

Pilot Plant Vacuum Drying of Tablet Excipients

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An investigation of the drying characteristics of three commonly employed tablet excipients was conducted under vacuum in an instrumented 1-cu. ft. rotary double-cone dryer. It was found that during the constant rate period the drying rate was roughly one-half of the limiting evaporative capacity of the system as determined in a control study with water. The greatest differences between drying characteristics of the materials occur during the falling rate period when internal factors become controlling. Of particular note was the fact that after drying, almost 50 per cent of the moisture added during granulation was still retained by the calcium sulfate. A hypothesis was presented that heat transfer is equivalent to mass transfer as a controlling factor in drying during the falling rate period. The heat transfer coefficient for the dryer used was calculated to be 20-22 B.t.u./hr./sq. ft./°F.

FOR A number of years Rovac drying has been employed at Ciba as a standard technique for the drying of tablet granulations (1). This method of drying employs a jacketed double-cone blender which can be operated under vacuum. Although such dryers have had a well-established position in chemical manufacturing operations, the use of this equipment in the preparation of tablet granulations has not gained wide acceptance until recent years. As observed by Fischer (2), the use of vacuum-tumbler drying should be contemplated when any of the following circumstances are of importance: (a) limit on maximum product temperature, (b) low final moisture content, (c) control of product contamination, (d) recovery of evaporated solvent, (e) retention of fine solids, (f) enclosure for safety, and (g) compact installation.

Because many of the above conditions are often encountered in the processing of pharmaceutical tablet granulations, the utility of the equipment is beyond question. It is only the technique which must be mastered.

Our early developmental studies which produced cycles for tablet granulation drying were carried out on production-size batches. Although this technique led to granulations with excellent tableting characteristics, the program was elaborated on an empirical basis utilizing parallels to principles previously connected with atmospheric drying. Though the feasibility of granulating by this technique was already proven, it was thought valuable to obtain a 1-cu. ft.

unit as a research and development tool in an endeavor to answer some of the questions and solve operating difficulties which studies in the larger units had uncovered. As Badger and Banchemo (3) have characterized the situation related to indirect dryers, "...as one goes into the subject further, he sooner or later realizes that in practice all such dryers must be designed by making a series of test runs of the material in question on a small model of the type of dryer under consideration."

Though tablet granulations are complex systems consisting of numerous agents, it was felt necessary first to study the drying processes of the single chemical entities which constitute the granulation. The initial objective was, therefore, to study the effects of external drying conditions under vacuum on selected tablet ingredients. The materials chosen for study were lactose, mannitol, and calcium sulfate dihydrate.

DESCRIPTION OF EQUIPMENT

The rotary vacuum dryer used is shown in Fig. 1. All wetted surfaces of the drying and condensing system are fabricated of type 304 stainless steel. The unit is fully jacketed, except for the hatches. The speed of rotation is variable between 5 and 25 r.p.m. although all runs were made at 8 r.p.m. The jacket heating system consists of a pump which is directly connected into the jacket circuit, and control valves which introduce either heated or cooled water into the circuit. By this means, the jacket temperature can be controlled to within $\pm 1^\circ$. Water is circulated through the jacket at high velocities, which serves two purposes: (a) It maintains a maximum heat transfer rate between the water and the surface of the dryer by minimizing the surface film coefficient. (b) The temperature of the entering

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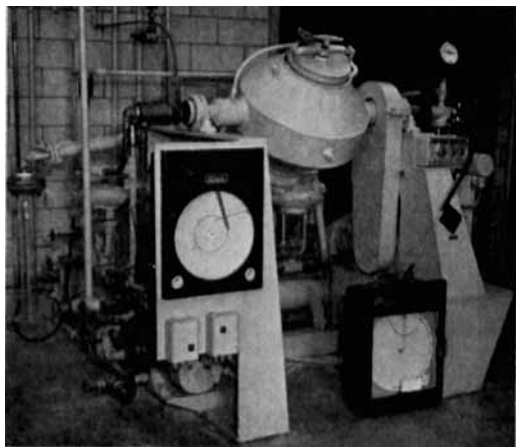


Fig. 1.—Front view of 1-cu. ft. rotary vacuum dryer installation.

and leaving water is essentially constant, producing no hot or cold spots on the inner surface of the dryer. This makes heat transfer calculations somewhat simpler by allowing the assumption of a constant jacket temperature.

The vacuum system consists of a filtered vacuum line, a vapor temperature thermometer, a water-cooled condenser, a condensate collector, and a vacuum pump. The filter is a felt ring type which is changed before each run. The condenser water temperature is 55°F., and the flow rate is such that the temperature rise is insignificant. The condensate collector consists of a 1,000-ml. cylindrical glass graduate with a Pyrex pipe end welded to it. In this equipment, the condensate collection is both visible and measurable. The vacuum is induced by a positive displacement, air ballast vacuum pump.

No attempt was made to measure the batch temperature since any conventional type of probe thermometer is essentially an averaging type. Thus, all that would be indicated is an average between the exterior surface of the granule and the vapor temperature. If it was possible to keep the probe in the granulation continuously during tumbling, the indicated temperature would be between the vapor and the surface temperature of the granule.

EXPERIMENTAL

The general conditions described below have been employed as reproducible test methods throughout the study. All experiments were performed in an air-conditioned temperature-controlled area. Although of no direct importance in our investigation, readings of relative humidity were taken during some runs and found to be fairly constant at 35 to 45%. All experiments described below were conducted with a charge of 10 Kg. of dry material wetted by 1 Kg. of water.

Procedure for Drying Experiments.—Dry material was screened through a No. 16 screen by hand, and 10 Kg. was weighed out. It was then placed in a Hobart model H-600T mixer and wetted with 1 L. of deionized water in accordance with

accepted techniques. The mixer was run at 22 r.p.m. for 15 min. The wet material was then passed through a Fitzmill using a 5A screen, medium speed, and knives forward. The material was then immediately loaded into the dryer and a sample removed. The initial moisture content was then determined by both the Karl Fischer method and a Cenco moisture balance.

Before each run, the rotational speed of 8 r.p.m. was checked with a stop watch. The temperature of the dryer was brought up to its operating point long enough in advance of the run to insure that there was no more than a 2° difference between the outlet and inlet temperature in the dryer jacket. The wet granulation was loaded, the hatch sealed, and the vacuum pump and the rotation of the dryer were started simultaneously.

Readings were taken periodically of the moisture collected in the condenser graduate, the absolute pressure on a mercury manometer, and the temperature of the effluent vapor. In addition, both the jacket inlet temperature and the absolute pressure in the system were both recorded continuously.

Whenever possible, the run was continued until 800 ml. of liquid was collected, or until repeated readings at the same liquid level in the collector were recorded. The dry material was removed, sampled, and observed. The sample was checked for residual moisture content by both Cenco and Karl Fischer methods as follows.

Cenco readings were taken following 10-min. exposure of the pan to a 125-w. lamp at 110 v. current. Karl Fischer analysis was conducted using a Beckman Aquameter. Sample size was based on estimated moisture content.

The first series of experiments were conducted to determine the maximum evaporative capacity of the unit at various temperatures. Employing these data, it could then be ascertained that as long as the drying rates of the granulated samples remained below those for pure water alone, heat transfer rather than dryer operating capacity would be the limiting parameter of drying rate.

Ten liters of water was placed into the dryer which was set at the desired operating temperature. Throughout the experiments to be described below, the unit was always rotated at a constant 8 r.p.m.

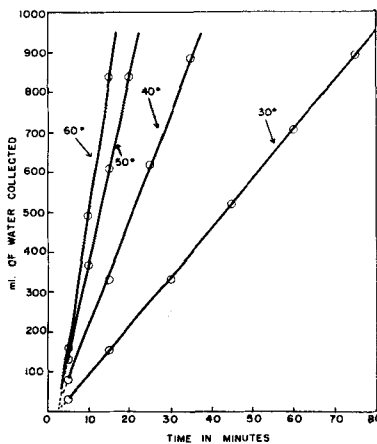


Fig. 2.—Drying-time curves for pure water in system.

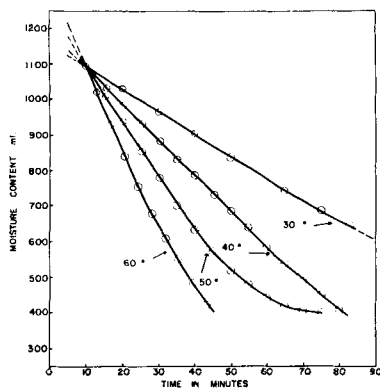


Fig. 3.—Drying of lactose U.S.P. Absolute moisture content vs. time.

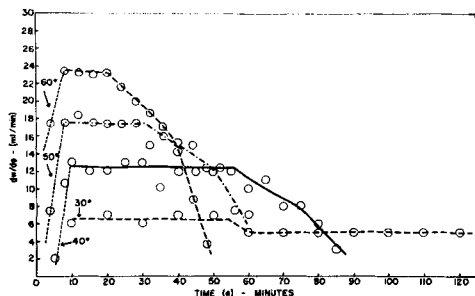


Fig. 4.—Effect of jacket temperature on drying rates for lactose U.S.P.

speed. The amount of water collected was then noted at regular time intervals and the results plotted in Fig. 2. As expected, the amount of water collected was directly dependent on temperature. The plot of milliliters collected versus time was in all cases a straight line, demonstrating the linearity of the heat transfer relationship. Although not presented, the recorded absolute pressure in mm. of Hg corresponded for each temperature to the vapor pressure of the water at the temperature of drying. It must be noted that the effects of temperature on drying rates for water are in a geometrical relationship for every 10° of temperature change. As a corollary to this, the system water losses were determined at varying temperatures and found to be constant at 50 to 60 ml. of water per run. This loss was, therefore, disregarded in calculations since it was a constant in all systems.

RESULTS AND DISCUSSION

Runs were then carried out, as described under *Experimental*, using powdered lactose U.S.P., mannitol N.F., and calcium sulfate dihydrate as the test substances. Representative data on a sample of lactose U.S.P. have been plotted in Fig. 3 for each of the temperature studies in this series. It can be seen from the plot that the decrease in moisture content (dry basis) is linear during the first part of the drying cycle and then decreases with time during the second phase. This relationship will be seen more clearly in drying rate plots to be

presented subsequently. All values shown in Fig. 3 have been corrected to the same moisture content after 10 min. of drying. The 50° curve (Fig. 3) is a typical curve which becomes asymptotic to an equilibrium moisture content. All of the other curves would have essentially the same appearance if they were extended. These curves represent the general case when a wet solid loses moisture first by evaporation from the surface of the solid, followed by a period of evaporation from a free water surface of gradually decreasing area, and finally, when water is evaporating only from the interior areas. The critical point is not in evidence on a plot such as this.

Figure 3 indicates that the drying rate is subject to variation with time, although this variation can be illustrated better by differentiating the curve and plotting drying rate, $dw/d\theta$ versus time (Fig. 4). These rate curves more clearly show that the drying process in the system described here is not a smooth, continuous one. The constant rate as well as the falling rate periods of drying are reasonably well defined in Fig. 4. It should be mentioned at this point that the figures shown are representative plots averaged from several runs at each temperature. Figures 5 and 6 represent the drying characteristics of mannitol and calcium sulfate. Figure 5 is very much the same as that encountered in Fig. 4 for lactose. However, this is not the case for the drying of calcium sulfate dihydrate. This plot (Fig. 6) shows the same over-all periods, but it can be seen that the constant rate drying is of much shorter duration than with the other materials. In fact, the primary drying of this substance is completed when almost one-half of the added moisture is still

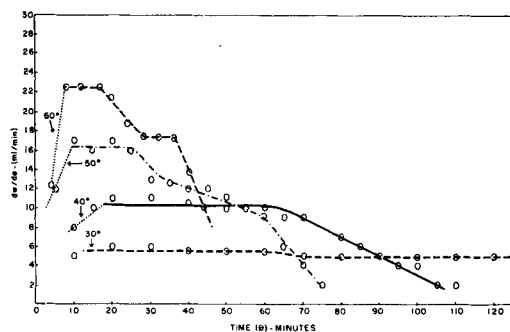


Fig. 5.—Effect of jacket temperature on drying rates for mannitol N.F.

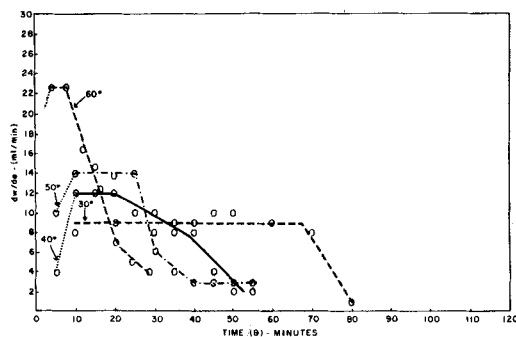


Fig. 6.—Effect of jacket temperature on drying rates for calcium sulfate dihydrate.

TABLE I.—VARIATION OF DRYING RATE WITH TEMPERATURE DURING CONSTANT RATE PERIOD

Temp., °C.	Lb. H ₂ O Evap./Ft. ² Drying Area/hr.			
	Granulation			
	Deionized Water U.S.P.	Lactose U.S.P.	Mannitol N.F.	Calcium Sulfate · 2H ₂ O
30	0.52	0.293	0.241	0.324
40	1.30	0.498	0.451	0.479
50	1.61	0.720	0.675	0.570
60	2.15	0.897	0.859	0.856

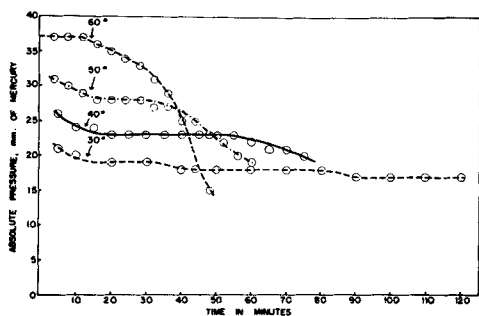


Fig. 7.—Variation in absolute pressure during drying at various temperatures.

retained by the CaSO₄·2H₂O. To the authors' knowledge, this unusual behavior has not been noted in the literature previously.

The effects of jacket temperature on the drying rate of the three excipients were calculated for the initial constant rate period of drying in all instances. These are presented in Table I in English rather than metric units since most engineering data in the United States are available in this form.

It can be observed from the table that the drying rate for all three materials during the constant rate is roughly one-half of the limiting evaporative capacity of the system as determined in the control study with water. In practically all instances the values are of similar magnitude, showing that the drying in this period is relatively independent of the solid employed. The great differences between the drying characteristics of the materials occur in the falling rate period where internal diffusion and capillary flow in the solid being dried together with heat transfer considerations begin to predominate as the rate-determining factor. It is in this phase that the observed differences noted in the drying of various granulations takes place. The effects of particle size as well as degree of moisture content of the granules have also been shown to have an important effect on the drying process. The authors hope to explore these areas in depth in a future report.

Figure 7 details the variation in absolute pressure during drying at the temperatures studied. It demonstrates quite clearly the relationship between the absolute pressure in the system and the drying rate, with the parallels between this figure and Figs. 4, 5, and 6 being readily evident. Since our vacuum system is considerably oversized, as less vapor becomes available for transport, the absolute pressure in the system would approach a minimum working value. In the 1-cu. ft. unit, this value has

been found to be from 4 to 6 mm. Hg at room temperature.

Calculation of Heat Transfer Coefficient in System.—The calculation of heat transfer rate was made by relating the total weight of liquid removed during the constant rate drying period and the time during which it was collected. The following relationship summarizes the specifics in this instance for both periods of drying (4)

$$U = \frac{q}{A(\Delta t)}$$

where

$$q = \text{rate of heat transfer in B.t.u./hr.} = \frac{\text{lb. of H}_2\text{O evaporated} \times \text{B.t.u./lb.}}{\text{time taken to evaporate}}$$

$$A = \text{total heat transfer surface exposed to wet material, sq. ft.}$$

$$\Delta t = \text{differential temperature } (t_2 - t_1)$$

$$t_2 = \text{the jacket temperature, } ^\circ\text{F.}$$

$$t_1 = \text{the saturation vapor temperature at the internal pressure existing in the dryer, } ^\circ\text{F.}$$

$$U = \text{over-all heat transfer coefficient based on temperature difference between heating medium and product, B.t.u./hr./sq. ft./} ^\circ\text{F.}$$

As noted earlier, drying can be divided into distinct periods, with the material during the constant rate period at substantially the boiling point of the evaporating liquid under the pressure conditions existing in the dryer and approaching the wall temperature during the falling-rate period. The authors have found that the over-all heat transfer coefficient is almost entirely dependent upon the coefficient between the material and the wall and varies with the type of material being dried. Other factors affecting heat transfer include (a) the total weight bearing on the drying surfaces (increasing with increasing bulk density) and (b) particle size.

It should be noted that if caking on the walls occurs, it has been shown that the coefficients are reduced by a factor of from 5 to 20 times (5).

In calculations of the heat transfer coefficient, it was necessary to make numerous assumptions. (a) Radiation constitutes a minimum effect. Calculations show that, assuming perfect conditions—gray bodies and perfect vacuum in the container—that at the maximum temperatures used (60°), the radiation effect could not be more than 2–3%, which is within the error of the data (6). (b) Heat transfer is due entirely to conduction. (c) The vapors leave the chamber dry and saturated. (d) The latent heat of steam is 1050 B.t.u./lb. at the pressure-temperature conditions existing within the dryer (approximately 50 mm.). (e) The starting moisture content for all runs puts the drying cycle in the constant rate drying period. (f) Fifty per cent of the dryer surface is in contact with the material at all times. (g) The temperature of the solid being dried is at the same temperature as the vapors being driven off.

The heat transfer coefficients for a series of runs with lactose U.S.P. are reported in Table II.

The discrepancy noted in the 30° run at first seemed in error until it was realized that the temperature used in the calculation was the one indicated on the thermometer in the vapor stream leaving the dryer. In the other three cases, the

TABLE II.—HEAT TRANSFER COEFFICIENTS FOR RUNS WITH LACTOSE U.S.P.

Temp., °C.	U.
30	56.0 (Corrected for superheat to 20.1)
40	22.2
50	20.7
60	22.1

indicated temperature and the true saturation vapor temperature were the same. However, in the case of the 30° run, the vapors leaving the dryer were superheated. When the actual saturation vapor pressure for the 30° run is used, the heat transfer coefficient is of the same order of magnitude as the higher temperature values.

It has been the authors' contention that heat transfer, rather than diffusion rate, capillarity, or any other single mechanism, is the controlling factor in the drying cycles of the materials tested in this study. The external factors limiting heat transfer in any method of drying remain fixed. During the constant rate drying period one of these external factors is the controlling resistance to the flow of heat. However, if we assume absolutely no moisture movement within the granule, which may not be entirely true, then the dry area of granule between the surface and the receding moisture front becomes a greater and greater resistance to heat flow. When the insulating effect of the dry periphery of the granule reaches a certain point, it, rather than the external factor which heretofore controlled the drying rate, becomes controlling. This would be the critical point. Drying during the falling rate period would then follow a curve which would be based on the physical shape of the granules and the insulating quality of the material.

CONCLUSIONS

The appearance of superheat in the vapor during the 30° run caused questions relevant to its effect on heat transfer at other temperatures. It can be theorized that if superheat exists, increasing the speed of rotation of the dryer would increase the heat transfer rate between the dryer and the granules and might tend to decrease drying time. However, if temperatures indicate that exiting vapors are at their saturation temperature, increasing the speed should have little effect on drying time.

Obviously, increasing temperatures increases drying rates; but decreasing the absolute pressure will accomplish the same end. In any case, once the

critical point has been reached, speed of rotation should affect the drying rate only slightly. Several studies (4, 5) have been conducted in this area but lead to few additional conclusions in tablet granulation drying.

Another external factor which can affect drying rates is the vacuum and condensing system. In the particular system reported here with a positive displacement vacuum pump and condenser, the only purpose of the vacuum pump is to remove air leakage into the system and any vapors not condensed. If the condensing surface is sufficient and the system is pressure tight, the vacuum pump can be shut off once the proper operating pressure is reached.

SUMMARY

The effect of external drying conditions, under vacuum, on the drying characteristics of lactose, mannitol, and calcium sulfate dihydrate has been investigated. An instrumented 1-cu. ft. rotary dryer was employed for the testing. Although lactose and mannitol were shown to have approximately the same drying cycles, the constant rate drying of calcium sulfate was shown to be of much shorter duration. In addition, it was observed that the drying of this substance is completed when almost one-half of the added moisture is still retained by the calcium sulfate.

The physical characteristics of the material being dried affect drying only during the falling rate period since during constant rate drying, the moisture evaporates only from the surface of the granule. As long as the surface moisture is replaced at the same rate that evaporation takes place, constant rate drying continues, and no differences in rate are observed. Once the critical point has been passed, heat and/or mass transfer become the controlling factors, and the physical characteristics of the material being dried become important.

Heat transfer coefficients are of value only during the constant rate period of drying. They were calculated for lactose U.S.P. and found to be 20–22 B.t.u./hr./sq. ft./°F.

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