. With all lots and all instruments, if the test was conducted at temperatures where the compound is thermodynamically stable, the tests took acceptably small amounts of time to complete. If, however, the temperature at which the compound lost water of hydration was exceeded, the tests took significantly longer to complete. When the lactose monohydrate powder was evaluated at temperatures up

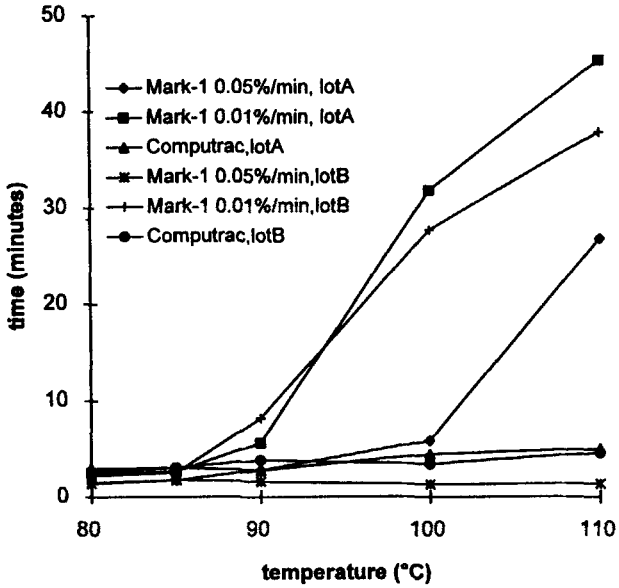

Figure 9. Time vs. temperature (lactose monohydrate).

to 90°C, the difference in the time required was insignificant. Past 90°C, the Computrac appeared to complete the tests more quickly; however, it also grossly underdried the samples.

Figure 10 shows the average absolute percent error versus temperature for the Mark-I and the Computrac analysis of a system of sand with 1% water. Both methods evaluated produced good results at all temperatures. The data indicated that for granulations which did not contain any volatile components of water of hydration other than the residual moisture or residual granulating solvent, both instruments produced accurate and comparable results at various temperatures. The Mark-I with

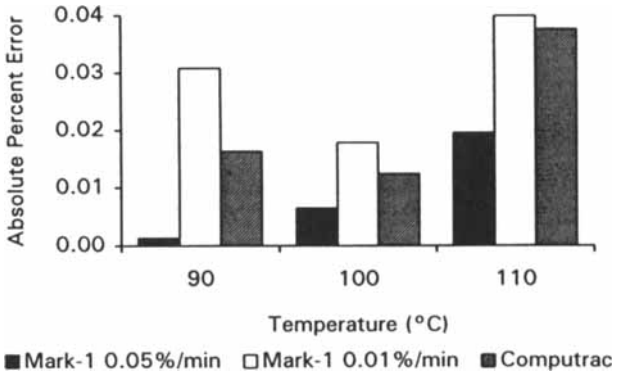

Figure 10. Absolute percent error vs. temperature.

0.05%/min slope has the overall smallest average error, while the same instrument using a 0.01%/min slope has the largest average error.

CONCLUSIONS

Since most pharmaceutical granulations contain materials which are in equilibrium with their bound waters of hydration and their evolved volatile components, selecting the optimal set temperature is very important, especially when Computrac is used. The Mark-I moisture analyzer, on the other hand, gives much closer values to those predicted for the compounds tested. For most materials tested, a good correlation existed between the LOD results measured by the Mark-I and the oven method. Using the Mark-I instrument, the set temperature should be 90°C or less for samples containing lactose monohydrate. Meanwhile, the set temperature for analysis of granulations containing A-50711 should be 80°C or lower.

REFERENCES

1. K. G. Van Scoik, M. A. Zoglio, and J. T. Carstensen, *Pharmaceutical Dosage Forms: Tablets*, Vol. 2, 2nd ed., Marcel Dekker, New York, 1990, Chap. 2: Drying, pp. 73–105.
2. A. R. Gennaro, ed., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Co., Easton, PA, 1990.
3. *The Merck Index*, 11th ed., Merck & Co., Rahway, NJ, 1989.
4. *Mark-I Moisture Analyzer Operating Instructions,* Denver Instrument Company, 6542 Fig Street, Arvada, CO 80004.
5. *Compu-Trac, Inc. Moisture Analyzer User's Manual*, Compu-Trac, Inc., 2078 E. University Drive, Tempe, AZ 85281.
6. *The United States Pharmacopeia*, 22nd rev., The United States Pharamcopeial Convention, Rockville, MD, 1990.
7. *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association, Washington, DC, 1986.
8. K. Nagase, H. Yolobayashi, M. Kikuchi et al., Thermochim. Acta, 35, 99 (1980).