Table III—Recovery Data

Product	Initial Assay	Saccharin Added, mg	Final Assay	Recovery, %
Tablet	16.9 mg/tablet	4.8	21.7 mg/tablet	100
Tablet	32.6 mg/tablet	9.3	42.0 mg/tablet	100
Suspension	5.1 mg/tablet	5.1	10.5 mg/5 ml	103
Suspension	5.1 mg/5 ml	10.5	16.3 mg/5 ml	105
Elixir	3.8 mg/5 ml	5.5	9.1 mg/5 ml	98
Elixir	3.8 mg/5 ml	10.2	13.6 mg/5 ml	97

Interferences—To establish the applicability of this procedure to various pharmaceutical dosage forms, synthetic formulations were made by adding sodium saccharin and were analyzed in addition to commercially available products. By the use of saccharin-free placebo formulations, it was found that pharmaceutically active ingredients such as ascorbic acid, nicotinyl alcohol, aprobarbital, dextromethorphan hydrobromide, chlorpheniramine maleate, acetaminophen, and sulfamethoxazole did not interfere with the analysis.

One pharmaceutical product contained a vitamin B-complex mixture made up of thiamine mononitrate, riboflavin phosphate, pyridoxine hydrochloride, niacinamide, and calcium pantothenate. The ingredients in the mixture did not cause any interference. Commonly used pharmaceutical excipients such as corn syrup, sucrose, citric acid, sodium citrate, sodium benzoate, propylene glycol, stearic acid, magnesium stearate, and mannitol also did not affect the utility of this method.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 7, 1974, from the *Analytical Research Laboratory, Quality Control Department, Hoffmann-La Roche Inc., Nutley, NJ 07110*

Accepted for publication July 19, 1974.

The authors thank Dr. C. G. Scott for GLC–mass spectroscopy and GLC–IR information and Mr. F. P. Mahn for helpful suggestions.

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PHARMACEUTICAL TECHNOLOGY

Drying Rates of Tablet Granulations I: Effect of Certain Granulating Adjuvants on Drying Rates

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Abstract □ The design and construction of a laboratory size dryer and other accessories suitable for investigating the drying rate kinetics of granules under controlled external conditions are described. Granulations of lactose and sulfathiazole, representing water-soluble and insoluble materials, were prepared using various commonly used binders, and their drying rates were determined. The binders and diluents affected the drying rate curves for these granulations both qualitatively and quantitatively. Granules made with starch paste and gelatin solution required maximum time and energy for drying and those made with simple syrup USP required the least among the binders studied. Generally, three linear slopes were observed when the drying rate was plotted against the moisture remaining, indicating that granulation drying may be considered as occurring through three distinct phases.

Keyphrases □ Tablet granulations—effect of granulating adjuvants on drying rates □ Granulating adjuvants—effect on drying rates of tablet granulations □ Drying rates, tablet granulations—effect of granulating adjuvants □ Excipients—effect of granulating adjuvants on drying rates of tablet granulations

The manufacture of pharmaceutical tablets requires the preparation of granular material for compression. One common method of preparing these suitable granules is by wet granulation. Although the industrial pharmacist is well aware of the cost savings in the choice of excipients, size of tablet, and speed of

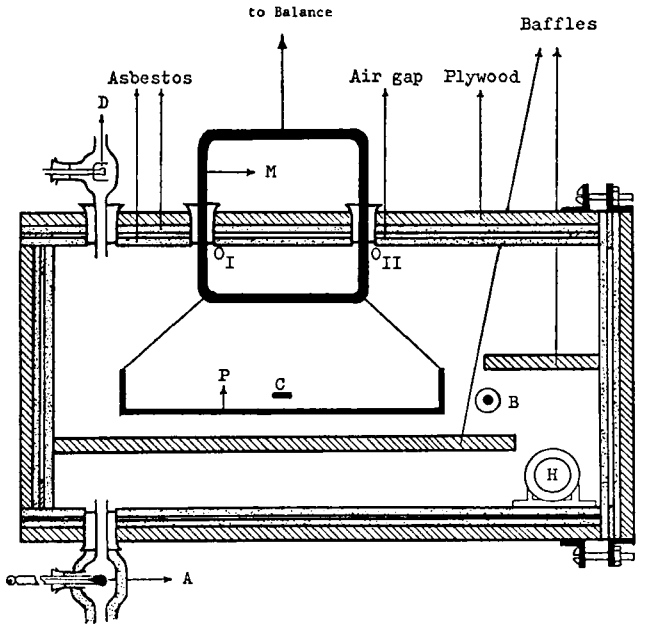

Figure 1—*Cross section of the dryer designed for this study. Key: H, heating coil; B and C, thermocouples; A and D, thermometers; M, metal loop; O_I and O_{II}, openings through the dryer; and P, drying pan.*

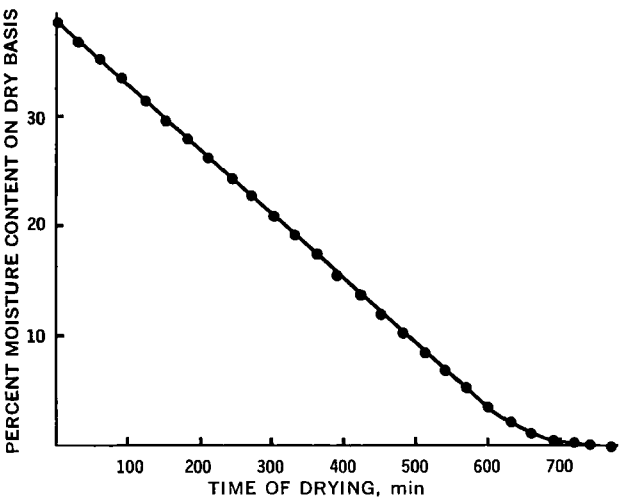

Figure 2—*Drying rate curve for sulfathiazole granulation prepared using distilled water as the binder and plotted as moisture content on dry basis* versus *time of drying.*

the tableting machines, little attention has been paid to the efficiency of the drying operation following the wet granulation. The high heat energy consumption involved in the drying of tablet granulations makes it a very expensive operation. This is particularly true for the last phases of the drying operation aimed at removing moisture in the range of 10.0–0.5% (w/w).

Even though the drying rates of various materials have been studied in the chemical industry (1–5), little effort has been made to understand the kinetics of drying of porous materials such as tablet granules. Pharmaceutical granulations can vary widely, based upon differences in porosity and the mechanism by which the moisture is held within them. Therefore, the drying rate kinetics of these pharmaceutical granulations must depend upon the physicochemical nature of the ingredients as well as the solutions of the binding agents used to form them.

Most binding agents used for wet granulations, such as starch paste, acacia mucilage, gelatin solution, simple syrup, methylcellulose solution, and corn syrup, are hydrophilic in nature. These binders increase the bulk density and reduce the porosity of the powder, thereby diminishing the effective surface area for evaporation. Hydrophilic binders also retard the rate of evaporation of moisture by lowering the vapor pressure of liquid moisture. In addition, the amount of moisture introduced into the granules and retained by them after drying varies greatly with different binding agents.

The purpose of the present investigation was to design experimental conditions to study the drying rate of the granules under controlled external conditions. Using such drying conditions, attempts were made to elucidate the comparative effect of some commonly recommended binding agents. These include starch (7, 8), gum acacia (7), corn syrup (7), gelatin (9), simple syrup (9), carboxymethylcellulose (10), and povidone (11, 12). Additionally, the effects of binder concentrations and diluents on the drying rates of the granulations were studied.

EXPERIMENTAL

Equipment Design—To study the rate of drying of granules based upon the internal mechanism of liquid flow and independent of external conditions of drying such as temperature, humidity, air flow rate, and state of subdivision, a special setup was required. An experimental apparatus was designed and fabricated, consisting of three sections: *(a)* dryer, *(b)* drying air humidity and flow rate control line, and *(c)* air heating chamber.

The dryer was a 54 × 46 × 30-cm well-insulated box (Fig. 1). The sides of the dryer were constructed from four layers consisting of (from outside to inside) 1.27 cm plywood, 0.64 cm asbestos, 0.32 cm air gap, and 0.64 cm asbestos. An additional insulation layer was added while studying the effect of physical properties of the granulations upon the rate of the first falling rate period.

The inner side of the dryer was sprayed with aluminum paint to cut down heat loss by radiation. The dryer was fitted with a reasonably quick opening door at one end. The rubber gasket was placed between the dryer and the door to make an airtight closure. To improve air circulation, the dryer contained horizontal baffles made of 1.27 cm plywood.

A square sample pan, P (30 × 30 × 3.8 cm), was suspended by its corners with a thick metal wire from two corners of a square-shaped metal loop, M (15 × 15 cm), made from a 0.64-cm diameter iron rod. The other two corners of the metal loop extended outside the dryer through the openings, O_I and O_{II}, in the upper side of the dryer. These two corners were connected to the weighing pan of the balance as shown in Fig. 1.

The two openings through which the loop M extended outside were fitted with rubber stoppers, each having a central hole equal to the diameter of the iron rod of the loop. These openings were always kept closed except when the weight was being recorded. A heating coil, H, connected in series to a variable resistor was placed inside to preheat the dryer to achieve the experimental conditions faster.

Thermocouples were placed at points B, C, and D in Fig. 1 and the temperature was read[1]. Thermocouple C was placed over the surface of the sample granules. The temperature at point A was measured using a mercury thermometer. Temperatures at points

[1] On a Tele-Thermometer, model 44, 12 channel, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio. It is capable of accurately measuring temperature differences of up to 1° F.

Table I—Initial and Final Moisture Contents, Critical Points, Slopes of Falling Rate Periods, and Drying Rates during Constant Rate Period of Sulfathiazole Granules Made with Various Binding Agents

Binding Agent	Initial Moisture Content, % w/w	Final Moisture Content, % w/w	Total Drying Time, min	Drying Rate during CRP[a]	Critical Points, % Moisture on Dry Basis		Slopes of Falling Rate Periods[b]	
					First Point	Second Point	First Slope	Second Slope
Distilled water	38.9	0.0	810	34.5	15.00	2.80	0.55	11.00
Starch paste, 10% (w/w)	37.5	0.3	875	31.7	20.05	2.50	0.45	11.00
Starch paste, 15% (w/w)	37.9	0.8	925	31.0	22.00	3.35	0.56	8.75
Acacia mucilage, 10% (w/w)	30.4	0.3	705	34.5	15.00	3.00	1.00	11.30
Acacia mucilage, 15% (w/w)	29.4	0.3	755	30.0	16.00	3.00	0.69	8.34
Gelatin solution, 10% (w/w)	28.7	0.8	840	30.5	22.00	2.50	0.63	10.61
Gelatin solution, 15% (w/w)	28.2	0.9	825	—	—[c]	3.00	0.52	9.30
Povidone NF solution, 10% (w/w)	29.0	0.2	755	28.0	12.00	2.00	0.67	11.00
Methylcellulose solution, 3% (w/w)	33.0	0.6	955	28.0	20.00	2.70	0.50	8.00
Simple syrup USP	11.2	0.1	525	—	—[d]	1.65	0.50	6.45
Corn sugar solution, 50% (w/w)	17.6	1.0	730	—	—[d]	2.80	0.88	6.50

[a] CRP = constant rate period [grams/(hour) (kilogram of dry solid)]. [b] Units are grams per hour kilogram. [c] Above 25.00 (projected). [d] Above initial moisture content.

A, B, C, and D will be referred to as heating chamber, inlet air, granules surface bed, and outlet air temperatures, respectively.

To obtain drying air at constant flow rate and humidity, incoming air from a blower was cooled in the range of from −10 to −15°, using a salt–ice bath to condense most moisture. Final traces of moisture were removed by bubbling the air through two successive containers of concentrated sulfuric acid. The air was then passed through two empty conical flasks plugged with glass wool to retain any suspended acid droplets, followed by passage through solid sodium hydroxide to remove the last traces of sulfuric acid. The air thus treated was considered perfectly dry[2].

This air was passed through a Rotameter[3] to measure the air velocity which could be adjusted by a Hoffman clamp. The resulting air was forced through an air heating chamber, which consisted of a metallic box, 15 × 15 × 18 cm, well insulated from the environment by a 1.90-cm layer of foam rubber. A heating coil controlled by a variable resistor was fitted inside the heating chamber to heat the air to a required temperature.

Sulfathiazole Granulation Studies—The granules were prepared by adding the binding agent to sulfathiazole powder in a blender mixer until a suitable wet mass was obtained. This mass was then forced through a 10-mesh standard screen. The initial moisture content of these granulations was determined using a moisture determination balance[4]. Enough wet granules were spread uniformly to provide a 1.27-cm bed over the sample pan P of the dryer. The pan was suspended inside the dryer, and a thermocouple was placed over the surface of the granules. The door of the dryer was closed and the dryer was heated to approximately 70° for 30 min, employing the heating coil H and the heated inlet air at a rate of 3.40×10^6 cm³/hr.

The electric current passing through the coil was then gradually reduced to zero, such that the inlet air temperature was stabilized at 50° and the weight of the entire suspended system (weighing assembly plus granules) was noted. From this point on, readings for the inlet air, granules surface bed, outlet air temperatures, and weight of the suspended system were recorded periodically until the weight of the suspended system was constant. The dryer was then opened and the final moisture content of the dried granules was determined using the moisture balance.

The data collected were used to calculate the drying rate [grams of moisture evaporated/(hour)(kilograms of dry solid)] and the amounts of moisture lost every 30 min during the drying operation for every batch of granulation. Each experiment was carried out at least twice. In most cases there was no statistically significant difference in the results, the range of variation being within ±1% (w/w) moisture content for the critical points. However, if the two experimental results differed significantly, the experiment was repeated until two consecutive experimental results fell within required limits.

Lactose Granulation Studies—The procedure employed to study lactose granulations was identical to that used for sulfathiazole granulations except for the drying conditions. In this case, the dryer was heated to approximately 60° for 30 min, employing the heating coil H and the heated inlet air at a rate of 2.83×10^6 cm³/hr after placing the granulation in the sample pan. The electric current passing through the coil H was then gradually reduced to zero, such that the inlet drying air was stabilized at 40°. The drying rate of lactose granulation was not studied at 50° because at this temperature lactose turned yellow, indicating a chemical change.

RESULTS AND DISCUSSION

When a solid is dried experimentally, the data usually obtained relating moisture content to time of drying can be plotted in various forms:

1. Moisture content (dry basis) *versus* time of drying
2. Drying rate [grams of moisture evaporated/(hour) (centimeters² of drying area)] *versus* moisture content [grams of free moisture/gram of dry solid]

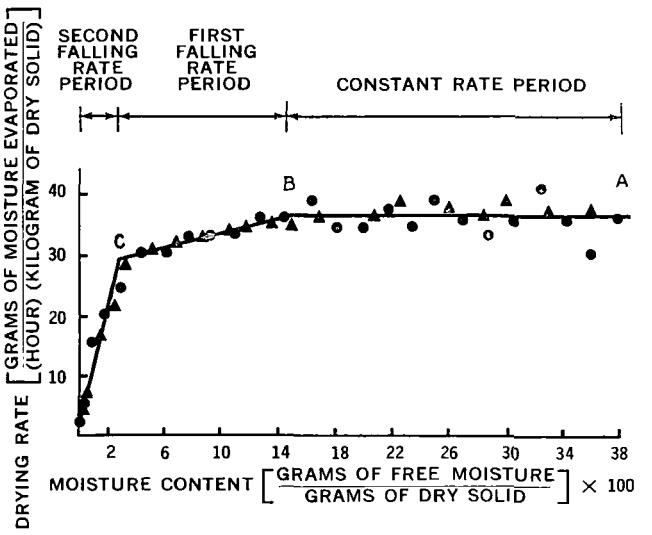

Figure 3—*Drying rate curve for sulfathiazole granulations prepared using distilled water as the binder and plotted as drying rate* [*grams of moisture evaporated/(hour)* (*kilogram of dry solid*)] versus *moisture content of granulation. Key:* ●, *points from Experiment 1; and* ▲, *points from Experiment 2.*

[2] Twenty cubic feet of the resulting air was passed through a drying tube containing Drierite and no increase in the weight of the drying tube was observed.

[3] Tube size R-6-25-B, Brooks Instrument Division, Hatfield, Pa.

[4] Model 6000, Ohaus Scale Corp., Union, N.J.

Table II—Initial and Final Moisture Contents, Critical Points, Slopes of Falling Rate Periods, and Drying Rates during Constant Rate Period of Lactose Granules Made with Various Binding Agents

Binding Agent	Initial Moisture Content, % w/w	Final Moisture Content, % w/w	Total Drying Time, min	Drying Rate during CRP[a]	Critical Points, % Moisture on Dry Basis		Slopes of Falling Rate Periods[b]	
					First Point	Second Point	First Slope	Second Slope
Distilled water	14.8	0.6	700	21.5	6.60	2.00	1.47	10.10
Starch paste, 10% (w/w)	19.5	1.5	780	20.7	11.50	3.00	0.95	8.70
Starch paste, 15% (w/w)	28.2	1.8	840	20.2	13.80	4.35	0.70	10.30
Acacia mucilage, 10% (w/w)	19.4	3.5	625	21.3	11.0	5.30	1.56	8.25
Acacia mucilage, 15% (w/w)	17.4	4.3	685	19.3	11.2	5.40	1.35	10.90
Gelatin solution, 10% (w/w)	19.2	3.0	840	17.8	10.8	4.50	0.91	7.50
Gelatin solution, 15% (w/w)	18.6	4.2	780	17.7	12.40	5.80	0.55	6.94
Povidone NF solution, 10% (w/w)	21.6	4.5	775	18.0	11.30	6.20	1.21	7.69
Povidone NF solution, 15% (w/w)	22.0	4.8	780	19.5	11.40	6.20	1.67	9.25
Methylcellulose, 30% (w/w)	17.2	3.7	600	17.3	9.6	4.45	1.00	7.08
Simple syrup USP	8.2	2.6	415	—	—	3.16	1.61	7.40
Corn sugar solution, 50% (w/w)	16.4	3.7	675	5.0	8.05	4.5	2.50	7.80

[a] CRP = constant rate period [grams/(hour)(kilogram of dry solid)]. [b] Units are grams per hour kilogram.

3. Drying rate [grams of moisture evaporated/(hour) (centimeters^2 of drying area)] *versus* time of drying

4. Drying rate [grams of moisture evaporated/(hour) (gram of dry solid)] *versus* moisture content [grams of free moisture/gram of dry solid]

The first method of plotting normally gives a smooth curve and shows no sharp breaks. The fact that the drying rate is subject to variation with time of drying and moisture content of solid can be better illustrated by the latter three methods. For example, when experimental data for sulfathiazole granulations, made using distilled water as the binder, were plotted using Method 1, a smooth curve was obtained (Fig. 2). However, when the same data[5] were plotted following Method 4, the curve showed three distinct phases of drying (Fig. 3).

The slopes of the straight lines in Fig. 3 were obtained using linear regression analysis. The drying rate curve showed a constant rate period segment, which is a straight line parallel to the X axis. This constant rate period was followed by two additional straight lines, representing the first and the second falling rate periods. The drying rate curve for lactose granulations was similar in nature (Fig. 4). The presence of three phases of drying could be explained based upon the mechanism of moisture movement within the solid phase during drying (1–4, 6).

All drying rate curves exhibited this typical drying pattern as described here. However, in some cases, the constant rate period was not observed since the initial moisture content of the granules was below the first critical moisture content. The critical points, the slopes of the falling rate periods, and the drying rates during constant rate periods obtained for each binder are presented in Tables I and II.

During the constant rate period, the rate of drying is constant since the surface conditions remain unchanged. The temperature of the bed, the humidity, the velocity, and the temperature of the drying air are constant. Furthermore, the fraction of wetted surface of the drying particles remains the same. Moisture movement within the solid is rapid enough to maintain a steady state such that the surface is always saturated with liquid moisture. The moisture diffusing to the drying air from the surface of the solids is immediately replaced by the moisture from the interior. The end of the constant rate period is reached when the concentration of the moisture in the solid corresponds to point B in Fig. 3. This point, termed the first critical point, initiates the first falling rate period.

After the first critical moisture content point has been reached, the rate of drying begins to fall off linearly with the moisture content of the solid. This falling rate period corresponds to the phase of the drying cycle when only part of the solid surface is wet because the internal moisture migration is inadequate to replace the moisture evaporated from the surface of the solids. As the liquid moisture is progressively removed from the solid, the fraction of the pore volume occupied by air increases and there is insufficient moisture left to maintain a continuous film across the pores. This initiates the second falling rate period (point C in Fig. 3). After this state is reached, evaporation of liquid moisture takes place inside the pores and then mass transfer occurs by a vapor diffusion process.

Since binding agents change the physical characteristics of the granulations, the curves were plotted as drying rate: grams of moisture evaporated/(hour) (kilogram of dry powder) *versus* moisture content (grams of free moisture/gram of dry solid). The percentage of moisture needed to prepare a suitable wet mass for granulation of lactose and sulfathiazole ranged between 8.3 and 28.2% (w/w) for lactose and 11.2 and 38.9% (w/w) for sulfathiazole. One commonly used binder, starch paste, introduced the maximum amount of moisture into the granules. More time and energy were required to dry the granules made with starch paste than the granules made with other commonly used binders such as acacia mucilage, solutions of povidone NF, and gelatin solution.

Of all the binders studied, simple syrup USP introduced the minimum amounts of moisture [8.2% (w/w) for lactose and 11.2% (w/w) for sulfathiazole]. These amounts were approximately one-

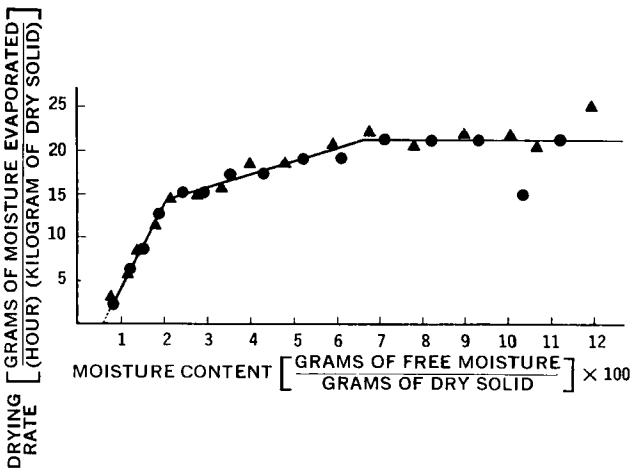

Figure 4—*Drying rate curve for lactose granulations prepared using distilled water as the binder and plotted as drying rate [grams of moisture evaporated/(hour) (kilogram of dry solid)] versus moisture content of granulation. Key: ●, points from Experiment 1; and ▲, points from Experiment 2.*

[5] Experimental data for two separate experiments for the same granulations were plotted on the same graph. This technique was used to minimize experimental errors.

third of those used for 15% (w/w) starch paste. Correspondingly, the time needed to remove the moisture from granules made with simple syrup was observed to be only about 40% of that needed for the granules made with 15% (w/w) starch paste. All of the other binders studied introduced moisture ranging between these two extreme values of 15% (w/w) starch paste and simple syrup USP.

The amount of moisture introduced into the granules during the granulation process also varied with the concentration of the solution or the suspension of the binding agent used. These amounts increased with increasing concentrations of binders in the case of starch paste, decreased with mucilage of acacia and gelatin solution, and remained almost constant for solutions of povidone NF. The increase in the initial moisture content of the granules in the case of starch paste is related to the considerable thickening that occurs with increasing concentrations of the paste. This thickening or reduced fluidity decreases the wetting ability of the paste.

The amount of moisture retained appears related to the affinity of granulation for water. With both lactose and sulfathiazole granulations, the binding agents increased the moisture-retaining capacity of the granules. The quantity of moisture retained by the granules increased with the increasing concentration of the binding agents used. Since moisture is often a major cause of deterioration of medicaments, the final moisture content of the granulations is usually a major concern for the industrial pharmacist.

The drying rates during the constant rate period were highest for granules prepared with distilled water as a binding agent, because it had the least effect on the bulk density and porosity of the chemical. The drying rate was the least for corn sugar solution. The rate of drying dropped by about 25% for granules made with corn sugar solution; 15% for granules made with 3% (w/w) methylcellulose, 10% (w/w) gelatin solution, 15% (w/w) gelatin solution, and 10% (w/w) povidone NF solution; and 5–10% for granules made with 15% (w/w) starch paste, 15% (w/w) acacia mucilage, and 15% (w/w) povidone NF solution.

In some cases (lactose granules made with simple syrup, gelatin solution, and corn sugar solution) the constant drying rate period was not observed since the first critical point apparently existed above the initial moisture content of the granules. In the case of sulfathiazole granulations prepared using gelatin solution, the economy of the drying process was greatly affected, since all moisture must be evaporated during the falling rate periods, which constitute more expensive phases of the drying process. When more concentrated solutions or suspensions of the binders were employed, most of the drying operation took place in the falling rate periods. This results due to a decrease in the granulations porosity whereby the moisture migration from the interior of the granules to the surface becomes more difficult so unsaturation of the surface occurs at earlier stages of drying.

The slopes of the first and second falling rate periods for lactose and sulfathiazole granules made with different binding agents represent the rates of decrease of drying rates in relation to decreasing moisture content of the granules. Higher values for these slopes represent a faster change in the lowering of the drying rate or a longer drying period. A comparative evaluation of binding agents for their effect on the slopes of falling rate periods as well as the effect of various physical parameters of the granulations upon this phase of drying will be the subject of future studies.

CONCLUSIONS

A laboratory size dryer as well as other accessories, designed and constructed to study the drying rate kinetics of porous granulations, was used to evaluate the effect of binders on the drying rates for lactose and sulfathiazole granules. The drying rate data obtained showed three distinct phases of drying, which were both qualitatively and quantitatively different for different binders and diluents.

Future uses of this setup will include studying the effect of physical properties of the granulations upon the drying rates and the mechanism of drying.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 1, 1974, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication July 11, 1974.

The authors thank Mr. Jack Ellis and Dr. Saul Borodkin for their helpful suggestions.

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