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A comparison of the fluidized bed drying technique with conventional methods of drying tablet granulations

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A COMPARISON OF THE FLUIDIZED BED DRYING TECHNIQUE WITH CONVENTIONAL METHODS OF DRYING TABLET GRANULATIONS

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INTRODUCTION

Drying procedures, like other important unit operations in pharmacy, have received little attention in pharmaceutical literature. Within recent years, however, growing interest in these pharmaceutical engineering areas has become apparent.

Fluidization operations, although relatively unexplored in pharmacy, have been firmly established on a broad scale in other industries. Fluidization may be defined as the suspension and agitation of a bed of particulate solids by a vertically rising stream of gas. Each suspended particle is surrounded by the gas. This relative velocity of the gas and solid particles is high, although the gas velocity itself is relatively low. Heat is transferred by a combination of conduction and convection and by the movement of the solid particles (1). Fluidized bed drying of moist phosphate rock, coal, and many other materials has been discussed in technical literature (1,2). However, relatively few reports have appeared on the applications of fluidized beds to materials of pharmaceutical interest.

These technical studies show that uniform bed temperatures with high heat and mass transfer rates are obtainable in fluidization systems. Product temperatures are controllable over narrow limits within the fluidized bed. These reported advantages would appear to have

particular importance in processing pharmaceuticals. It is difficult to understand, therefore, why only a few studies on fluidized bed drying have appeared in pharmaceutical literature. Apparently no comprehensive studies dealing with finished tablets, compressed from granulations dried by the fluidization technique, have appeared in pharmaceutical literature.

Accordingly, it would seem appropriate that more studies be conducted, in pharmaceutical fields, concerning drying procedures, especially the fluidization process. The present project will consist of conducting a series of tests on identical granule formulations dried by the conventional air drying and oven drying processes as well as the fluidized bed drying technique. The present work will also include the performance of tests on specific physical properties of tablets compressed from the test granulations.

SURVEY OF THE LITERATURE

Precision of dosage, durability, stability, appearance, and simplicity of administration are all features which recommend the tablet to patient, physician, and manufacturer as a satisfactory dosage form. Although tablets have become the most widely employed mode of administering drugs orally, the predominant techniques for their preparation have not changed significantly over the past years (3).

The most widely used and most general method of tablet preparation is the wet granulation method. The first step in the wet granulation process consists of uniformly mixing the powdered medicinal agents with the diluent and a portion of the disintegrant. The mixture thus obtained is passed one or more times through a suitable screen and subjected to additional blending. This is followed by careful moistening with the proper binding solution until the mixture has the consistency of a crumbly mass. The wet mass is then sized. The wet granules are then air-dried at room temperature or in forced-air drying ovens at about 50°C. After drying, the material is sized once again by screening. The lubricant is then added to ensure uniform feeding into the dies and to prevent the material from adhering to the punches and dies of the tablet machine after compression. The final step is the compression of the

granules to form tablets (4).

History of Compressed Tablets

Tablets may be defined as solid pharmaceutical dosage forms prepared by compressing or molding (5).

Compressed tablets for medicinal purposes are a modern invention. The first tablet appeared in the U.S.P. IX as recently as 1916. Miller (6) reported that machine-made medicinal tablets have been in existence for about a century. On December 8, 1843 Professor William Brockedon of England was granted British Patent Number 9977 entitled, "Shaping Pills, Lozenges and Black Lead by Pressure in Dies." Brockedon was concerned primarily with compressing graphite for use in lead pencils. This, in effect, constituted the invention of the tablet machine and the discovery and development of the compressed tablet. The invention was put to prompt use in England, on the European continent, and in this country. A large variety of compressed tablets of questionable therapeutic value promptly appeared (6).

The first compressed tablet machine in America, a simple hand punch, was constructed by a Philadelphia druggist, Jacob Dunton, in 1864 (7).

The term "compressed tablet" was originated by John Wyeth and his brother. They received the United States Trade Marks Numbers 1001 and 1002 (March 13, 1877) to protect and restrict this term. The use of the term

"compressed tablets" grew very rapidly and was soon declared to be public property since no other suitable descriptive phrase existed (6).

Today, millions of tablets are produced and consumed daily. The U.S.P. XVII now recognizes 119 official tablets, and the N.F. XII recognized 139 official tablets (6).

Granule Formation

The active ingredients of tablets are often available as fine powders. These fine powders must usually be converted to granules with free-flowing qualities in order to assure uniform filling and packing in the tablet machine die cavity.

The addition of liquids during the preparation of a granulation permits the formulation of granules. Some of the most commonly used liquids are: aqueous solutions of gelatin, sucrose, sorbital, and cellulose; hydroalcoholic solutions, and certain alcoholic solutions. With proper control of the drying phase of the operation an optimum residual moisture content, a necessity in high speed tablet compression, is obtained. This residual amount of moisture is approximately 2 per cent. This is necessary to maintain the various granulation ingredients, such as gums, in a hydrated state. It also contributes to the reduction of the static electric charges on the particles. This reduction of the static charge on the

granulation due to the presence of a suitable quantity of moisture often prevents bridging in the hoppers and feed frames during compression, with the added advantage of providing better interparticulate bonding.

Unlike chemical manufacturing where moisture is present as the result of precipitation or washing techniques, tablet granulations contain moisture deliberately added to a dry mixture in order to obtain specific operational advantages. For each type of tablet press and feed frame, optimum quantities of residual moisture are dependent on the physical characteristics of the particular solids and will, therefore, vary from one formula to another (3). The necessary residual moisture in the finished tablet granulation has generally been obtained by drying on trays, using air at room temperature or warmed air as the carrier medium for the moisture which is vaporized.

Fundamental Concepts of Drying Solids

The two most important factors in drying are heat transfer and mass transfer. Heat must be supplied to the material in order to vaporize the liquid, and the resulting vapor must be carried away by some means, such as an air stream or vacuum (1).

Wet solids may contain both bound and unbound moisture. The former exerts an equilibrium vapor pressure that is less than that of pure water, while the latter

exerts the same vapor pressure as pure water. When any of these moist solids are exposed for a long enough period of time to an unlimited supply of air having a small but fixed relative humidity, the moisture content of the solids will approach an equilibrium value. The equilibrium moisture content will, of course, depend upon the temperature, the nature of the solids and upon the relative humidity of the air (8).

The drying heat must be transferred from the drying gas or hot surface to the center of the material, or to the point in the material that is furthest from the source of heat. The rate at which this heat transfer occurs varies inversely with the distance between the heat source and the material. The rate also varies with the area exposed to the heat source, the amount of agitation in the material, and the turbulence in the heating gas (1).

Sloan (1) has stated that "the principal factors governing the speed of drying are:

1) Moisture dispersion--rapid drying requires the maximum possible exposure of moist surface. A cake of material has unfavorable drying characteristics, whereas individual particles suspended in an air stream have favorable characteristics.
2) Temperature differential--rate of drying is

roughly proportional to the difference between the temperature of the heating medium and the temperature of the material being dried.

3) Agitation--rapid movement of material and of the heating medium promotes faster drying.

4) Particle size--drying is accomplished by evaporating moisture from the surface of the particle. In order to remove internal moisture, it is necessary that the moisture reach the surface by diffusion. This transfer will take place most rapidly with small particles. The small particles provide the greatest surface area.

5) Particle structure--since moisture must reach the surface of a particle to be evaporated, materials having capillaries or interstices dry readily. Dense particles, having few voids, that contain occluded moisture are difficult to dry."

Factors Influencing the Selection of a Dryer

Selection of a dryer for a particular operation requires a good deal of judgment that cannot be reduced to mathematical formulas or charts. The number of possible combinations of equipment for a particular drying operation is very large. There are, however, many unique requirements in the pharmaceutical industry which tend to

rule out most of the configurations and principles which are so widely applied in other industries.

Cooper, Schwartz, and Suydam (3) have stated that one of the prime considerations in drying granulations is the relatively small batch size involved. This tends to eliminate most types of continuous equipment. Most continuous equipment is large and relatively difficult to clean. This large size necessitates high capital investment. The difficulty involved in complete cleaning between batches introduces the problem of high labor costs. Therefore, continuous dryers are impractical for use in most cases and are only economically justifiable in the largest volume products.

The requirement for easy cleaning has the attendant consideration of low product retention. The small quantity, high value ratio inherent in pharmaceuticals makes it important to have an absolute minimum amount of material lost in cleaning. This factor would again eliminate most continuous dryers and many batch dryers with internal baffles or pockets which would tend to collect portions of the granulation being dried (3).

Material handling is an important aspect of drying processes. For tray drying procedures, it is generally agreed that the labor involved in loading and unloading the material by hand represents about one-third of the total operating costs (9). Capital investment cost and

additional cleaning problems are associated with the use of conveyors, chutes, adapters, and the like which are often incorporated with either continuous dryers or automated batch dryers.

In addition to the previously mentioned physical characteristics of the dryer itself, Cooper et al. (3) stated that there are many chemical and physical requirements of the granulations and the drugs which they contain. The trend in drugs seems to be toward more potent and reactive chemicals which are frequently susceptible to oxidation and decomposition. Therefore, anything which can be done to decrease the possibility of chemical reactions taking place during drying will make the dryer that much more acceptable. To decrease the possibility of oxidation as well as other types of decomposition, low temperature and the exclusion of oxygen are both important.

The problems of instability can be approached from several directions. One method is the substitution in air dryers of an inert gas such as nitrogen, a change which is prohibitively expensive. An alternate is to use reduced temperature air drying, an operation usually too lengthy to be practical. A logical solution is the use of vacuum drying which solves the problem from both approaches. In the first place, it excludes air from the drying chamber. Secondly, it permits the granulating solvents to be vaporized at a much lower temperature or at a much higher rate

with the same temperature (3).

As stated previously, an optimum residual moisture content is required for each granulation. Also, an optimum particle size range for each granulation is required to facilitate flow to the dies of the compressing machine, for proper disintegration of the tablet, and for the control of the various physical properties of the tablet. Therefore, if the drying process causes too much attrition, there will be too many fines in the finished tablet granulations. In solving any drying problem there are many points to be considered, and the advantages of one system must be weighed against the disadvantages.

Drying Systems and Equipment

1. Tray and Shelf Dryers

Tray drying is the most widely used method of drying tablet granulations. Due to changing economic conditions and the development of more potent and sensitive drugs, these dryers are gradually being replaced in some plants. An economic drawback is that tray dryers require a great amount of manual labor to spread the wet granulation on paper lined trays and then empty the trays into a comminuting machine after the granulation is dry. A second difficulty with tray drying is that the medium is heated or unheated air, even for materials prone to oxidation. The greatest disadvantage seems to be that tray drying is quite slow, often requiring twenty-four hours or more of

drying prior to the attainment of the optimum residual moisture content.

The advantages of this type dryer are low cost, simplicity of construction, ease of mechanical operation, and absence of cleaning required to accommodate product changes. Vacuum shelf dryers have been used to counter some of the disadvantages of conventional shelf dryers, but these dryers are considerably more expensive and still have the disadvantage of high labor cost and poor control of uniformity of moisture remaining in the granulation (3).

2. Flash Dryers

Flash dryers, like several other types of dryers, find wide application in the chemical industry but are not used to any great extent in pharmaceutical fields. The flash, or pneumatic-conveyor dryer in its simplest form is merely an air conveyor into which heated air is introduced.

A pneumatic conveyor system consists of a long tube or duct carrying a gas at high velocity, a fan to propel the gas, a suitable feeder for addition and dispersion of particulate solids in the gas stream, and a cyclone collector or other separation equipment for final recovery of solids from the gas. Dryers of this type operate on the basis of simultaneously mixing, conveying, and drying a wet solid in a high velocity

stream of hot gas. Temperatures up to 1400°F can be used in these dryers. The short contact times involved, 0.1 to 5.0 seconds, permit using gas temperatures above the decomposition temperature of the material. The gas stream acts as both the conveying, heating, and drying medium, and gas velocities in the range of 75 to 700 feet each second can be used. Dryers of this type may be used for free-flowing granular materials which are dispersible in high velocity gas streams (10).

Drying is rapid because the factors governing the speed are optimized. Material is dispersed in the gas stream so as to present a maximum surface to the stream. High inlet-gas temperatures are used. Maximum agitation results from turbulence due to high gas velocities (1). Disadvantages of this system are the great volume of air used, extremely high temperatures, and the amount of product retention within the unit if changeover is required very often (3). A dryer of this general type used in preparing granulations and in coating tablets has been described by Wurster (11). This type of dryer is useful as a tool in the area of granulating and coating technology.

3. Turbo Dryers

The turbo or rotating shelf dryer is essentially a continuous dryer which circulates hot air over a granulation being fed from tray to tray by a cleaning arm and

a spreading arm. The granulation is fed in wet at the top and comes out dry at the bottom.

The advantage of this type of dryer is the moving bed which allows uniform drying to optimum moisture with a minimum of attrition, as compared to many other types of moving bed dryers. However, for small quantities of granulation, batch control would be most difficult as would be cleaning for changeovers. Also, the limitations of high temperatures and contact with oxygen would be present. Therefore, even for a high volume specialty this dryer would add little except speed and automated materials handling to the drying cycle (3).

4. Radiation Dryers

Usually, radiation dryers are of the infrared variety. Drying materials by means of radiant heat is somewhat limited because of: its inability to penetrate into solid materials, relatively high cost, some difficult problems related to temperature control in order to assure even heat distribution and uniform product quality (1). An advantage of this type of dryer would be a shorter drying cycle resulting in less exposure time to the high temperatures involved in drying.

5. Dielectric Dryers

The dielectric dryer is actually a type of radiation dryer although heat is transferred by means of radio frequency emissions. The difference between this type of

dryer and other radiation type dryers is that heat can be transmitted throughout the granules, not to the surface alone. This type of dryer is still somewhat of an oddity with few industrial applications of dielectric drying being reported (3).

6. Ultrasonic Dryers

Although ultrasonics is a relatively expensive form of energy, it may eventually find application in the drying of heat sensitive products or chemicals which have very long drying cycles. The use of ultrasonics is closely analogous to the applications of beams of ultraviolet light or X-rays (12). Ultrasonics may be a tool to be applied to increase the effectiveness of any existing dryer by either reducing required drying temperatures or increasing the speed of end point drying (3).

7. Spray Dryers

Spray drying is usually reserved for products which are in a liquid or slurry form. A spray dryer consists of a large cylindrical, and usually vertical, chamber into which material to be dried is sprayed in the form of small droplets, and into which is fed a large volume of hot gas sufficient to supply the heat necessary to complete evaporation of the liquid. Heat transfer and mass transfer are accomplished by direct contact of the hot gas with the dispersed droplets. After completion of drying, the cooled gas and solids are separated. This may be accomplished

partially in the drying chamber itself by classification and separation of the coarse dried particles. Fine particles are separated from the gas in external cyclones, frequently with secondary bag collectors (13). Spray drying has been considered useful for some specific ingredients. Raff, Robinson, and Svedres (14) have described a process for spray drying of tablet granulations. They manufactured a basic tablet granulation, having a uniform distribution of particle sizes within a very narrow range, by spray drying a slurry comprising a filler, disintegrant, binder, and vehicle.

8. Rotating Dryers

Rotary dryers are applicable to either batch or continuous process, some designs being used for both types of drying. Cooper et al. (3) have stated, "The advantages of a rotating dryer are as follows:

1) a continuously changing surface is presented to both the drying medium and the heating medium.
2) attrition can be adjusted so that desired particle size is maintained. Product build-up or agglomeration can be kept at a minimum by selecting speed of rotation.
3) where the tendency for agglomeration is pronounced, internal baffles or paddles can be put into the dryer chamber to break up lumps.

4) the construction of a rotary dryer lends itself to simplicity in cleaning and maintenance.

5) almost any range of heating temperature can be attained.

6) in continuous drying, time of exposure to drying media can be controlled so that almost any degree of dryness can be achieved.

7) most types of rotary dryers are adaptable to vacuum drying."

Sloan (1) stated, "The disadvantages of rotary dryers include:

1) the dryers are difficult to seal.

2) floor and building space requirements are fairly large.

3) very fine and dusty materials are blown out of the dryer and require expensive equipment for collection.

4) dynamic structural load is high."

Kovats (15) has suggested a method to increase the capacity of rotary dryers by increasing the air-duct system used on these dryers.

Rotary vacuum dryers have found application in the pharmaceutical industry. Schwartz and Suydam (16) have stated, "the use of vacuum-tumbler drying should be contemplated when any of the following circumstances are of importance:

1) limit on maximum product temperature.

2) low final moisture content.

3) control of product contamination.

4) recovery of evaporated solvent.

5) retention of fine solids.

6) enclosure for safety.

7) compact installation."

9. Fluid Bed Dryers

The term "fluidization" defined in its simplest terms is an operation in which a solid powder is made capable of behaving in many respects like a liquid (17). The fluidized solids seek their own level, flow over weirs or in pipes, exhibit hydrostatic pressure, and may have a definite gas-to-liquid interface (1). Fluidization techniques have been used in various process industries for over 20 years (18).

The fluidized bed technique has become popular in processes involving contact between solids and gases, because of the high rates of heat and mass transfer possible. A schematic drawing of a simple fluidized bed is presented in Fig. 1. In a fluidized bed, a stream of gas is blown up through a mass of solid particles at a high rate. The particles become suspended in the fast moving gas stream and are highly agitated. The mass of particles as a whole takes on many of the properties of a fluid. The rapid movement of the particles in the fast

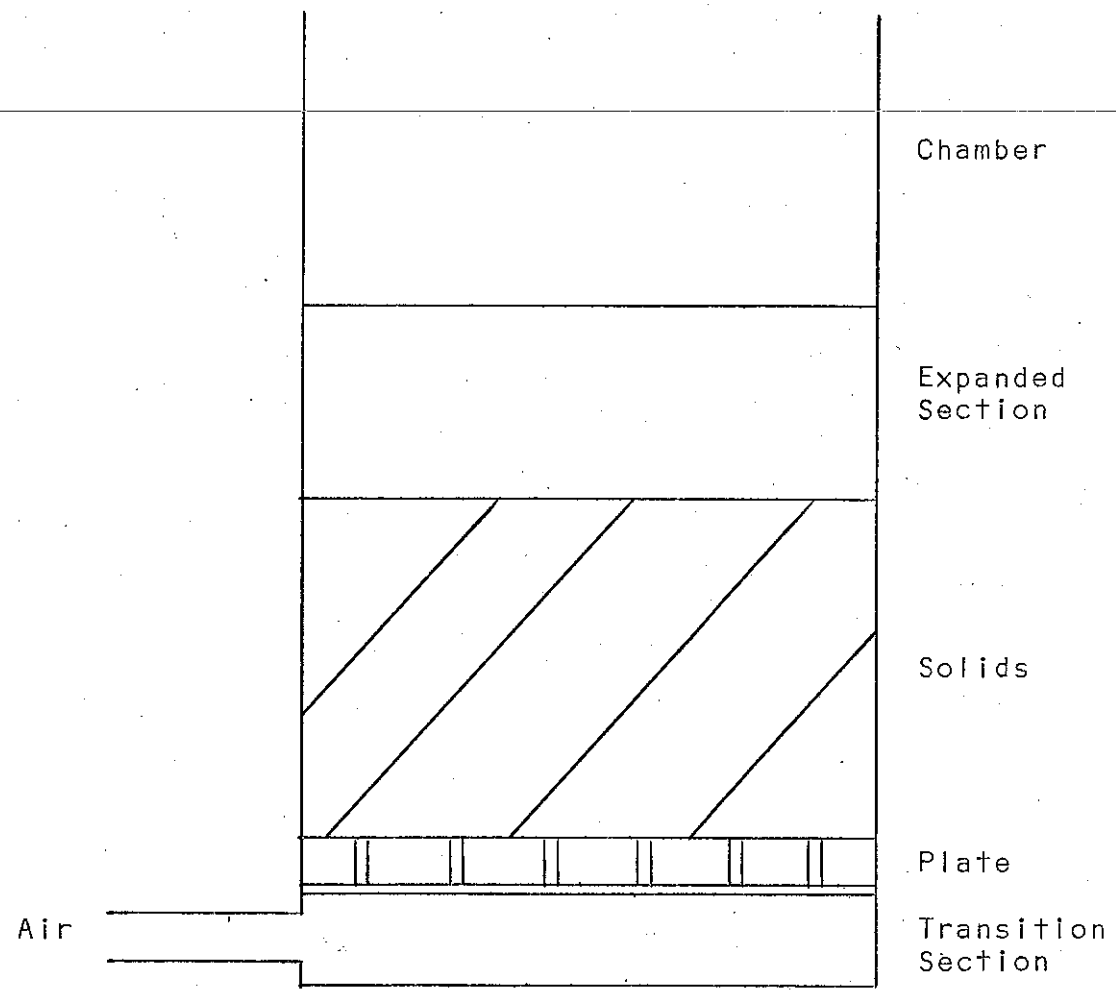

FIGURE 1

SCHEMATIC DRAWING OF A SIMPLE FLUIDIZED BED (18)

moving gas accounts for the high heat and mass transfer rates.

The mixing of particles in gas-fluidized beds is rapid, so that in reactors a relatively uniform temperature exists throughout the fluidized bed (19).

The fluid bed dryer is an air agitation type of dryer in which the granulation is dried by means of passing a heated air stream through the batch from the bottom. Losses are minimized by collecting any particles which might be blown out of the system in collector bags. The rapidity with which drying is achieved (less than one-half hour in most cases) keeps the granulation contact time with heat and air at a minimum (20). The reduced amount of material handling is another advantage of this system over conventional drying methods.

Hardin, in a recent publication (21), has suggested that baffles may improve the performance of a fluid bed dryer under certain circumstances. The baffles create an improved flow pattern within the fluidized bed. This results in an increase in rate capacity, a more reliable operation, and a significant gain in product uniformity. A fluid bed drying system that controls final product moisture to within $\pm$ 0.1 per cent has also been mentioned in the literature (22).

Scott and his associates (18,23) have developed a continuous fluidization system. When the rate of adding

solids to the fluidized bed equals the rate of withdrawal, no net accumulation or loss of solids will occur. Therefore, the weight of solids in the bed remains constant. The magnitude of the pressure at any depth is equal to the weight of a column of particles of unit cross section reading from that point to the top of the particles (24). Since the hydrostatic pressure drop across the bed is determined by the weight of solids it contains (18), pressure drop values can be used as a convenient indicator of bed inventory. In continuous operations, feed rates and/or product withdrawal rates are controlled and adjusted in accordance with the pressure drop across the bed.

As previously mentioned, drying procedures, like many other important unit operations in pharmacy, have received little attention in pharmaceutical literature. Fluidization operations, although relatively unexplored in pharmacy, have been firmly established on a broad scale in other industries. Accordingly, it would seem appropriate that more studies be conducted in pharmaceutical fields concerning drying procedures, especially the fluidization technique. Thus, the objectives of this research project will be:

1) to determine drying rates of common tablet excipients, in granular form, using the air drying, oven drying, and fluidized bed drying

techniques.

2) to determine relative drying capacity per unit floor space of the three methods.

3) to determine the relative ease or difficulty in working with the three methods.

4) to compare and correlate, if possible, results obtained from testing compressed tablets formed from granulations dried by each method.

EXPERIMENTAL

Granulation Ingredients and Preparation

One tablet granulation, containing the usual standard excipients, was used in this study. Results obtained from testing this type of granulation would seem to be more generally applicable than those obtained from testing a specific active ingredient. The granulation contained the diluent lactose, the disintegrant starch, the lubricant magnesium stearate, and the binder syrup. The granulation was prepared as follows:

Lactose U.S.P.	70.5%
Starch U.S.P.	7.9%
Sucrose solution	20.6%
Magnesium stearate U.S.P. . . .	1.0%

The sucrose solution used in the formula was prepared using one part Syrup U.S.P. mixed with two parts water on a weight basis. The granulation was prepared in 600 Gm. batches by mixing the lactose and starch together in a Hobart mixer[a] for thirty minutes. A powerstat[b] was used to control the speed of mixing. The solid materials were not sized prior to mixing because the particles were already sufficiently small and free of lumps. The sucrose solution was added in 10 ml. portions during the mixing which continued for an additional twenty minutes.

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a - Available from Hobart Manufacturing Co., Troy, Ohio.

b - Available from Aloe Scientific Division, A.S. Aloe Co., St. Louis, Mo.

This mixture was then granulated by passing through a number 10 (25) screen using an Erweka granulator[a] and rheostat. The granules were then dried by one of the appropriate drying methods. Following drying, the granules were sized using a number 16 sieve (25) and the Erweka granulator. These sized granules were then blended with 1 per cent magnesium stearate in a Patterson Kelley twin shell blender[b] for fifteen minutes prior to compression.

Drying Equipment

The fluidized bed dryer used in this work was the Glatt dryer[c], laboratory model TR-2. This dryer consists of a fan located in the top of the machine, a drying chamber fitted with a wire mesh support for the granulation, a nylon bag dust collector, an air filter, and electrical heating elements. Controls are provided for adjustment of air flow, using vent flap[d] settings, and inlet air temperature. The instrument operates by forcing, by induced draft, heated air through the drying

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a - Available from Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.

b - Available from Patterson Kelley Co., Inc., East Stroudsburg, Pa.

c - Available from Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.

d - The vent opening controls the amount of air that is blown through the drying chamber. Vent flap settings provide a minimum air setting "0" to a maximum air setting "7".

chamber at velocities which are sufficient to fluidize the granulation charged in the chamber.

The term "fluidize" refers to the suspension and agitation of a bed of particulate solids by a vertically rising stream of air. The air escapes through the bag collectors and is vented through an exit port. The granulation is quickly charged and discharged from the drying chamber by pouring. The Glatt dryer temperature readings were verified using a standard centigrade thermometer placed inside the drying chamber.

The oven dryer used in these experiments was a conventional Lab-line oven[a]. The oven was fitted with four shelves and automatic thermostat controls. Air temperatures were measured with auxiliary thermometers installed on each shelf and in the thermometer holder in the top of the oven.

The air drying process was performed using conventional drying trays placed in the open air at room temperature.

Drying Methods

Equilibrium inlet air conditions were established at the start of each fluidized bed run. This was accomplished by letting the machine run for five minutes prior to placing the drying chamber inside. A period of five

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a - Available from Lab-line Instruments, Inc., Melrose Park, Ill.

minutes was sufficient to establish a uniform temperature and air velocity. All experiments were conducted using a 600 Gm. charge of wet granulation. This was the weight of the granulation after the addition of the liquid and prior to the drying procedure. Four levels of air temperature inside the drying chamber and three levels of air velocity were the experimental variables. A minimum of three tests were conducted for each set of variable conditions, and in all cases a final moisture content of 1 to 2 per cent was desirable.

Oven dryer experiments were performed, using 600 Gm. wet granulations as the charge for each tray. This was equally distributed to give a uniform bed thickness of approximately three quarters of an inch. Three levels of inlet air temperatures were varied in these experiments.

Air dryer experiments were run, using 600 Gm. wet granulations as the charge for each tray. The material was equally distributed to give a uniform bed thickness of approximately three quarters of an inch.

Product Evaluation Techniques

Aliquots of granulation were obtained by combining random spot samples from representative locations within each drying unit. Samples and instrument measurements were taken at five or ten minute intervals in fluidized bed experiments, at hourly intervals in oven dryer studies, and at hourly or other intervals, as indicated in TABLE III,

in air dryer tests. Moisture analyses were performed on each sample, using a Cenco moisture balance[a] for five minutes.

I. Results

A. Fluidized Bed Dryer

Results of the fluidized bed experiments are shown in TABLE I.

TABLE I

THE EFFECT OF VENT OPENING, TEMPERATURE, AND DRYING TIME ON THE MOISTURE CONTENT OF THE GRANULATION USING THE FLUIDIZED DRYING METHOD

Vent Opening[b]	Temperature[c]	Initial Moisture[d,e]	Time 5 min.	10 min.	15 min.	20 min.
3	r.t.[f]	13.4		4.2	2.8	1.3
		13.4		4.8	3.0	1.3
		13.4		4.3	2.8	1.2
5	r.t	13.4		4.2	2.5	1.6
		13.4		3.8	2.5	1.6
		13.4		4.2	2.5	1.6
7	r.t	13.2		3.9	2.3	1.3
		13.3		4.2	2.6	1.3
		13.2		4.2	2.6	1.3
3	40°C	13.4	4.3	1.6		
		13.4	4.6	1.8		
		13.4	4.2	1.4		
5	40°C	13.4	2.2	1.3		
		13.4	2.3	1.3		
		13.4	2.2	1.3		
7	40°C	13.4	2.4	1.3		
		13.4	2.4	1.4		
		13.4	2.2	1.4		

a - Available from Central Scientific Co., Chicago, Ill.

TABLE I (continued)

Vent Opening[b]	Temperature[c]	Initial Moisture[d,e]	Time 5 min.	10 min.	15 min.	20 min.
3	50°C	13.4	2.3	1.3		
		13.4	2.2	1.3		
		13.4	2.4	1.3		
5	50°C	13.4	2.4	1.3		
		13.4	2.4	1.2		
		13.4	2.3	1.2		
7	50°C	13.4	3.4	1.3		
		13.4	3.1	1.2		
		13.4	3.3	1.3		
3	60°C	13.4	1.3	1.2		
		13.4	1.2	1.1		
		13.4	1.2	1.1		
5	60°C	13.4	1.5	1.3		
		13.4	1.4	1.3		
		13.4	1.4	1.2		
7	60°C	13.4	1.6	1.3		
		13.4	1.8	1.3		
		13.4	1.5	1.2		

b - The vent opening controls the amount of air that is blown through the drying chamber. Vent flap settings from the minimum air setting of "0" to the maximum air setting "7" are available.

c - The temperature was determined using a standard thermometer located inside the drying chamber.

d - All moisture readings were made on random samples of the test granulations using a Cenco Moisture Balance.

e - The values represent per cent moisture based upon the initial weight of the sample.

f - "R.t." refers to room temperature which is considered 25°C.

B. Oven Dryer

Results of the oven dryer studies are tabulated in TABLE II.

TABLE II

THE EFFECT OF DRYING TIME AND TEMPERATURE ON THE MOISTURE CONTENT OF THE GRANULATION USING THE OVEN DRYING METHOD

Drying Procedure	Initial Moisture[a,b]	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
40°C[c]							
	13.2	9.8	9.2	7.3	5.6	2.7	2.4
		9.0	8.2	7.4	4.8	2.9	2.5
		10.5	9.0	7.3	3.9	3.7	2.5
		8.8	5.5	3.7	2.5		
50°C							
	13.3	8.6	5.0	3.6	1.9		
		9.4	4.4	3.6	2.2		
		10.3	6.0	3.6	2.4		
		8.6	3.4	2.0			
60°C							
	13.3	8.2	4.4	2.0			
		9.8	7.0	2.0			
		9.9	6.3	2.3			
		8.5	1.7				

a - All moisture readings were made on random samples of the test granulations using a Cenco Moisture Balance.

b - The values represent per cent moisture based upon the initial weight of the sample.

c - The temperature was determined using standard thermometers located on each tray in the drying oven.

C. Air Dryer

Results of the air dryer experiments are presented

in TABLE III.

TABLE III

THE EFFECT OF DRYING TIME ON THE MOISTURE CONTENT OF THE GRANULATION USING THE AIR DRYING METHOD

Initial Moisture[a,b]	1 hr.	2 hr.	3 hr.	5 hr.	10 hr.	24 hr.
13.2	13.0	11.9	9.0	8.4	6.8	2.3
13.3	13.0	12.1	9.3	8.7	7.0	2.3
13.3	13.2	12.5	11.3	10.7	7.6	2.3

a - All moisture readings were made on random samples of the test granulations using a Cenco Moisture Balance.

b - The values represent per cent moisture based upon the initial weight of the sample.

Drying Capacities Per Unit Floor Space

The floor space occupied by each dryer was measured, and this information was related to the rate of drying of the tested granulations. From this information, the drying capacities per unit floor space of the three methods can be seen.

1. Results

The results of the drying capacity per unit floor space studies can be seen in TABLE IV.

TABLE IV

COMPARISON OF DRYING CAPACITY
PER UNIT FLOOR SPACE

	Square Feet Occupied	Drying Rate[a]	Rate Comparison[b]
Fluidized Bed Dryer	6	5/hr.	1
Oven Dryer	9	4/4hr.	7.5
Air Dryer	9	4/24hr.	45

a - This is the number of procedures possible per time indicated for the drying methods.

b - This is the number of fluidization operations which could be conducted on an equal amount of material in the same time and with comparable floor space.

Evaluation of the Physical Properties of Compressed Tablets

The tablets were compressed on a Korsch single punch tablet machine[a] using an Erweka motor[b] and powerstat to control the speed. The tablet machine produced fifty tablets per minute using a 3/8 inch concave punch. The first twenty and the last twenty tablets produced were discarded to prevent weight variation due to initial flow resistance and insufficient weight of granules in the hopper. The production rate remained constant to

a - Available from Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.

b - Available from Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.

eliminate another source of tablet variation, changing compression speed.

In the evaluation of the physical properties of compressed tablets, many test procedures have been developed and conducted (26,27).

1. Granulation Particle Size

Since the fluidized bed dryer was a turbulent system, it was thought that more fines[a] might be present in the granulations dried by this method than in the granulations dried by the other procedures. Particle size (27) has been shown to have an effect on certain physical properties of tablets.

The particle size of the granulations was determined using United States Standard Testing Sieves[b] that met all official U.S.P. XVII requirements (25). One hundred gram batches randomly selected from each dried granulation were run through the sieves with the aid of a Cenco-Meinzer sieve shaker.[c] The shaker was operated for five minutes at a number 3[d] powerstat setting. The amount of granulation remaining on each of the six sieves

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a - "Fines" in this study are particles of 100 mesh or smaller.

b - Available from W. S. Tyler Co., Cleveland, Ohio.

c - Available from Central Scientific Co., a division of Cenco Instruments Corp., Chicago, Ill.

d - Ten powerstat positions are available on the instrument.

and the collecting pan was then weighed. The sieves were brushed clean to ensure complete removal of any adhering particles. The results were expressed as per cent of granulation retained on the sieves.

A. Results

The results of the granulation particle size study are indicated in TABLE V.

TABLE V

THE EFFECT OF THE DRYING PROCEDURE ON THE GRANULATION PARTICLE SIZE

Drying Procedure	Sieve Size[a] 20[b]	40	60	80	100	120	pan
Air	37.14	37.13	9.31	3.70	2.12	2.05	8.55
	27.61	37.06	10.62	4.80	2.98	3.01	13.92
	44.00	31.18	9.09	4.00	2.02	1.91	7.79
Oven 40°C	47.79	31.98	7.88	3.22	1.74	1.64	5.75
	27.92	36.59	11.80	5.89	3.40	3.12	11.29
	25.04	41.03	13.22	6.11	3.43	2.90	8.26
	18.86	42.21	13.87	6.57	4.20	3.52	10.76
Oven 50°C	39.20	39.93	9.48	3.15	1.51	1.40	5.32
	37.50	36.63	10.52	4.14	2.01	1.78	7.43
	34.32	36.89	11.15	4.63	2.35	2.07	8.59
	41.27	38.59	9.35	3.17	1.47	1.30	4.86
Oven 60°C	41.73	32.72	9.31	3.93	2.05	1.92	8.34
	33.69	37.50	11.30	4.75	2.31	2.01	8.44
	35.54	38.79	11.16	4.13	2.01	1.78	6.59
	41.34	38.86	9.06	3.10	1.46	1.24	4.93
Fluidize Bed-rt[c] Vent 3[d]	38.28	37.71	10.99	3.41	1.69	1.68	6.24
	32.87	38.65	12.39	5.02	2.94	2.65	5.47
	16.52	44.80	15.89	6.79	3.80	3.39	8.80

TABLE V (continued)

Drying Procedure	Sieve Size[a] 20[b]	40	60	80	100	120	pan
Vent 5[d]							
	21.75	44.50	14.26	4.47	2.14	2.29	10.59
	14.43	45.84	16.80	5.08	2.57	2.77	12.51
	14.10	41.97	15.98	5.65	3.06	3.32	15.92
Vent 7							
	33.97	42.82	13.52	3.94	1.46	1.18	3.11
	25.80	37.85	13.40	5.98	3.61	3.27	10.09
	16.77	41.84	16.54	6.64	3.84	3.54	10.84
Fluidize Bed-40°C							
Vent 3	35.12	36.94	10.28	4.15	2.13	2.02	9.36
	22.41	39.98	14.07	5.78	3.06	2.77	11.93
	31.32	42.35	11.87	4.07	1.92	1.68	6.80
Vent 5							
	24.07	44.80	14.34	4.37	2.05	1.93	8.45
	27.52	44.01	12.27	4.35	1.96	1.78	8.11
	27.42	44.12	12.44	4.38	2.05	1.89	7.70
Vent 7							
	29.91	43.23	11.75	3.77	1.86	1.75	7.74
	29.68	44.08	11.59	3.76	1.79	1.68	7.43
	29.83	44.69	11.57	3.72	1.74	1.58	6.86
Fluidize Bed-50°C							
Vent 3	26.28	47.73	13.75	3.86	1.61	1.49	5.28
	27.84	41.89	14.62	4.49	2.06	1.97	7.12
	38.32	34.41	11.18	4.13	1.99	1.90	8.06
Vent 5							
	37.56	41.97	11.00	3.16	1.20	1.06	4.05
	29.80	39.04	12.78	4.80	2.52	2.40	8.67
	19.62	42.41	15.71	6.03	2.94	2.69	10.60
Vent 7							
	36.12	36.69	11.05	4.20	2.08	1.94	7.92
	32.06	38.31	12.51	4.65	2.23	2.01	8.23
	38.19	34.32	11.81	4.41	2.07	1.91	7.29
Fluidize Bed-60°C							
Vent 3	21.52	47.33	13.89	4.67	2.28	2.08	8.23
	31.24	46.20	10.87	2.98	1.39	1.37	5.94
	21.60	43.51	15.69	5.40	2.64	2.45	8.71

TABLE V (continued)

Drying Procedure	Sieve Size[a] 20[b]	40	60	80	100	120	pan
Vent 5[d]							
	16.40	47.87	15.91	5.48	2.62	2.39	9.34
	22.41	44.63	13.84	4.92	2.49	2.35	9.35
	25.16	48.22	12.69	3.95	1.79	1.58	6.62
Vent 7							
	27.57	41.32	12.99	4.88	2.47	2.22	8.56
	29.23	40.49	12.94	4.70	2.33	2.12	8.19
	26.89	45.22	12.91	4.03	1.95	1.80	7.20

a - The sieve size refers to standard sieves conforming to dimensions listed in the U.S.P. XVII.

b - The values refer to granulation material remaining on the sieves expressed as a percentage of original weight of granulation material being tested.

c - "R.t." refers to room temperature which is considered 25°C.

d - The vent opening controls the amount of air that is blown through the drying chamber. Vent flap settings provide a minimum air setting "0" to a maximum air setting "7".

2. Tablet Weight

Tablet weights were checked routinely during the operation of the tablet machine. Tablet weights may vary due to flow resistance of the granules, changing weight of granules in the hopper, and excess fines (27). Tablet weight is an official U.S.P. XVII test (28). The tablets tested were weighed on a Sartorius balance[a]. Twenty whole

a - Available from Aloe Scientific Division, A. S. Aloe Co., St. Louis, Mo.

tablets were weighed individually, and the average weight was calculated. The U.S.P. XVII states that "the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed (TABLE VI) and no tablet differs by more than double that percentage."

TABLE VI

WEIGHT VARIATION TOLERANCES FOR UNCOATED TABLETS

Average Weight of Tablet, mg.	Percentage Difference
130 or less	10
From 130 through 324	7.5
More than 324	5

A. Results

The results of the tablet weight tests are summarized in TABLE VII.

3. Friability

Another test that is applied to compressed tablets is the friability test. The friabilator is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping (29).

Twenty weighed tablets were placed in the Erweka friabilator[a]. They were exposed to rolling and repeated shocks resulting from free-falls within the apparatus.

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a - Available from Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.

After being tested in the apparatus for several five minute intervals, the tablets were removed and weighed again. The loss in weight indicates the ability of the tablets to withstand abrasion in packaging, handling, and shipping.

A. Results

The results of the friability studies are tabulated in TABLE VII.

4. Tablet Disintegration Time

The tablet disintegration test provides a means of control in assuring that a given tablet formula has the same disintegration time (within limits) from one production batch to another.

The tablet disintegration test was conducted in accordance with U.S.P. XVII standards using a suitable apparatus[a] (30). Since there was no specific disintegration time for the tested tablets, one-half hour was considered the maximum time for satisfactory disintegration.

The apparatus consisted of a basket rack holding six plastic tubes, open at the top and bottom; the bottom of the tubes was covered with 10 mesh screen. The basket rack was immersed in a water bath held at

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a - Erweka disintegration apparatus, available from Chemical and Pharmaceutical Industry Co., Inc., New York, N. Y.

37°C. The rack moved up and down in the fluid at 30 cycles per minute with the basket moving between 5 and 6 cm. The volume of the fluid was such that on the upward stroke, the wire mesh remained at least 2.5 cm. below the surface of the fluid and descended to not less than 2.5 cm. from the bottom on the downward stroke. One tablet was placed in each of the six cylinders along with a plastic disk over the tablet. The plastic disks had a density which enabled them to float above the tablets. The plastic disks helped to force any soft mass which formed through the screen. The end-point of the test was indicated when the tablets passed through the screen.

A. Results

Results of the tablet disintegration tests can be seen in TABLE VII.

5. Tablet Hardness

The resistance of the tablet to chipping, abrasion, or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. The degree of hardness varies with different manufacturers and with different tablets, but tablets must be sufficiently hard to maintain their shape during the expected life of the tablet. Exceptionally soft tablets may powder or crumble, while excessively hard tablets may chip or fracture. If a tablet is too hard, it may not

disintegrate in the required period of time. An excessively hard tablet could pass through the gastro-intestinal tract without disintegrating, and it would, therefore, be of no therapeutic value to the patient. For control purposes a number of attempts have been made to quantitate the degree of hardness.

In the present work, both the Stokes hardness tester[a] and the Strong Cobb Arner hardness tester[b] model B were used. The Stokes tester is a manually operated screw-type tester that indicates the final breaking point in Kg. As the plunger is tightened, the force on the tablet in the anvil is increased. In the Strong Cobb Arner instrument, the force is produced by a manually operated air pump. As the pressure is increased, a plunger is forced against the tablet placed on the anvil. The final breaking point is indicated on a dial calibrated into 30 arbitrary units. The hardness values of the Stokes and Strong Cobb Arner instruments are not equivalent. The literature (29) states that the values obtained with the Strong Cobb Arner tester are usually about 1.6 times those of the Stokes tester.

A. Results

The results of the tablet hardness tests are tabulated in TABLE VII.

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a - Available from F. J. Stokes Machine Co., Philadelphia, Pa.

b - Available from Strong Cobb Arner, Inc., Cleveland, Ohio.

TABLE VII

PHYSICAL PROPERTIES OF TABLETS COMPRESSED FROM GRANULATIONS DRIED BY THE SPECIFIED DRYING METHODS

Drying Procedure	Tablet[a] Weight (mg.)	Per Cent[b] Weight Variation	Friability (%)[c]	Disintegration[d] Time (minutes)	Hardness[e] Strong Cobb	Hardness[e] Stokes (Kg.)
Air	325.7	4.76	0.816	5.8	5.15	4.75
	315.7	3.01	0.938	5.2	3.95	2.70
	342.7	2.60	1.53	10.2	5.70	5.60
Oven at 40°C	339.6	7.16	0.964	9.8	6.10	5.95
	350.0	5.11	0.989	11.2	5.50	4.35
	351.0	4.84	1.04	4.7	5.20	4.40
	344.2	4.74	1.37	4.2	4.80	3.10
Oven at 50°C	316.6	4.61	0.293	12.5	17.00	15.50
	327.5	3.63	0.336	14.5	15.40	14.75
	328.7	6.78	0.338	15.0	17.00	16.00
	327.9	5.82	0.334	15.0	15.55	12.90
Oven at 60°C	334.0	2.43	0.374	15.3	13.95	12.85
	323.1	3.84	0.368	15.0	14.05	10.50
	294.6	5.60	0.372	14.5	11.45	9.20
	327.9	2.99	0.352	13.2	14.75	13.20

TABLE VII (continued)

Drying Procedure	Tablet[a] Weight (mg.)	Per Cent[b] Weight Variation	Friability (%)[c]	Disintegration[d] Time (minutes)	Hardness[e] Strong Cobb	Hardness[e] Stokes (Kg.)
Fluidized Bed at r.t.[f]						
Vent flap 3[g]	334.0	4.90	1.51	7.3	6.15	5.25
	349.1	1.72	1.71	8.7	5.80	5.30
	345.2	1.45	1.84	8.2	5.95	5.50
Vent flap 5	357.8	4.75	1.53	5.3	5.90	5.25
	355.7	4.36	1.69	9.2	5.85	5.25
	355.7	3.82	1.71	8.0	6.00	5.35
Vent flap 7	312.6	4.61	0.937	4.7	6.90	6.05
	350.7	3.39	1.36	6.7	5.90	5.50
	332.8	4.72	1.46	4.8	6.05	5.20
Fluidized Bed at 40°C						
Vent flap 3	294.9	6.71	0.447	13.0	9.30	9.15
	300.0	4.77	2.78	8.3	8.80	4.95
	303.8	2.30	2.07	7.0	8.45	4.95

TABLE VII (continued)

Drying Procedure	Tablet[a] Weight (mg.)	Per Cent[b] Weight Variation	Friability (%)[c]	Disintegration[d] Time (minutes)	Hardness[e] Strong Cobb	Hardness[e] Stokes (Kg.)
Vent flap 5[g]	293.1	3.55	0.418	10.8	13.25	12.00
	301.8	4.37	0.498	13.2	10.95	9.60
	278.8	4.77	0.397	11.0	12.55	10.40
Vent flap 7	292.0	4.49	2.11	7.8	5.75	4.60
	294.9	3.26	0.519	14.0	10.05	8.35
	295.2	3.25	0.443	12.8	12.55	9.35
Fluidized Bed at 50°C						
Vent flap 3	288.5	3.88	0.415	13.0	8.10	6.05
	276.6	5.35	0.650	10.2	8.05	5.50
	282.4	4.46	0.430	9.5	9.90	9.45
Vent flap 5	286.1	3.04	0.402	12.2	10.45	10.40
	292.2	2.46	0.480	15.7	8.15	6.95
	286.1	3.43	0.451	12.3	7.80	7.65
Vent flap 7	320.3	2.72	2.49	10.3	8.40	5.00
	292.5	2.84	0.526	12.3	9.70	8.00
	287.7	3.23	0.418	12.8	10.90	10.50

TABLE VII (continued)

Drying Procedure	Tablet[a] Weight (mg.)	Per Cent[b] Weight Variation	Friability (%)[c]	Disintegration[d] Time (minutes)	Hardness[e] Strong Cobb	Hardness[e] Stokes (Kg.)
Fluidized Bed at 60°C						
Vent flap 3[g]	302.7	6.11	0.414	13.0	9.40	6.65
	305.8	5.30	0.379	9.3	8.90	6.80
	291.0	2.54	0.516	10.2	7.95	6.10
Vent flap 5	309.2	3.10	0.405	12.3	9.20	7.65
	311.0	2.57	0.383	11.5	10.15	7.35
	312.4	5.83	0.443	11.3	9.05	6.55
Vent flap 7	296.7	3.37	0.401	9.0	11.30	10.10
	296.7	3.24	0.516	11.0	8.95	8.75
	294.3	3.50	0.696	10.0	7.50	5.65

a - This value is the average of twenty individual tablet weights.

b - This value represents the largest percentage variation of a tested tablet from the average weight of the tablets tested.

TABLE VII (continued)

c - This value represents per cent weight loss based upon the initial weight of twenty tablets.

d - This value represents the average disintegration time of six tablets.

e - These values represent the average hardness of ten tablets.

f - "R.t." refers to room temperature which is usually considered 25°C.

g - The vent opening controls the amount of air that is blown through the drying chamber. Vent flap settings provide a minimum air setting "0" to a maximum air setting "7".

DISCUSSION

The results obtained from the experiments conducted on the three drying procedures were very informative and indicated some useful possibilities.

The drying rates were increased substantially with the use of the fluidized bed system. Fluidized beds are turbulent systems which give rise to good mixing effects, and, as a consequence, uniform product temperatures are readily achieved and easily controlled. In tray drying procedures, however, non-uniform tray and product temperatures appear to be the rule rather than the exception. For example, in the present study, it was observed that oven temperatures varied as much as $\pm$ 10°C. from location to location within the dryer. The close control of product temperature in the fluidized bed drying suggests that the operation may be particularly suited for processing heat-sensitive materials.

Tablets compressed from granulations dried in the fluidized bed compared favorably in all respects to those made from air dried or oven dried granulations. In this study, tablets dried in the oven showed the largest weight variation, and tablets compressed from granulations dried at the two upper oven temperatures were also quite hard. Friability results showed that there was no appreciable difference in tablets dried by

any of the methods. All tablets disintegrated within the required one-half hour; however, the tablets from the granulations dried at the two upper oven temperatures had the longest average disintegration time.

Increased drying capacities per unit floor space were observed with the fluidized bed dryer. This would appear to free more space for other operations in a manufacturing plant, and as a result of less total area requirements there is the possibility of cost reduction.

For tray drying procedures, it is generally agreed that the labor involved in loading and unloading represents about one-third of the total operating costs (9). About one-half man-hour was required for these steps in the present experiments. In comparison, charging and emptying the fluidized bed dryer was completed in less than two minutes. On this basis, therefore, fluidized bed drying offers significant opportunities for reductions in labor costs.

Caking of the granulation was observed at the start of a few of the fluidization operations. This was easily corrected, however, by rapidly increasing and decreasing the air velocity two or three times. In all of the air drying procedures, the problem of "crusting" was observed. A hard crust formed on the surface of the granules spread on the drying trays resulting in an increase in drying time.

The results of the particle size determinations showed that there was no significant difference in "fine" production (100 mesh and smaller) in any of the drying methods. The granules dried by the fluidization technique, however, did show an increase in percentage of 40 mesh particles and a decrease of 20 mesh particles. This particle size difference did not present any problems in the present study. In fact, the smaller particles probably resulted in a more uniform die fill.

The results obtained from this study should be valid for other excipients and tablet formulations. The drying principles used are not limited to a specific formulation. Therefore, this study seems to indicate that the fluidized bed dryer would be a very useful and economical apparatus for use in pharmaceutical manufacturing.

SUMMARY

1. The literature surveying the history of compressed tablets, methods of granule formation, fundamental concepts of drying solids, and drying systems and equipment has been presented.

2. Experiments to determine drying rates using the air drying, oven drying, and fluidized bed drying techniques have been conducted.

3. Studies to determine comparative drying rates per unit floor space of the three methods have been performed.

4. The relative ease or difficulty in working with the three drying methods has been discussed.

5. Tests conducted on selected physical properties of tablets compressed from the test granulations have been presented to show differences, if any, caused by various drying methods.

CONCLUSIONS

A comparative study has been conducted to determine possible methods of improving the technique of drying tablet granulations.

The results of this study seem to indicate that the fluidized bed dryer offers significant advantages over the oven and air drying methods commonly used in the pharmaceutical industry. The advantages do not appear to be limited to the particular drying unit or specific granulation formula tested but rather arise from the inherent qualities and characteristics of the fluidization process itself. Tests on selected physical properties of tablets compressed from granulations dried by the various methods indicated that all of the tablets were equally acceptable. Due to the increased drying rates, increased capacity per unit floor space, and decreased handling costs the fluidization system seems to offer many economic advantages to the pharmaceutical manufacturer. Small capacity fluidized dryers would also be useful in pilot plant operations. The apparent ability to closely control product temperature during drying also suggests that this method could be used to facilitate the handling of heat sensitive materials.

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