THE UNIVERSITY OF MICHIGAN

INDUSTRY PROGRAM OF THE COLLEGE OF ENGINEERING

GRANULATION BY EXTRUSION

Prabhakar R. Sheth

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in The
University of Michigan
1960

February, 1960

IP-418

Doctoral Committee:

Professor Albert M. Mattocks, Chairman
Assistant Professor John Autian
Professor Frederick F. Blicke
Professor Lloyd L. Kempe
Associate Professor Lee F. Worrell

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Professor Albert M. Mattocks, for his suggestion of the problem, aid and criticisms during the course of the investigation and his assistance in preparation of this manuscript.

To the Eli Lilly Endowment Fund, for a four-year research fellowship, which permitted the author to complete his studies and pursue this research.

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INTRODUCTION

With the greatly increased demand for tablets of medicinal substances in recent years has come a need for improvements in the tablet making process which would give higher production rates and more uniform products. High speed mixing equipment and tablet presses have been marketed which would enable the pharmaceutical industry to increase rates of manufacture significantly, but the drying of granules has remained as a stumbling block to advances in production methods. No generally satisfactory method has yet been advanced which overcomes the retardation due to time involved in removing water from granulations.

Not only is the present method of granulation a slow process, but, also, it is costly. It involves the transfer of wet mixes to granulators, then to trays for oven drying, back to granulators for sizing and finally to dry mixers for blending with other excipients. Most of this transfer is accomplished by hand labor, and it involves much floor space and numerous pieces of equipment.

As practiced today the granulation process is little understood and poorly controlled. The variables of the procedure are generally left to the decision of the operator who judges the amount of binder, time of mixing and time of drying by his sense of touch. Thus, the granules obtained are variable from batch to batch, and preparation of tablets from them requires corresponding adjustments in the tablet presses and in quantities and types of excipients.

Thus, it appears that the key to advances in tablet making is granulation. The development of faster, more efficient and better controlled methods for granulating would make it possible to utilize the newer machines for mixing and compressing at full efficiency, and to produce tablets of greater uniformity.

LITERATURE REVIEW

Granulation has been defined as the "act or process of forming or crystallizing into grains."(1) Since crystallization is used only in the preparation of granules of pure chemicals, granulation may be defined in a more practical manner as the agglomeration of fine powders into particles of relatively large size. Many aggregates exist, however, which are not considered to be granules, such as those contained in most bulk powders. For example, samples of powdered sugar contain lumps of rather large size which do not exhibit satisfactory flow properties or compression characteristics to be characterized as granules. Thus, the terms granulation, granule and granular are poorly defined and have meaning only in light of the practical use to be made of the material.

Granulation is an important step in tablet making. Although a few materials of medicinal use, such as sodium and potassium chlorides and bromides,(2) lend themselves to direct compression, most substances have to be granulated first. Cooper and Gunn(3) have summarized the advantages of granules over powders for tablet compression as follows:

	Powder	Granules
a.	Fine powder does not flow evenly through the hopper of the machine. The irregular supply of fine powder to the die produces tablets of varying weight.	Granules flow evenly and a given volume of granules is more constant than that of a powder.
b.	In a powder containing several ingredients the vibration of the machine promotes separation; the denser ingredients would tend to gravitate to the bottom of the powder and the tablets would not be uniform in composition.	The granules are uniform in composition and the ingredients are "bound together" and cannot separate. Gravitation of the smaller granules is, therefore, unimportant.

c.	Air is imprisoned during compression and causes "capping", i.e. splitting off of the upper surface of the tablet either as it leaves the die or subsequently. Also the tablets tend to crumble during transport and handling.	Upon compression the granules knit together to form sound tablets.
d.	Fine powder tends to blow out of the die at the top and to seep downwards around the stem of the lower punch, causing sticking.	The granules, being heavier, do not blow out of the die and do not clog the lower punch.

Other authors have emphasized the better flow properties of granules as the chief advantage over powders.(4-6)

Better insight into the function of granules in tablet making can be gained through a step-wide summary of the compression process. First, the granules are placed in a funnel-shaped hopper approximately 24 in. high with an opening of 1-2 in. diameter. The granules are subject to continuous vibration of the tablet press and must not separate or classify in the hopper. Further, they must remain free-flowing so as to pass through the opening at a uniform rate under the influence of gravity. From the hopper the granules flow into a feed frame which distributes them over an area of about 15-20 in.^{2} in a bed about 0.5 in. thick. The granules drop by gravity into the holes of the dies which pass beneath the feed frame at rates up to about 3000 dies/min.; thus, the granules must flow quite freely to fill the die and must be sufficiently small to give uniform weight. The granule bed within the die is then compressed into a tablet by means of the punches which pass between pressure rolls. The compression stage is a critical one, requiring that the granules not exert excessive friction against the die walls in order for a firm compact to be formed. The tablet is finally ejected from the die, at which point, again, die-wall friction is important. Lubricants, mixed with the granules, are generally required to maintain low levels of die-wall friction.

Two methods of granulation are in common use by the pharmaceutical industry today. The more widely used of these is termed wet granulation, which consists of the following steps:(4-6)

a. Mixing the powdered ingredients, consisting generally of one or more therapeutic agents and a filler such as lactose, sucrose or starch.

b. Incorporation of a liquid binder solution such as starch paste, acacia solution or gelatin solution.

c. Formation of wet granules by forcing the moist material through a coarse screen, usually 4-8 mesh.

d. Drying of the wet granules on trays in a forced-convection oven.

e. Size reduction of the dried granules by forcing them through a screen of suitable size.

The second method of granulation in common use is called dry granulation or slugging. It consists of the following series of operations:

a. Mixing the powdered ingredients. In this case a lubricant is generally incorporated along with a disintegrating agent in the initial powder mix.

b. Precompression or slugging. The powder mix is fed to a large press capable of exerting higher pressure than the usual tablet press, and large dies are used, generally about 1 in. in diameter.

c. Size reduction of the slugs. The large tablets or slugs, which are usually irregular in weight and may be fragile, are forced through a screen of suitable size.

Most pharmaceutical materials can be granulated satisfactorily by the wet process, although selection of a suitable binder and lubricant may require a large amount of developmental work in some instances. Dry granulation is used primarily when the drug to be tabletted is sensitive to moisture. Both methods are tedious and time-consuming and are so poorly understood and controlled that an occasional batch will be unsatisfactory for tabletting and must be re-worked, even for products which have been made for years.

Newer Methods of Granulation

Numerous methods and machines have been investigated for preparation of granules for tablets, but most of the work has been conducted with a specific product in mind, using a selected set of conditions, so that it is difficult to obtain a meaningful comparison of two or more methods. It is also unfortunate that most of the information is available only through manufacturers' technical brochures. The few methods which have attracted widespread interest and which appear to have broad application are presented in this review.

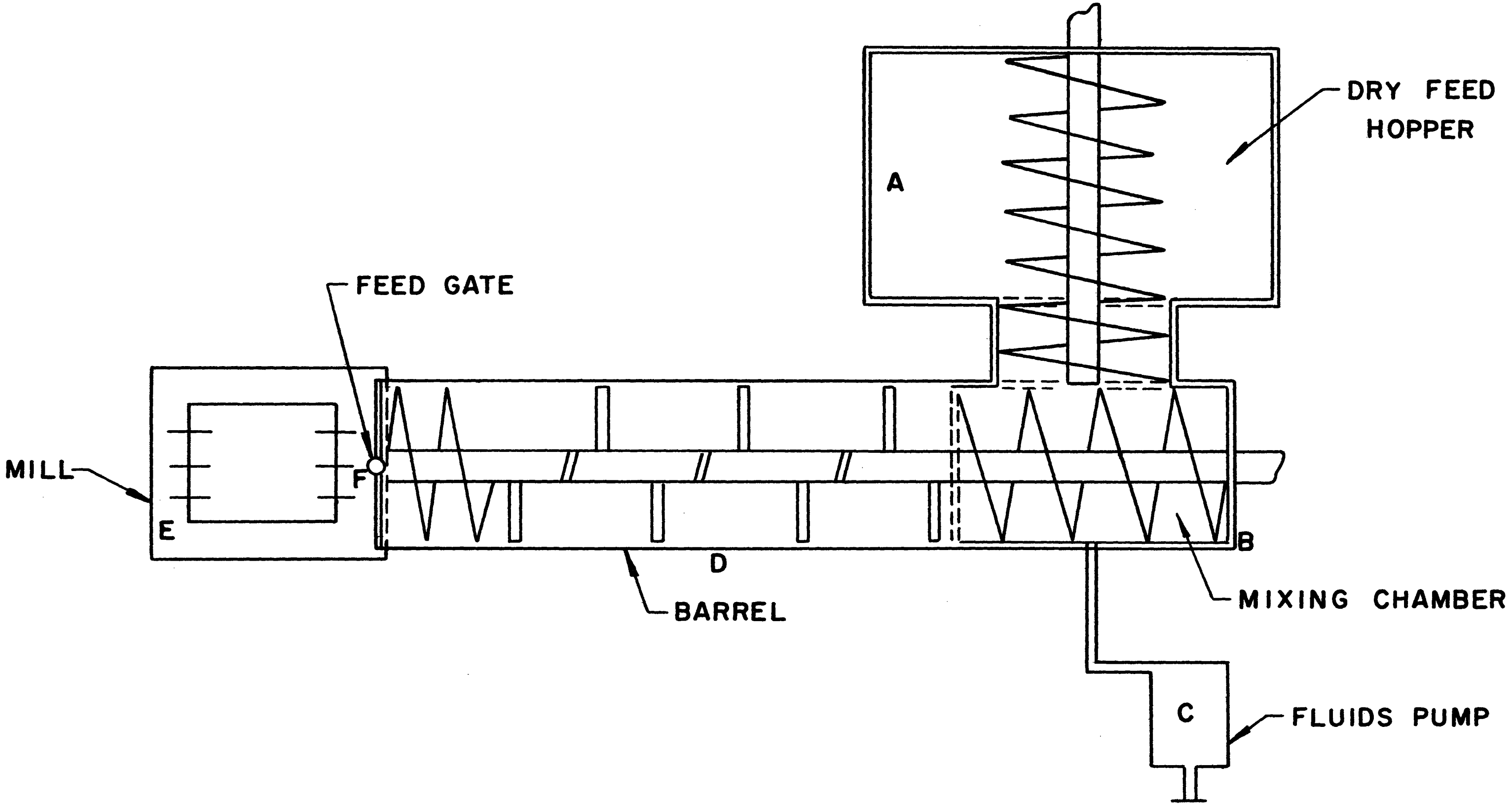
The Malaxator

A new machine, called a Malaxator,(7) has been marketed which allows continuous formation of wet granules at high rates of production. It consists of five basic parts, as shown in Figure 1, a dry feed hopper, A, a mixing chamber, B, a fluids pump, C, a barrel for additional mixing and some compression, D, and a mill for breaking the material into granules, E. The operation consists of feeding the powder mix to the dry feed hopper with a suitable auxillary unit, adding the binder solution to the mixing chamber at a uniform preselected rate and removing the granules from the mill as they are formed. Mixing of the binder and powder takes place in the barrel, especially that portion with the broken thread, as well as in the primary mixing chamber. A feed gate, F, is adjustable so that the material in the barrel can be subjected to a small amount of back pressure, causing some compression.

No publications have yet appeared on the use of the Malaxator, but it is being used commercially in several installations. Zappapas(8) reported on numerous comparisons of this method with the standard procedure for wet granulation using the same formulas. He expressed the opinion that the granulations obtained were equal or superior to those from the standard method.

The Chilsonator

The Chilsonator(9) manufactured by Fitzpatrick Company, Chicago, is a unit designed to compress powders directly into granules. It was first used several years ago for a specific product but has not attracted



THE MALAXATOR

Figure 1. The Malaxator.

much attention, probably due to the fact that not many pharmaceutical formulas could be granulated readily with this machine. In recent years the Chilsonator has been redesigned in an effort to broaden its usefulness, and changes are still being made. A sketch of this instrument is shown in Figure 2.

The powder mix is fed from the feed hopper, A, onto grooved pressure rolls, B, which are water-cooled. Pressure on the rolls is regulated by a hydraulic system and with the speed control of the powder feeder. The powder is compressed into the grooves of the rolls, and interlocking of the ridges of the rolls tends to free the compressed material while breaking it into pieces of variable size. The compressed solid is then reduced in size by the usual methods.

No publications have appeared describing the Chilsonator or the granules produced by it; so that it is not possible to assess its usefulness. It is being investigated at the present time, however, being of interest particularly because of the possibility of eliminating drying in the granulation process.

The Double Cone Blender

A system has been described recently by Cooper(10) which utilizes a double cone blender for granulation in a unique manner. The powder mix combined with a dry binding agent, such as tragacanth or acacia powder, is placed in the blender and steam is pumped into the system during the tumbling, and moisture is then removed by means of vacuum and heat, thus furnishing dried coarse granules in one operation. The equipment for this purpose is elaborate and costly, but it offers an opportunity to eliminate several transfers of material in the granulation process.

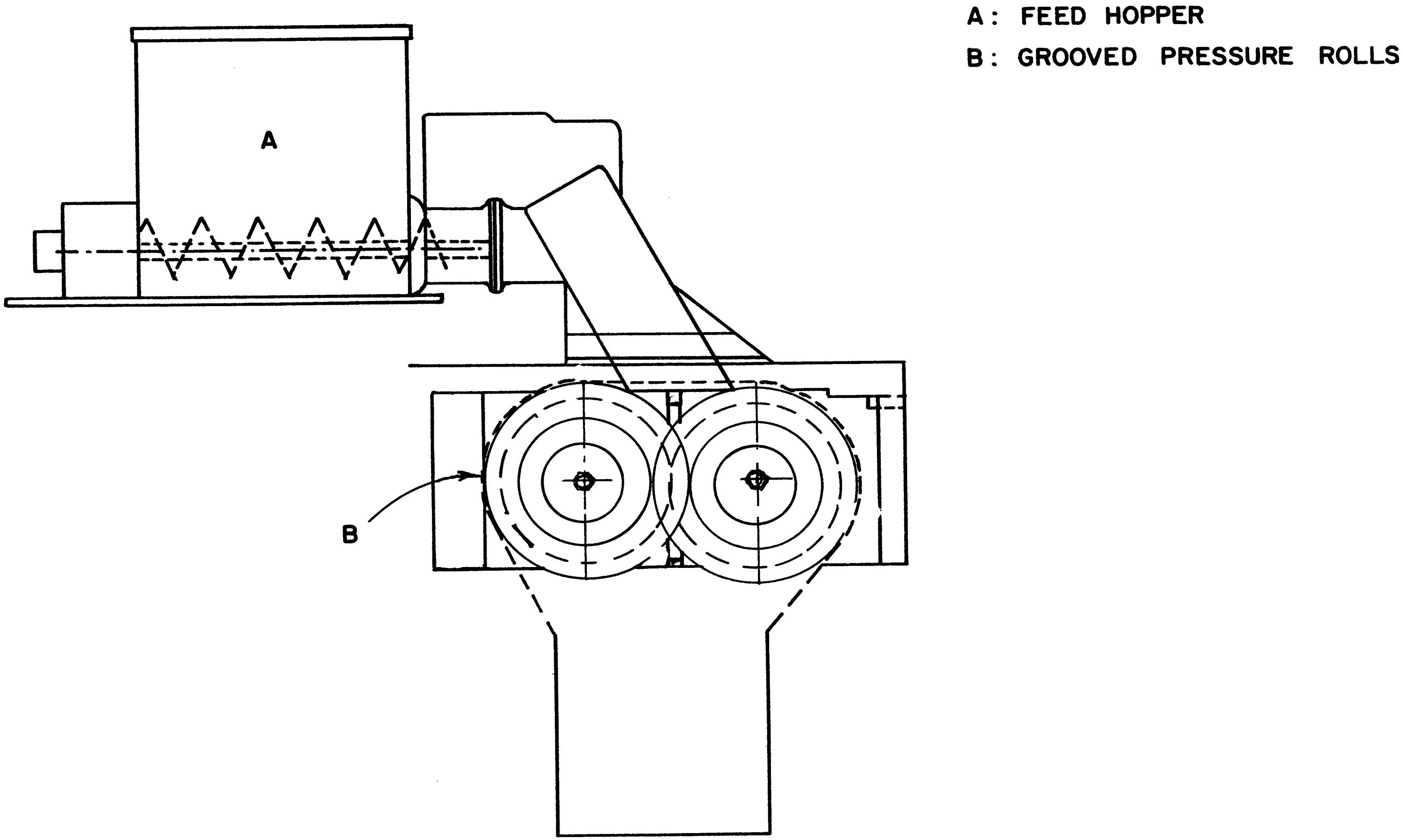


Figure 2. Chilsonator.

The Pellet Mill

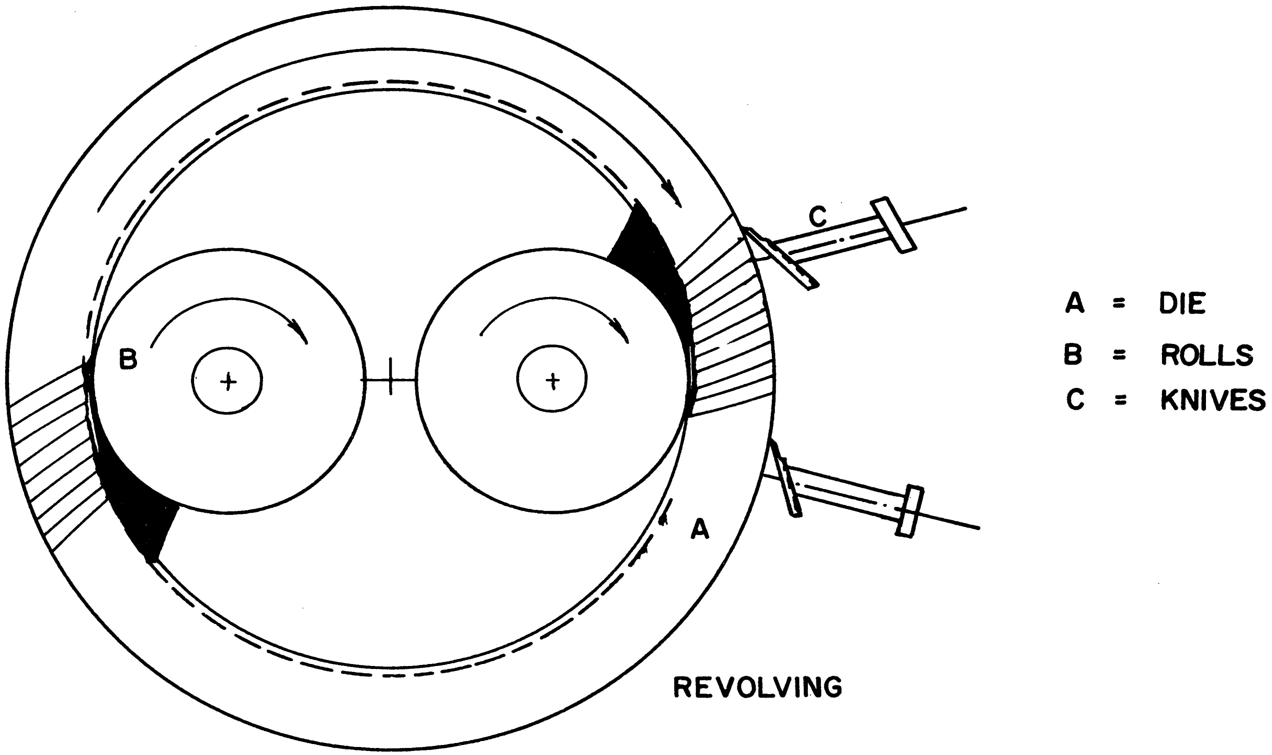
Gardner and Dean,(11) in 1957, reported the use of a pellet mill, manufactured by California Pellet Mills, San Francisco, for granulation of pharmaceuticals. This mill has been used commercially for the preparation of animal feeds. A sketch of the pellet mill is shown in Figure 3. From the sketch it is seen that the outer shell or die, A, is rotating against inner rolls, B, to force the material through the die openings. The material emerging is scraped off by knives, C. In this manner pressures up to several tons per square inch are said to be obtainable. A screw conveyer, not shown in the sketch, moves the material into the center of the mill.

Gardner and Dean used three tablet fillers, lactose, sucrose and calcium carbonate, and for binders employed gelatin, 5 and 20% solutions, and Carbowax^{R} 4000 in isopropyl alcohol or diluted isopropyl alcohol. A die with 3/16 in. holes was used in all tests. All formulas required a lubricant, calcium stearate, for successful pelletizing.

The pellets were dried and reduced to granules of suitable size by means of an oscillating granulator. The granules were then compressed into tablets which were measured for hardness. All granules formed tablets of suitable hardness except two types made from sucrose using high concentrations of isopropyl alcohol as a binder. No other tests were made to describe the physical properties of the granules.

The Wurster Process

An air suspension apparatus and technique have been developed by Wurster(12-14) for the preparation of granules for tabletting. A sketch



REVOLVING DIE

Figure 3. Pellet Mill.

of the apparatus is shown in Figure 4. Particles of therapeutic agent or inactive carrier can be used as starting material, being placed in Chamber A. A stream of air is introduced in three places, labeled B on the sketch, so as to suspend the particles and keep them in turbulent motion. Suitable binder and powder are thrown into the air stream through the tubes marked C so as to have them impinge on the suspended particles. The flow of air is said to be adjusted so that the finished granules will fall from suspension back into chamber A for collection. Thus granules of controlled and rather uniform size can be prepared.

The Wurster machine has been utilized primarily for coating purposes to date rather than for preparing the common type of granules for tablet making. On the other hand, use of this process would eliminate the mixing, drying and grinding procedures of the conventional granulation method.

Pan Granulation

Tuerck, Walters and Carkhuff(15) reported on the development of a method for preparing granules in a rotating pan similar to that used for tablet coating. They place the material in the pan and, with continuous rotation, spray in a suitable binder to cause granule formation. Once agglomeration is complete, hot air is blown into the pan to remove the moisture.

These workers used several variations; they sprayed a binder solution and sprayed water into a mix containing a powdered form of the

A : CHAMBER

B : COMPRESSED AIR

C : TUBES

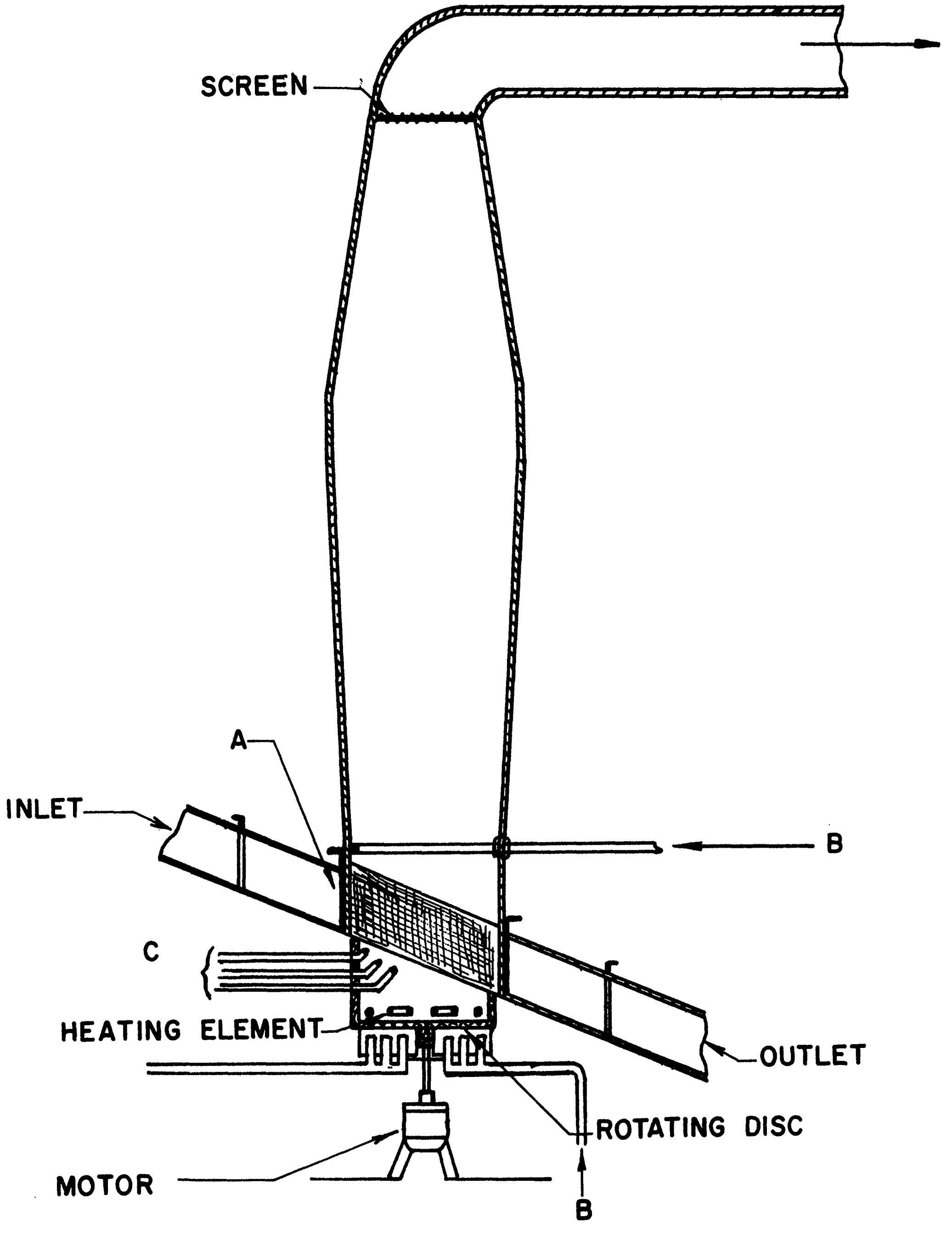


Figure 4. The Wurster Apparatus.

binder. At the moment, this method has the disadvantage of requiring a rather large proportion of sucrose or other hygroscopic substance in the mixture for satisfactory granules to be formed, but work is in progress with the aim of overcoming this drawback. This method offers the advantages of combining the powder mixing, wet mixing, screening and drying into a single operation requiring no transfer of material.

Evaluation of Granules

Numerous measurements of physical properties of granules might be made, but no single property or group of properties has been shown to be indicative of the usefulness of granules in the formation of tablets. Thus, the evaluation of granules has been accomplished only through measuring the physical properties of the tablets made from them. Disintegration rate of tablets is an important characteristic but is generally associated with the type and amount of disintegrating agent added to the granules before compression and not considered to be characteristic of the granules themselves. This leaves only two general criteria for tablets; namely, tablet hardness and friability, which can be used to judge tablet quality and, in turn, to judge the granules from which they are made.

Tablet Hardness Tests

The hardness of tablets is still estimated in many places simply by breaking the tablet with the fingers and noting the force required or the snap resulting from the breakage. This procedure has some merit but offers no definite specifications to be applied to a formula and no suitable means for comparing formulas. Several instruments have been developed to furnish more meaningful and reproducible measurements of tablet hardness, the Monsanto Hardness Tester(16,17) and the Strong-Cobb Hardness Tester(17,18) being the most widely accepted. The Monsanto instrument consists of a stationary anvil and a movable plunger attached to a helical spring. The tablet is placed on edge between the anvil and plunger, and pressure is applied by increasing the compression of the spring with a knurled screw. The Strong-Cobb machine works on the same principle but uses air pressure generated by a hand pump to move the plunger. Results are obtained with both instruments in arbitrary units.

Hardness tests for tablets have been criticized as being subject to the same errors as crushing tests of concrete, marble and other materials.(19) It was demonstrated that breakage in these tests always occurs along lines of stress established by the test conditions and not necessarily at the weakest points of the tablet structure.

Tablet Friability Tests

Friability of tablets, or the ease with which a tablet is crumbled or reduced to powder, has been recognized as a better index to quality than hardness. The physical deterioration of tablets occurring in packaging, shipping and handling is thought to be due primarily to repeated dropping and rubbing of the tablets against hard surfaces, and these factors cause crumbling of the tablet edges and abrasion of the surfaces. Practical methods for estimating friability used by tablet makers for many years have been dropping the tablets onto a hard surface from a measured height and shaking a group of tablets in cupped hands, followed by visual inspection.(20,21) In recent years efforts have been made to establish tests which could be repeated in the laboratory and which might be used to establish specifications for products. Smith(20) placed tablets in a cylinder held in a horizontal shaker with a four inch stroke and subjected them to 250 vibrations a minute. The loss of weight incurred by the tablets over a given period of time was taken as the friability. Shafer et al.(22) designed a more elaborate apparatus, called the Roche Friabilator, which consisted of a lucite drum 12 in. in diameter containing a curved scoop. The design was such that tablets contained in the drum would slide against the plastic surface for a period and then be picked up and dropped a distance of 6 in. with each revolution of the drum. Friability was taken as the loss in weight of tablets after four minutes of rotation at 25 rpm. The authors claimed that tablets which lost no more than 1% of their weight under these conditions would resist normal shipping and handling in a satisfactory manner.

A type of friability which does not involve crumbling or abrasion is the splitting or capping of tablets due to a peculiar structural weakness. Tablets exhibiting this property generally split into two distinct pieces, the upper portion or cap resembling a lense in shape. This separation occurs quite suddenly following a series of shocks. It does not lend itself to the usual friability measurement since it cannot be expressed as a loss in weight per unit of time. The only test for capping which has been described is that by Lowenthal(23) which was used primarily for compression-coated tablets. He devised a method in which tablets were tumbled in flat-end glass cylinders and the time required for capping to occur was taken as the index.

Physical Properties of Granules

Bulk Density

Bulk density as applied to granules is the apparent density of a granular bed or the weight of a unit volume of the bed. This property is used as an index of the amount or type of packing occurring in the particulate bed. Bulk density varies according to the treatment given to the mass of granules, and two different methods of measurement may yield results which are quite different. Numerous methods for measurement of bulk density have been proposed with carefully stated conditions aimed at increasing precision.

Skaupy(24) determined the tap volume of powders by pouring 10 Gm. of powder into a graduated cylinder and tapping the cylinder, either by hand or automatically, until a constant volume was reached.

Cocking(25) described a device for bulk density determination, like a tilt-hammer apparatus, which drops a graduated glass tube through a distance of 20 mm. at a rate of 160 times per minute. He placed the powder in the glass cylinder and allowed tapping to continue until no change in volume resulted. He used this method for such powders as bismuth carbonate, bismuth salicylate and magnesium carbonate, the bulk densities of which vary appreciably with changes in conditions of manufacture.

Roller(26) obtained reproducible results of the bulkiness of small amounts of microscopic particles by adding the powder to a small tube and tapping by hand until no more powder could be added to make the bed occupy a fixed volume. He used a glass tube 4 mm. in diameter and 32 mm. long and calibrated the volume with mercury.

Neumann(27) devised a machine for determination of bulk density consisting of a platform supporting a glass cylinder which was raised gradually by a spiral cam and then dropped a distance of 1 cm. The cam was rotated by an electric motor at a speed of 220 rpm. Neumann placed the powder in the glass cylinder and rotated the cylinder carefully to loosen the powder bed. She then subjected the cylinder to tapping until equilibrium was reached. Use was made of the untapped to tapped volume ratio in an attempt to correlate packing properties of powders with various other factors, such as moisture content and particle shape.

Chepil(28) used an apparatus similar to that of Neumann in a study of packing of particles of varying sizes.

Leadbeater and co-workers(29) made a rather extensive study of the bulk density of iron powders, using six different powders. They examined two of the powders by pouring them into a 25 ml. cup from conical funnels with different sized orifices at a fixed distance above the cup. The densities obtained are shown below:

Powder	Bulk Density - Gm./ml.	
	4.58 mm. orifice	2.54 mm. orifice
8	2.766	2.745
20	2.382	2.342

These workers then subjected the six powders to five types of packing as follows:

a. Free fall, operated manually. The cylinder was dropped a distance of 1.5 in. onto a table top.

b. Free fall, operated mechanically. The cylinder was raised and dropped by a cam a distance which could be varied at a rate of 80 falls/min.

c. Vertical vibration produced electromagnetically. A steel reed was used as the cylinder support and vibrated with alternating current at 50 cycles/sec.

d. Horizontal vibration produced mechanically. The cylinder was vibrated by means of eccentric cams at rates varying from 900 to 1500 cycles/min.

e. Horizontal vibration produced pneumatically. A pattern type of pneumatic vibrator was used of unstated frequency.

With each system the tapping or vibration was continued to equilibrium. Different sizes of cylinders were used, but results did not vary greatly as the size varied from 25 ml. to 100 ml. The results were quite interesting, as can be seen from Table I, where some of Leadbeater's data are presented. It is noted that pneumatic vibration gave highest densities with the first four powders but not with the last two. Also, vertical fall gave essentially the same results whether operated mechanically or by hand, but a much larger number of falls was needed for the hand operation.

Leadbeater _et al._ concluded that any of the methods is satisfactory for bulk density, provided a sufficient number of vibrations is used; that the pneumatic vibration is probably to be preferred, giving maximum density and approximating conditions of use of the powder; and that the smaller cylinders are probably best for measurement, because of greater accuracy of reading.

In 1949, it was noted by several pharmaceutical manufacturers that no standard method existed for the measurement of bulk density of drugs and chemicals. A need was expressed for such a method for the

TABLE I

BULK DENSITY OF IRON POWDERS BY DIFFERENT METHODS
LEADBEATER'S RESULTS

Powder	Bulk Density - Gm./ml.				
	Methods*				
	a	b	c	d	e
9	2.99	3.09	3.05	3.05	3.21
8	3.52	3.60	3.52	3.57	3.70
17	3.20	3.23	3.23	3.13	3.40
18	2.72	2.72	2.70	2.75	2.83
25	2.00	1.92	1.89	1.58	1.66
26	4.17	4.03	4.03	4.07	4.03

*-The details of the methods are presented according to letter in preceding text. All data are for 25 ml. cylinders.

establishment of container sizes, in controlling uniformity of capsule fill and in insuring proper density for tablet production; hence a subcommittee of the Combined Contact Committee was formed to establish a standard procedure for bulk density. Nine different laboratories participated, each of which examined 16 powdered materials by three methods.(30) The powders were sifted through a U.S. Standard No. 20 screen and slid, not poured, into graduated cylinders. Bulk density was determined by reading the volume of the powder without tapping, by dropping the cylinder onto a hardwood surface from a height of 1 in. for three times, and by dropping the cylinder in the same manner at 2-second intervals for 150 times. Results were reported in unusual units of bulk as ml./oz. A portion of the data, recalculated as Gm./ml., is shown in Table II.

It is interesting to note that the method using 3 taps of the cylinder was selected as the standard by the subcommittee. The choice was apparently based on the smallest average deviations and the ease of performance. The large differences obtained between methods are somewhat surprising, for example, the bulk density of sulfathiazole was 0.3 Gm./ml. for untapped and 3-tap methods and 0.6 Gm./ml. for 150-tap method. No mention was made in this report of the type of measurement which would offer results most indicative of performance in the use to be made of the powders.

TABLE II

BULK DENSITY OF SEVERAL DRUGS BY THREE METHODS
FROM BUTLER AND RAMSEY

Drug	Untapped		3 Taps		150 Taps	
	Gm./ml.	Avg. Dev. %	Gm./ml.	Avg. Dev. %	Gm./ml.	Avg. Dev. %
Bismuth subcarbonate, heavy	0.867	3.9	1.01	2.5	1.86	2.9
Bismuth subcarbonate, light	0.193	4.0	0.222	4.1	0.427	5.0
Calcium gluconate	0.182	4.0	0.217	3.3	0.422	7.2
Calcium phosphate, dibasic	0.532	1.7	0.570	2.2	0.993	2.2
Lactose	0.804	2.4	0.870	1.2	0.965	1.4
Sodium salicylate	0.300	4.0	0.323	3.2	0.654	2.8
Sulfathiazole	0.300	5.8	0.332	5.5	0.606	8.4

In spite of the wide interest in bulk density of powders, only one report is available on the measurement of bulk density of granules for tablet making. Lowenthal(31) compared bulk densities of granules determined by vibration and by tapping until no further change in volume was noted. He selected the tapping method as being the one of choice for his purpose, since it gave closer packing of the granule bed. Lowenthal designed an apparatus after that of Neumann,(27) utilizing a cam for raising the cylinder then dropping it a distance of 1 cm. He incorporated four cylinders in the apparatus to allow several samples to be run simultaneously, and he increased the speed from the 220 rpm used by Neumann to 380 rpm.

No correlation has yet been shown between bulk density of granules and quality of tablets produced from them. Lowenthal(31) proposed that granule beds containing fewer voids would be expected to form firm compacts with less pressure and that less die-wall friction might be expected. He was unable to test his hypothesis, however, since he could not change the bulk density of granules prepared from a given material by any of the methods tried. Utilizing conventional granulation equipment, he varied binders, lubricants, screen sizes and particle size of starting material but obtained no significant differences in bulk density of finished granules by these variations.

Bulk density is of use primarily to describe the packing of a particulate bed. A more useful expression of packing is void fraction which is independent of the true density of the particles. Void fraction, $\underline{V}$, is readily calculated from bulk density, $\underline{d_a}$, and true density, $\underline{d}$, by the following equation:

$$V = d_a(1/d_a - 1/d),$$

where void fraction is the volume of intergranular space per unit volume of the packing. Void fractions obtained in this manner for tablet granules are misleading, however, since the granules, themselves, contain pores, and the value for voids includes this intragranular space. Thus, any study of the packing of granules must take into consideration the granule porosity in order to be meaningful.

Size Distribution

Size distribution is used as an index to the mean size of particles and the spread about this mean. Measurement of particle size is an important area of powder technology, and many methods have been developed.(32) For particles as large as tablet granules the most satisfactory and most commonly used method appears to be sieving.

In the United States, two types of wire-cloth screens are recognized for sieve analysis, the Tyler series and the U. S. Standard series. The Tyler standard screen scale consists of openings whose sizes are in the fixed ratio of $\sqrt{2}$. It is based on the size of the opening in 200 mesh wire cloth, which is prepared from wire 0.001 in. diameter and has an opening of 0.0029 in. diameter. The U. S. Standard series was proposed by the National Bureau of Standards, and in general the sizes advance in the same ratio as the Tyler series, but a 1 mm. opening is used as the base.

The method of rotation or vibration of sieves has been examined by Fahrenwald and Stockdale(33) who compared rotary motion, rotary motion accompanied by tapping, vertical jarring motion, horizontal jarring motion and high frequency vibration. They concluded that vibratory motion is best, provided the proper amplitude and frequency are selected.

Fahrenwald and Stockdale(33) also found that thin beds of material gave higher sieving efficiency than thick beds. They stated that the time required for sieving was almost proportional to the weight of material placed on the screen. Gulinck (34) investigated the time of sieving, using times of 2, 4, 8, 16 and 32 minutes and found that the amount of material passing a screen varied logarithmically with time. A large proportion of granules just smaller then the mesh size would require greater sieving time, according to Gulinck. He suggested that a sieving time of 15 minutes may yield an error in the separate fractions of 5 to 6% of the total weight.

Humidity was pointed out as a factor affecting results of sieve analyses by Pollard.(35) This effect he thought to be due probably to varying degrees of aggregation of particles with change in humidity.

The determination of size distribution from sieve analysis data is generally accomplished through log size-probability plots. The basis for this method was derived by Hatch and Choate.(36) They applied the normal probability equation to particle size distributions and used the parameters of this equation to define the most common types of distributions. For particles exhibiting symmetrical frequency curves when plotted as percent versus size the following equation was presented.

$$F(d) = \frac{\Sigma n}{\sigma\sqrt{2\pi}} \exp\left[-\frac{(d-d_{av})^2}{2\sigma^2}\right],$$

where $F(d)$ is the frequency of observations of diameter d, Σn is the total number of observations, d_{av} is the arithmetic average of observations and σ is the standard deviation. The value of σ is given by the following equation:

$$\sigma = \sqrt{\frac{\Sigma\left[n(d-d_{av})^2\right]}{\Sigma n}}$$

Thus, for particles following the normal probability curve, that is, exhibiting a linear relationship when plotted as cumulative percent less than stated size versus stated size on arithmetic - probability paper. The distribution can be described in terms of $\underline{d_{av}}$ and $\underline{\sigma}$. The value of $\underline{d}$ corresponding to 50% on the probability scale is $\underline{d_{av}}$, and $\underline{\sigma}$ can be taken as the value of $\underline{d}$ corresponding to the 84.13% point minus that of the 50% point, or the 50% point minus the 15.87% point.

Most commonly it is found that size-frequency distribution of powder particles are not symmetrical so that the above equations do not apply. Hatch and Choate recognized this and pointed out that in the majority of such cases a plot of frequency versus log size was symmetrical; this gave rise to the following form of the probability equation:

$$F(d) = \frac{\sum n}{\ell n \sigma_g \sqrt{2\pi}} \exp \left[- \frac{(\ell nd - \ell ndg)^2}{2 \, \ell n \, \sigma_g} \right] ,$$

where $\underline{dg}$ refers to the geometric mean, the expression for $\underline{\ell n \sigma_g}$ is as follows:

$$\ell n \sigma_g = \sqrt{\frac{\sum [n(\ell nd - \ell ndg)^2]}{\sum n}}$$

The term $\underline{dg}$ is called the geometric mean diameter and $\underline{\sigma_g}$ is the geometric standard deviation.

In this case, when cumulative percent versus log size is linear on a log-probability plot, $\underline{dg}$ is taken as the 50% point and $\underline{\sigma_g}$ is $\underline{\log d}$ corresponding to 84.13% minus $\underline{\log d}$ of the 50% point or $\underline{\log d}$ of the 50% point minus that of the 15.87% point. The distribution is defined completely by these two values, $\underline{dg}$ and $\underline{\sigma_g}$.

The equations of Hatch and Choate are based on number of particles of stated size or may be said to be on a count basis. Since sieve analysis data is obtained as weight of particles of stated size it is thus on a weight basis. Hatch(37) extended these equations to make possible their application to sieve analysis. Substituting $\rho\alpha_v nd^3$ for the weight of a fraction of stated size, d, he obtained the equation:

$$\rho\alpha_v nd^3 = \frac{\Sigma\rho\alpha_v nd^3}{\log \sigma'_g \sqrt{2\pi}} \ \exp\left[-(\ln d - \ln d'_g)^2/2\ \ln^2\sigma'_g\right] \quad ,$$

where ρ is the density of the powder, d is the particle diameter, α_v is the volume shape factor, n is the number of particles retained on a sieve corresponding to d, dg' is the geometric mean diameter by weight and σ'_g is the geometric standard deviation by weight.

The arithmetic mean diameter by weight, d_w, is the sum of the weights retained on each sieve multiplied by the corresponding diameter and dividing by the total weight:

$$d_w = \Sigma(\rho\alpha_v nd^3)d/\Sigma\rho\alpha_v nd^3 = \Sigma nd^4/\Sigma nd^3.$$

Applying the probability equation to d_w, Hatch obtained the expression:

$$d_w = \frac{\Sigma nd^4}{\Sigma nd^3} = \frac{\Sigma n}{\Sigma n \ln \sigma'_g \sqrt{2\pi}} \int_0^\infty \frac{d^4}{d^3} \exp\left[-\frac{(\ln d - \ln d'_g)^2}{2\ln^2 \sigma'_g}\right] d\ln d,$$

which, upon integration, yielded the equation:

$$\ln d_w = \ln \frac{\Sigma nd^4}{\Sigma nd^3} = \ln d'_g + 0.5 \ln^2 \sigma'_g \ .$$

In a similar way Hatch obtained the expression for mean volume diameter, d_v^3:

$$\ell n\ d_v^3 = \ell n\left(\frac{\sum nd^3}{\sum n}\right) = 3\ \ell n\ dg + 4.5\ \ell n^2 \sigma_g ,$$

where dg and σ_g are parameters by count. Adding the equations for $\ell n d_w$ and $\ell n d_v{}^3$ yields:

$$\ell n\ \left(\frac{\sum nd^4}{\sum n}\right) = \ell n\ d\acute{g} + 0.5\ \ln^2\ \sigma'_g + 3\ \ell n\ dg + 4.5\ \ell n^2\ \sigma_g.$$

Applying the probability equation as before for $\sum nd^4/\sum n$ and integrating, Hatch obtained the expression:

$$\ell n\ \left(\frac{\sum nd^4}{\sum n}\right) = 4\ \ell n\ dg + 8\ \ell n^2\ \sigma_g.$$

Substituting this value for $\sum nd^4/\sum n$ in the previous equation, he solved for $\ell n d\acute{g}$:

$$\ell n\ d\acute{g} = \ell n\ dg + 3.5\ \ell n^2\ \sigma_g - 0.5\ \ell n^2\ \sigma'_g.$$

He then showed that σ_g and σ'_g were equal and arrived at the expression:

$$\ell n\ dg = \ln\ d\acute{g} - 3\ \ell n^2\ \sigma_g.$$

This equation makes it possible to convert values of geometric mean diameter from a count to a weight basis.

Using these relationships, Hatch suggested a method for calibration of sieves. He sieved a representative sample and examined each sieve fraction microscopically to determine dg and σ_g. These values of dg were then converted to calibration values on the weight basis, $d\acute{g}$, to be used for subsequent sieve analysis.

A report illustrating the usefulness of the Hatch equations was written by Ames, Irani and Callis.(38) These workers obtained essentially the same values for size distribution of several powder samples using these different methods and appropriate equations for conversion of parameters. They pointed out the need for calibration of sieves using standard samples approximating the material to be analysed.

Only a few workers have examined the relationship between granule size or size distribution and the quality of tablets obtained from the granules. Arambulo et al.(39) examined the effects of change in particle size of granules fractionated by sieving on the weight variation and weight of tablets. They used granules of lactose-starch mixture ranging from 3,045 microns to 324 microns in size and found that as particle size decreased the tablet weight variation decreased to a minimum at 400-800 microns, then increased. Similar results were obtained with sodium chloride granules. Arambulo and Deardorff(40) examined the change in average weight of tablets with particle size of sodium chloride granules, using a fixed volume setting for fill of the tablet die. They found that as particle size decreased the tablet weight increased to a maximum at 150-350 microns and then decreased.

Raff et al.(41) observed that granulations containing a disproportionate amount of fines gave tablets of higher weight at the beginning than at the end of the run.

The amount of void space in a packed bed of particles is influenced by the size distribution of particles. Theoretically, if the particles were of uniform size the amount of voids between particles would be the same regardless of particle diameter.(42) In the packing of spheres two ideal arrangements occur, open or cubic packing, which contains 47.64% of voids and close or rhombohedral packing, containing 25.95% voids. Actual measurement of spheres packed in random fashion generally yield intermediate values. Also, measurements of beds of powders of different size have been found to exhibit varying void fraction as the size changes.

Offermann(44) decreased the particle size by prolonged ball milling and found increase in apparent density. Meyer and Eilender(45) observed a decrease in apparent density with increasing time of milling of powders. Roller,(26) working with particles below 100 microns, found that the apparent density was practically independent of particle size for particles having diameter larger than 14 microns, while for smaller particles the apparent density decreased with decreasing particle size. Jones(46) claimed that in many cases the total voids of powders increases with decreasing particle size.

When particles of a powder bed are not of uniform size closer packing is frequently observed due to the ability of small particles to fit within the void spaces between larger ones. Probably the most practical application of theories of packing was made by Furnas,(47) who developed systems for preparing concrete of maximum density. For packing to maximum density he calculated particle size distributions corresponding to the most complete filling of voids between large particles with smaller sizes. On this principle a system of continuous grading was devised. When put into practice Furnas' system was found to give concrete of maximum density.(48) It is interesting to note that a continuously graded system of particles of same density prepared according to Furnas' equation would exhibit a linear relationship between cumulative percent and particle size with a slope equal to the constant ratio described by the Furnas equation. This type of distribution is seldom found in particles prepared by the usual operations of grinding or milling.

Porosity

The term porosity refers to the spaces within the body of a particle or granule. Solid particles prepared by crushing, grinding or forming into granules will usually have cracks, cavities or pores within their structures.(49) It is important in many cases to know whether the internal pores result from very narrow and extensive cavities or from relatively large pores.

Numerous methods have been used for the determination of diameter and volume of pores. If a porous material can be sectioned, the pores can be measured by microscopic techniques, but difficulties arise in sectioning, identifying, and measuring a large number of pores. Such methods have been employed, however, for materials with large pores.(50)

Another simple procedure is to boil a weighed quantity of the material in a suitable liquid. The excess liquid is then decanted and the powder superficially dried. The increase in weight is assumed to be that of the liquid held in the pores. Drying only the external surfaces of particles is difficult to accomplish but in some cases this method gives satisfactory results. A more reproducible and reliable result is obtained with the use of mercury and helium.(51) A bulb of accurately known volume is filled with the powder, and the dead space (pore volume and void volume) is determined by allowing helium to expand into the bulb and measuring the quantity required. The helium is then pumped out, and the volume of mercury necessary to fill the bulb is measured. Since mercury does not wet most solids, it fills the void volume and leaves the pores unfilled; thus the difference between the helium and mercury readings is the pore volume.

Washburn(52) was the first to suggest that one could determine the diameter of pores by measuring the pressure necessary to force mercury into them. Ritter and Drake(53) developed equations for the penetration of mercury into pores at high pressure. Assuming the cross section of the pore to be circular, the force due to surface tension acting along the circle of contact for a length equal to the circumference of the circle was stated to be: $\underline{2\pi r\sigma}$, where $\underline{r}$ is the radius and $\underline{\sigma}$ is the surface tension. The force tending to squeeze the mercury out of the pore, normal to the plane of the circle of contact was written as $\underline{2\pi r\sigma \cos\Theta}$, where Θ is the contact angle of the mercury on the solid. The opposing force due to the pressure $\underline{P}$ on the mercury, acting over the area of the circle of contact, was expressed as $\underline{\pi r^2 P}$. Assuming equilibrium, Ritter and Drake set the opposing forces equal to one another:

$$2\pi r\sigma \cos\Theta = \pi r^2 P,$$

or

$$r = \frac{2\sigma \cos\Theta}{P} .$$

For most materials the contact angle is assumed to be 130° and the value of 470 dynes cm. for the surface tension of mercury at 20°C is used, so that the final formula becomes:

$$d = 175/P,$$

where d is the diameter of pores in microns, and P is in units of lb./in.^{2}.

A simplified pore size distribution apparatus suitable for routine testing was described by Bucker et al.(54) Cochran and Cosgrove(55) concluded that mercury porosimetry gives satisfactory pore size distributions for pores as small as 30 A° in diameter using pressures upto 60,000 lb./in.^{2}.

It was shown by Briscoe and Warren(56) and others that samples of material containing pores of colloidal dimensions give a low-angle scattering pattern representative of the pores. Low-angle scattering is in fact due to regions of colloidal size which differ in electron density from the surrounding medium. If the pores are in an homogeneous medium, X-ray scattering results can be indicative of pore size instead of particle size.

Using the assumption that if a porous material is broken into pieces, the density of the pieces will be found to be greater than the density of the original material because of the elimination of pores, Ergun(57) developed a method for determining the particle density of crushed porous materials from measurements of the gas-flow rate and the pressure drop through beds of material having a series of bulk densities.

Both pore volume and pore size distribution may be obtained from an analysis of gas adsorption isotherms.(58) When just the pore volume of a porous adsorbent is required, it is necessary only to determine the volume of gas adsorbed at the saturation pressure. If the amount of gas adsorbed on the external surface is small compared to the total amount adsorbed, the pore volume is essentially equal to the volume of gas in the adsorbed phase.

An indication of average pore size can be obtained by assuming that all the pores are cylinders. Then if all the surface is attributed to the walls of the pores the average pore radius r is:

$$r = 2\ V_p/S_w,$$

where V_p is the pore volume and S_w is the surface area per gram of adsorbant. V_p can be calculated from the volume of gas adsorbed per gram of adsorbant at saturation pressure, V_s, by the following equation:

$$V_p = \frac{v_s M}{M_v p_a} \quad ,$$

where M is the molecular weight, M_v is the molar volume and p_a is the density of the adsorbed phase.

Although many gases can be used as adsorbates, nitrogen is generally preferred because accurate surface areas can be calculated from the same data. The smallest pores that can be measured satisfactorily with nitrogen isotherms are about 20 A° in radius. Juhola et al.(59) found that water isotherms served to indicate pores as small as 10 A° in radius. McDermot and Arnell(60) used low temperature nitrogen and water isotherms for pore distributions of three activated charcoals and reported substantial agreement between the results of the two methods. The desorption portion of the isotherm is generally used for pore size distribution, since thermodynamic equilibrium is more nearly complete.

A convenient method for determining pore volumes in a porous material would be to weigh directly the quantity of a vapor condensed at its saturation pressure. This type of measurement, however, often yields high values because of the vapor that condenses in the small interstices formed by particles in partial contact with one another. Benesi et al.(61) overcame this difficulty simply by dissolving enough non-volatile solute in the saturating liquid to lower the vapor pressure to the desired extent. Carbon tetrachloride (a relatively volatile fluid) and centane (a relatively non-volatile solute for carbon tetrachloride) form the desired composition. Basically, the procedure of Benesi et al. consisted of weighing the carbon tetrachloride adsorbed after equilibrating samples with a solution of carbon tetrachloride, the vapor pressure of which had been lowered 95% of its saturation value with centane. Pore volume was calculated from the gain in weight of the sample. Values obtained by this method were slightly lower than by the nitrogen adsorption method. This method is recommended when it is desired to know the volume accessible by hydrocarbon molecules.

Upon analysing data from the literature, Bond and Maggs(61) found that heat-of-wetting values on a unit weight basis for a series of organic liquids sorbed on any one charcoal were approximately the same in many cases. These investigators concluded that the heat liberated on wetting surface area of any one solid is essentially the same for a large number of organic wetting liquids. Since the molecular sizes of the several organic liquids which can be used cover a considerable range, this finding suggested a means for estimating pore size distribution. Curves of heat of wetting versus molecular volume were obtained. A typical result was that liquids composed of small molecules upon contacting some burnt charcoals gave much higher heat-of-wetting per gram of substance than liquids composed of larger molecules. Presumably, this results from the inability of the larger molecules to enter many of the pores. The slope of the above curve at any point represents the area per unit range of pore diameter. Therefore, a plot of the first derivative of the curve against molecular volume gives the area distribution curve for the pores.

When liquid is stirred into a porous powder, the powder appears dry and free-flowing up to a point, after which further small additions bring about a marked change. It is explained that the liquid first fills the pore spaces, and later additions fill the spaces between the particles. Innes(63) adapted these phenomena to pore volume determinations.

Goetzel and Seelig(64) studied the effects of porosity on fatigue strength and average tensile strength on different particle sizes of copper and iron. In all cases they found that decreasing the porosity increased the fatigue strength and average tensile strength.

Strickland et al.(65) devised a mercury pycnometer for measurement of porosity in pharmaceutical granulations. They found that potassium bromide crystals and aspirin granules made by slugging had low porosity (3-5%), while sulfathiazole, sodium bicarbonate and phenobarbital granules prepared with starch paste binder had about 30% porosity, though the maximum diameter of pore that can be penetrated by their method was to 10 microns.

Recently Matsumaru(66) measured the porosity of compressed granules of aluminum silicate, using water vapor adsorption. He concluded that compression caused formation of bottle-neck type capillaries of large volume.

Flow Properties

There is no general definition for flow properties of a powder or granular bed, and the description of flow properties must be related to a specific method of measurement.

One measurement used is the time required for a given weight of material to pass through an orifice of specified size.(67) Hardy specified a flow meter for metallurgical powders consisting of a 60° strainless steel cone with a cylindrical orifice 1/8 inch long and 0.1 inch diameter. A removable brass cup is placed below the cone. The amount of powder is specified by weight, and the time required for the powder to flow through the orfice is taken as measure of the flow.

Flow has been also measured from the angle of repose.(68) Newmann used a small glass funnel with the stem drawn out to about 3 mm. diameter and cut perpendicular to the axis, fixed 2 cm. above a horizontal base. A piece of tracing paper was placed on the base and the powder poured through the funnel taking care to avoid blocking the tube. When the heap underneath the funnel was just high enough to reach the end of the stem, the addition of powder was stopped and the base of the heap was then calculated as $\underline{\theta} = \underline{\tan^{-1}}(h/r)$, where $\underline{h}$ is the height of the powder bed and $\underline{r}$ is the radius of the base. This method was claimed to give reproducible results.

By either of the above methods it has been shown that flow is dependent on particle shape and size.(68,69) Neumann observed that spheres or cubes with smooth surface had lower coefficient of friction than powders of rougher surface and more irregular shape. Also the amount of moisture was shown to affect the results.

Leadbeater *et al.*(69), working with iron powders, tested a flowmeter designed after Hardy's apparatus. They found that flow was directly proportional to the weight of the sample and inversely proportional to the nth power of the radius of the cone, where n, calculated from the experimental data, was approximately 2.5.

Working with tablet granules, Nelson(70) observed that sulfathiazole granules exhibited minimum angle of repose at 500 micron size. Addition of fines caused a marked increase in angle. He also observed that addition of lubricants to the granules changed the angle of repose, depending on the type of lubricant.

Compression Characteristics

Another property of granule beds is that called compressibility. It is defined as the ratio of the bulk density of the tablet to the bulk density of the powder bed.(71) This ratio is generally termed compression ratio.

Most of the work on compressibility has dealt with metal powders. Balshin(72) developed a mathematical relation between pressure and volume of the powder as the compression proceeds. He started with a short cylinder of powder of height h, and diameter d, subjected in a mold or die to a pressure P. A small increase in pressure, dP, would result in a decrease in height, dh. The work so performed, per unit area of cross-section, was stated as:

$$dw = -Pdh.$$

Making the assumption that increase in pressure is proportional to work performed, Balshin obtained:

$$dP = idw,$$

where, i is the factor of proportionality. Combining these relations yielded:

$$\frac{dP}{P} = - i\ dh.$$

The proportionality factor, i, was said to be dependent on the speed of pressing, the temperature, the particle size and shape, the presence of lubricants, etc. The equation was integrated to give:

$$\ell n\ P = - ih + C,$$

and a plot of $\ell n\ P$ *versus* h should be linear and have a slope of -i. To obtain a dimensionless slope, Balshin introduced the terms V_o and L:

$$V_o = \frac{h}{h_k},$$

$$L = i\ h_k,$$

where h_k is the height of the cylinder in the final compact. The differential equation then reduced to:

$$\frac{dP}{P} = - L\ dV_o,$$

and on integration this gave:

$$\ell nP = - LV_o + C.$$

L is dimensionless and is called the modulus of pressing. V_o is called the relative volume which is the ratio of the volume at any particular pressure to that at the final pressure.

Huffine(73) showed that crystals and granulations used in tabletting follow the Balshin equation. Also, Train(74) demonstrated that heavy magnesium carbonate follows a similar relationship. He used a horizontal split die of eight sections, with a maximum pressure of 2,000 Kg./cm.^{2}. From the work of Train and others(73,74,75), the different slopes of the compression curve, ℓnP versus V_O, is generally described as representing interparticulate slippage, temporary structure formation, crushing or plastic flow and plastic deformation of particles, as illustrated in Figure 5.

Compressibility is said to decrease with smaller particle size due to large amounts of adsorbed air on the surfaces of particles.(75) Goetzel(76) found that powders of high bulk density were difficult to mold. It has been found(75,77) that the highest density in compacts pressed from one side is found at the circumference of the face opposing the movable plunger, and the lowest density at the circumference of the face opposing the die bottom. The density decreases, first rapidly and then more slowly, with increasing distance from the punch. Train(74) showed that there are greatly increased frictional forces occurring at the face of an unlubricated die wall, opposing the movement of the adjacent compact material which is tending to move as a result of the thrust from the top punch. On the other hand, the material at the center is relatively free to move, being subject only to interparticulate friction. Nelson(78) reported that pressure distribution is not uniform in the die cavity during tablet compression although presence of lubricants on granules tends to equalize the distribution.

Higuchi et al.(79) worked with sulfathiazole granulation prepared with starch paste binder. They found a linear relationship between Strong-Cobb hardness of tablets and logarithm of maximum compressional force up to 5,000 pounds on the tablet, above that hardness increased

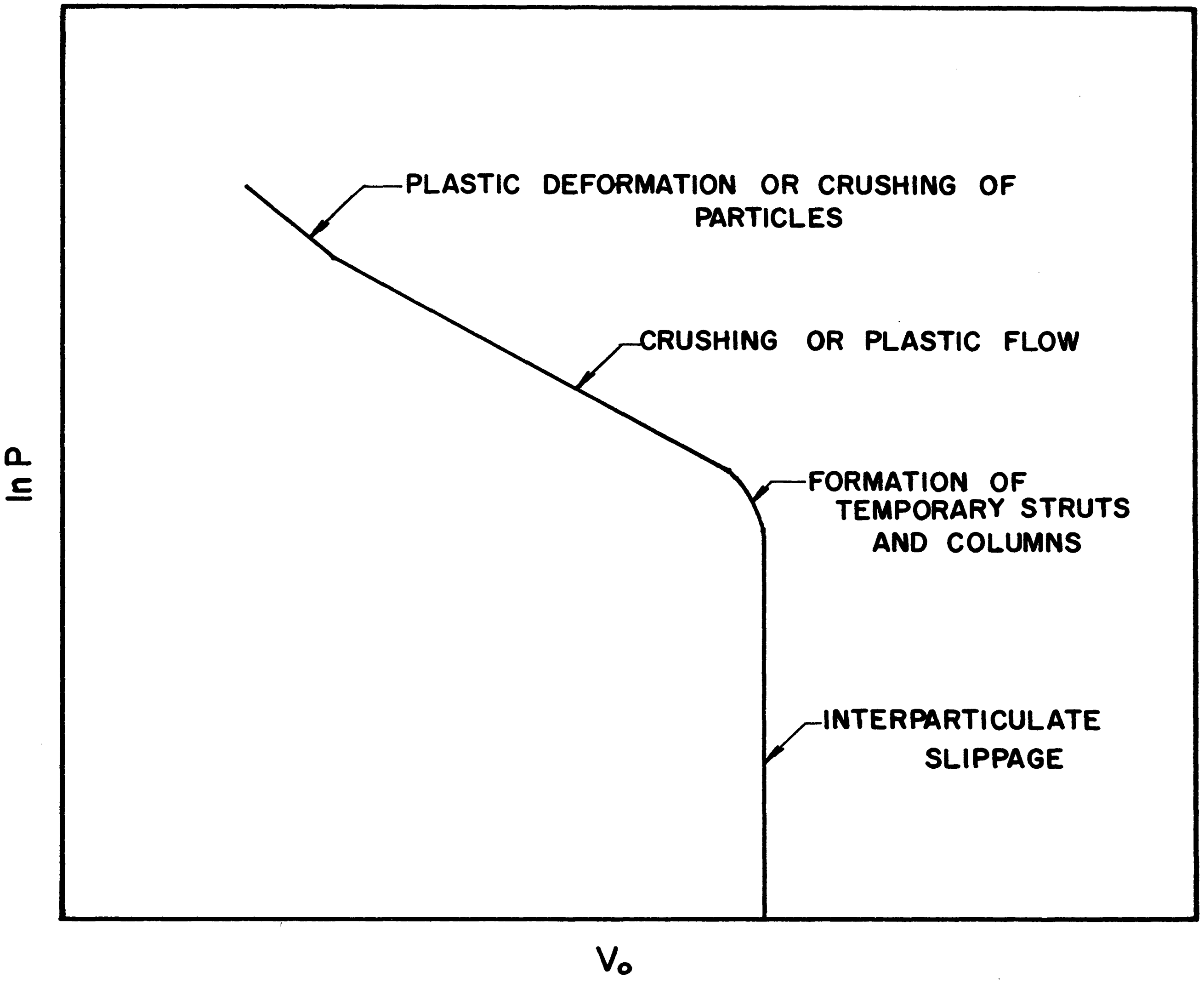


Figure 5. Compression Curve.

less rapidly. In further work(80) similar results were obtained with aspirin, lactose, lactose-aspirin and sulfadiazine tablets.

Extrusion

Extrusion can be best defined as flow under pressure. Extrusion is basically a transformation of a raw material into a continuous specifically shaped product by forcing the material through a die.(81)

The first commercial application of extrusion was probably the fabrication of lead pipes, a development made by Joseph Bramah, in 1797.(82) Before 1850 the Italian food industry had adapted extrusion to the production of macaroni, and in about 1880 cellulose nitrate rods and tubes were on the market, though long tubes were not available until 1931. Early progress in extrusion was limited primarily to Germany, but with the development of the screw-type extruder in the United States in 1938 and its subsequent application to rubber and thermoplastics rapid progress took place in America. These developments in the United States have been summarized by Simonds, Weith and Schack(83) as follows:

1870	Wet extrusion of cellulose nitrate.
1880	Dry extrusion of rubber.
1919	Wet extrusion of casein.
1927	Wet extrusion of cellulose acetate.
1934	Continuous dry extrusion of cellulose acetate.
1936	Extrusion of ethyl cellulose.
1937	Extrusion of methyl methacrylate.
1939	Extrusion of cellulose acetate butyrate.
1939	Extrusion of vinylidene chloride.

1940 Extrusion molding.

1940 Extrusion of polystyrene.

1941 Extrusion of polyethylene.

1944 Extrusion of nylon.

1948 Application of twin-screw extruders.

1949 Extrusion of wide thin sheets (over 100 in. wide).

1950 Development of the extruder-extractor.

Although the chief use of extrusion has been the production of plastic and rubber articles, the advantages of the process, such as high production rates, simplicity of operation and small space requirements, have attracted other interests, and numerous applications of extrusion to production of foods, metal parts, ceramic articles and glass products are now being made.

The first extruders to be used consisted of pistons which forced the material through a cylinder and out through a suitable die. These were appropriately named stuffer presses. The later type, more popular in recent years, is the screw extruder, which utilizes a screw to force the material through the cylinder and die. Numerous types of extruders are now marketed, differing principally in the mechanisms used for feeding material to the unit, controlling temperature and flow rate and in construction details, while the basic principles of extrusion are essentially the same as on the original machines. Extruders are generally rated by production capacity which is based on the diameter of the screw. This does not take into account the pitch of the thread, but the method of designation has been well established in industry. Machines are available with screws of 1 to 5 inch diameter, and units up to 10 inch diameter have been operated successfully. A list of the manufacturers of extrusion equipment in the United States has been published.(84)

Numerous articles have appeared aimed at evaluating extruder design.(85-88) These workers have attempted to describe accurately the flow patterns occurring within the extruder and relate them to temperature, power requirements, screw pitch and clearance. This information is of value particularly in the selection of a machine for a given operation and in the design of new equipment.

Pearson(89) noted that the properties of extruded materials are influenced by the manner in which the substance flows during the process. By study of this flow and by observing how it is affected by variation in the conditions of operation, much valuable information has been obtained regarding the degree and distribution of deformation of the substance. Pearson proposed that substances undergoing deformation adapt themselves to the new shape in a manner resembling flow in liquids, following a streamline course of flow determined by geometrical conditions. The plastic deformation which occurs during extrusion was said to be no exception to this, although the flow generally departs from a simple streamline form, partly due to frictional effects and due to its not being in a uniformly plastic condition. Thus, although the patterns of flow in extruders are generally complex, it is believed that the principles of flow of liquids can be successfully applied to extrusion. Rather than attempt the evaluation of materials in so complicated a machine as a screw-type extruder, however, simple rheometers have been used to measure rheological properties which can then be applied to extruders.

Rheological testing equipment for the study of flow for this purpose fall into three categories, rotational instruments, compression instruments and extrusion instruments.

In a rotational rheometer a sample is maintained in a state of continuous shear until a steady or quasisteady state is reached. The earliest such instrument suitable for rubbers was the rheometer developed by Mooney.(90) It consisted of an outer cylinder or stator, in the form of a split block, which opened up for easy insertion of the sample. The inner cylinder or rotor was maintained on a hollow shaft, driven by weights. Both inner and outer cylinder surfaces were covered with fine, longitudinal V-groves to prevent slippage of the sample. The angular velocity of the rotor was measured with a stop watch. Though useful as a research tool, this instrument was too slow for routine control tests, and for this purpose Mooney developed another instrument in which the rotor was a flat disk and the stator a shallow cup.(91) The rotor was driven by a synchronous motor and the reaction of the sample was measured with a spring. The deflection of the spring thus indicated the viscous resistance of the sample under the imposed shear.

An interesting variation of the disk viscometer was introduced by Piper and Scott.(92) They substituted a biconal rotor for the flat disk. Claiming the biconal form has the advantage that the rate of shear in the sample is uniform over the face of the rotor while the flat disk rotor gives only an average viscosity over a range in rate of shear. Many other rotational instruments of cylindrical form have been described.(93,94)

For a rotating cylinder viscometer of small intercylinder clearance, the well-known formulas are(95):

$$S = \Omega \frac{R_2^2 + R_1^2}{R_2^2 - R_1^2} , \qquad F = \frac{C}{4\pi L} \left(\frac{1}{R_1^2} + \frac{1}{R_2^2}\right) ,$$

where S is the rate of shear, F is the shearing stress, R_1 and R_2 are the radii of the inner and outer cylinder, respectively, L is their length, Ω is the angular rotor velocity and C is the driving torque. The viscosity is:

$$\eta = F/S = \frac{C}{4\pi L\Omega}\left(\frac{1}{R_1^2} - \frac{1}{R_2^2}\right)$$

where η is the viscosity of the sample. The viscometric theory of the disk and the biconical rotor viscometer is complicated by geometry of the boundary conditions and special equations have been presented.

In the viscometers of the compression type, a sample, initially in the form of a small pallet, is pushed between flat plates under a given load. The thickness of the sample after a given compression time is generally taken as a measure of plasticity. The Williams plastometer(96) was the first instrument of this type to be used extensively. It consisted essentially of a flat base plate and a 5-Kg. weight mounted on guides to hold it straight. He used a 2-ml. sample which was preheated and then pressed for 5 minutes at 100° to determine the plasticity of the sample. Elastic recovery was measured by the height of the sample a minute or more after removal from the plastometer. Many minor variations of the Williams plastometer have been developed.(97,98)

A variation in testing procedure, the Defo method(99), which is much used in Germany, involves two or more tests with different compressing loads to permit interpolation to the load required to compress the sample to the standard compressed thickness in the standard time.

For the compression plastometer it is assumed that there is no slip of the sample on the compressing surfaces. For a Newtonian liquid in a plate plastometer the following formula was derived(100):

$$\frac{1}{h^4} - \frac{1}{h_o^4} = \frac{8\pi Mgt}{3\eta V^2} ,$$

where,

h_o is the initial height of the sample,

h is its height at time t,

M is the compressing weight,

g is the acceleration due to gravity,

η is the viscosity,

V is the sample volume.

In extrusion instruments, a sample is placed in the cylinder and is forced by a piston through a die with small hole at the end of the cylinder. Marzetti(101) was the first to introduce an extrusion type viscometer. His instrument consisted of a conical bottom terminating in a hole through which the sample was extruded by compressed air. The extrusion rates employed by Marzetti were quite slow; nevertheless, the instrument was used to obtain much data on the viscosity of raw rubbers and mixes in various stages of processing.

The most elaborate and at the same time the most practical plastometer is the Dillon extrusion plastometer.(102) All mechanical movements are powered with compressed air, including the operation of charging the hemispherical extrusion chamber with the sample. Electrical connections on the extrusion ram automatically record the time of extrusion of a fixed volume.

The McKee viscometer(103) has the advantage that, unlike other extrusion instruments, it can bring the sample essentially to a state of thixotropic breakdown. This is accomplished by pushing the sample back and forth any number of times through one or several holes in a plate dividing the extrusion cylinder into two halves. The pistons, one in each half of the cylinder, are mechanically driven at a controlled speed while the force required is being observed.

A number of other extrusion viscometers have been used by other investigators.(104-105)

Mooney and Black(106) worked with various rubber samples using extrusion viscometers with cylinders of varying length and dies of various sizes. They found that the shearing stress at the wall was much higher than that obtained by rotational viscometers. Also, they noted a large amount of surface slippage.

Eccher(94) compared measurements on extruded material by use of a rheometer of the Couette type and a 2 inch extruder with discharge holes of various diameters. He found a reasonable agreement between values obtained by the two methods.

Brown and Cutler(107) extruded lead and wax using different lengths and diameters of extruder holes. They found that log of flow rate was a linear function of pressure. Also, the major part of the pressure required for extrusion was said to be that needed to force the solids into the die.

Salisbury and Higuchi(108) studied the extrusion pressure or the critical pressure at which material begins to flow on simple inorganic electrolytes, common lubricants and organic tablet ingredients. Mixtures of sodium chloride and potassium chloride, and sodium chloride and magnesium stearate were extruded. They used a metal cylinder as an extrusion cylinder with the opening at right angles to the extruding force. Also, the die opening was quite small. Under these conditions, they found that the extrusion of organic tablet ingredients except for urea and acetophenetidin, was impossible or implosion occurred.

STATEMENT OF THE PROBLEM

Because of the need for better methods of granulation for tablet making, the first purpose of this work was to investigate new methods for preparing granules of pharmaceutical materials. Extrusion was selected as one of the most promising approaches to an improved method.

The formation of granules from dry powders involves close packing of the powder particles, hence extrusion was thought to have potential value for direct compression, and it was planned to investigate this possibility. The high pressures which can be generated and the opportunity of deaerating the powders during compression were thought to be special advantages of extruders.

It was also the purpose of this project to investigate the extrusion of granules using aqueous binders. It was believed that the compression which could be achieved with an extruder might serve to produce granules of greater density and strength. Also, the use of a die of suitable size on the extruder might make possible the elimination of the size reduction step in granulation. At the same time, the granules would be of a narrower size range, and this might constitute an important advantage.

Because extrusion would be expected to give closer packing of particles than the methods now used, it was thought that non-aqueous binders might be used satisfactorily, and thus it was planned to investigate granulation by extrusion with the use of binders containing a volatile solvent. Successful granulation in such manner would make possible the use of solvents which could be evaporated quickly and thus eliminate the slow drying operation now required.

Along with these three broad areas of application, dry extrusion, extrusion with aqueous binders and extrusion with non-aqueous binders, it was planned to examine the granules obtained in an effort to learn more of the relationship between physical properties of granules and their function in tablet making.

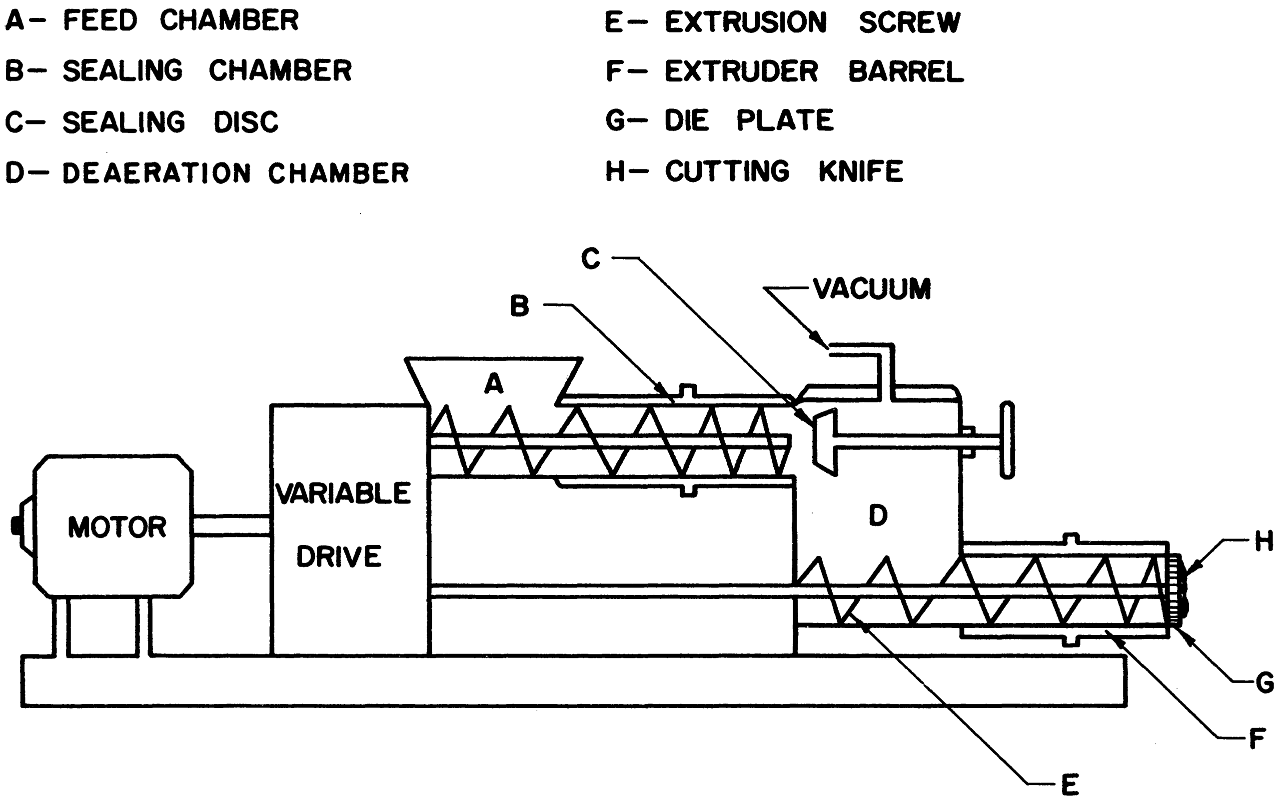
EXPERIMENTAL

Apparatus and Methods

The Bonnot Extruder

For this research an extruder was needed which was capable of handling heavy pastes and powdered solids. Also, since it seemed possible that pharmaceutical powders might be extruded directly, it was desired to have an extruder with a deaeration chamber to facilitate the packing of powders. The Bonnot machine was selected as having these qualities and yet having much versatility. A diagram of the Bonnot Extruder is shown in Figure 6, and the two types of die used with this machine are shown in Figures 7 and 8.

Operation of the Bonnot Extruder was generally carried out by beginning extrusion at low speeds, then increasing the rate if desired after extrusion through the die had begun. The material was placed in the feed chamber, A, from which it was fed through a sealing chamber, B, designed to prevent entry of air from the feeding chamber into the body of the extruder. A sealing disc, C, was used to maintain the seal and regulate flow from the feeding chamber to the extrusion chamber. The material dropped into the deaeration chamber, D, which was connected to a vacuum pump of high capacity and was then moved by the extrusion screw, E, into the extruder barrel, F, and through the die, G. The barrel was jacketed for passage of water to cool the barrel during operation. A detailed sketch of the extrusion screw is shown in Figure 9. The layer of



BONNOT EXTRUDER

Figure 6. Bonnot Extruder.

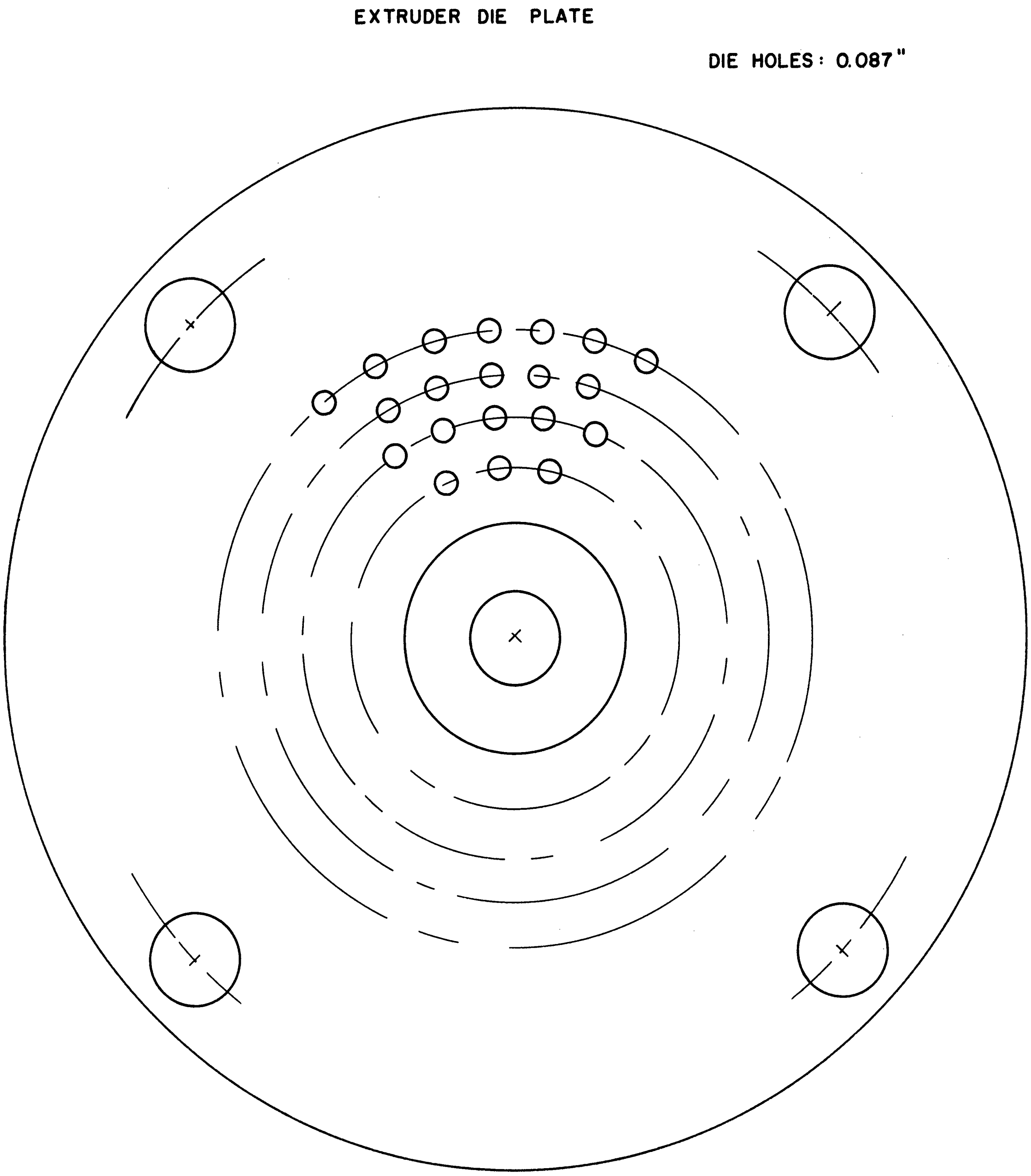


Fig. 7 Extruder Die Plate 0.087 inch.

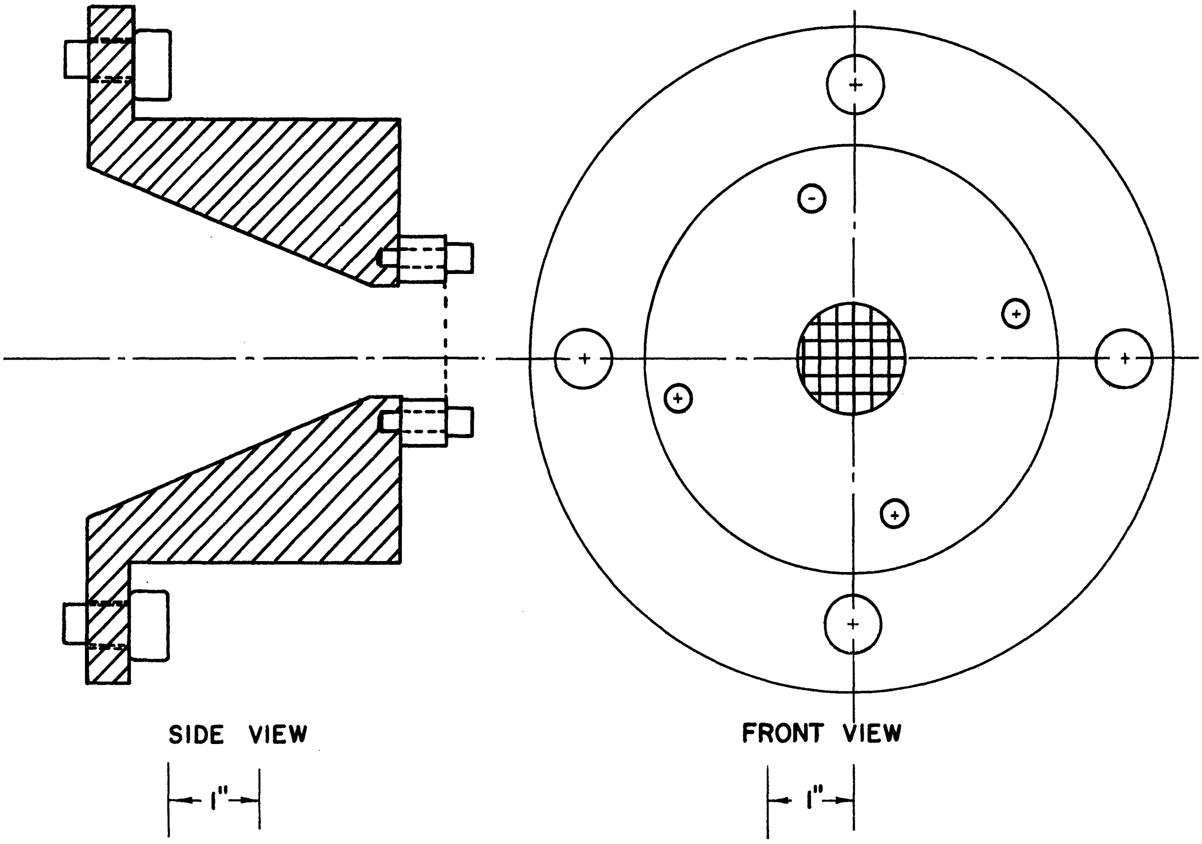


Fig.8 Conical Shape Extruder Die.

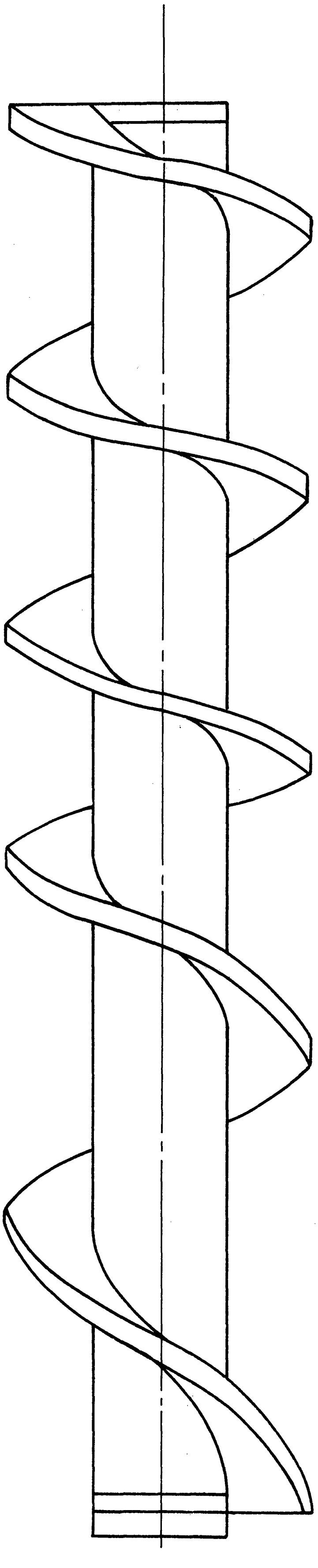


Fig. 9 Extrusion Screw.

material at the face of the die and that in the extruder barrel acted as the second seal to prevent entry of air into the deaeration chamber. The cutting knife, H, shown in detail in Figure 10, was used with the plate type of die to cut off extrusions as short pieces.

When deaeration was not required, the top of the deaeration chamber was removed, and the material to be extruded was frequently added directly to this chamber.

3/8-Inch Laboratory Extruder

This apparatus, shown in Figure 11, was constructed at the University of Michigan, Chemistry Machine Shop. Operation consisted simply of placing a weighed amount of substance in the die, inserting the punch and applying pressure until movement of the punch indicated the onset of extrusion. The powder bed was frequently compressed at a fixed pressure prior to measurement. This was done by replacing the die plate with a solid metal disc.

2-Inch Laboratory Extruder

This equipment is supplied by Loomis Engineering and Manufacturing Co. and a sketch is shown in Figure 12. By use of a die with small opening it is possible to maintain a constant pressure on the plunger over a period of several minutes. The extruder is operated on a laboratory hydraulic press. As can be seen from the sketch, the unit can be easily taken apart for cleaning.

Porosity Measurements

To determine the volume and diameters of pores contained in granules or in a tablet, an Aminco-Winslow Porosimeter (American Instrument

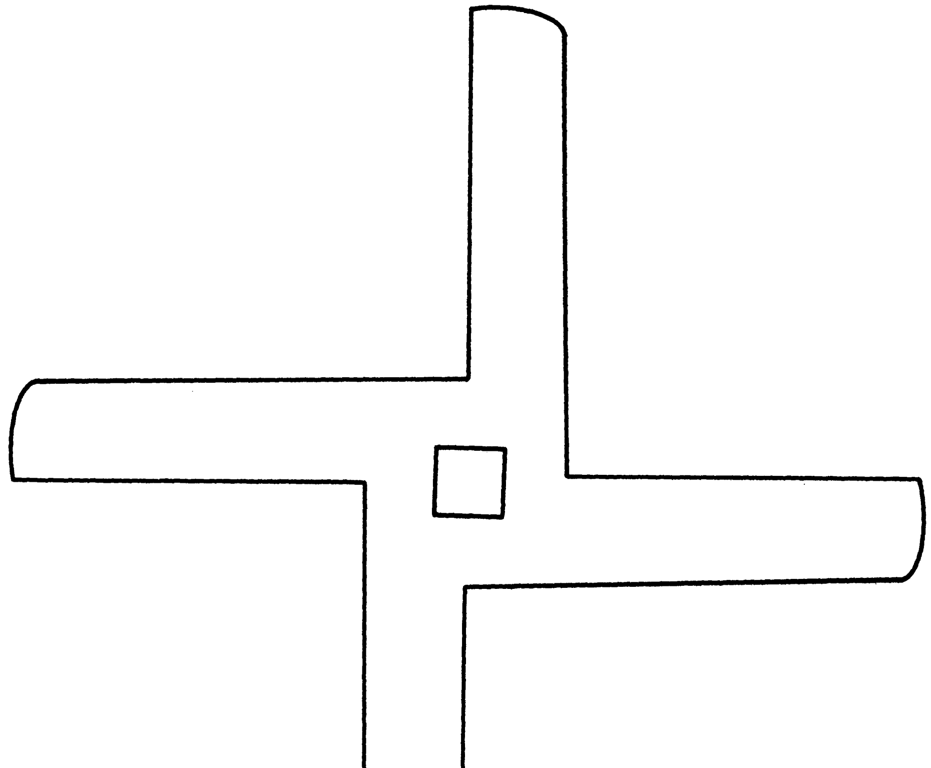


Figure 10. The Cutting Knife.

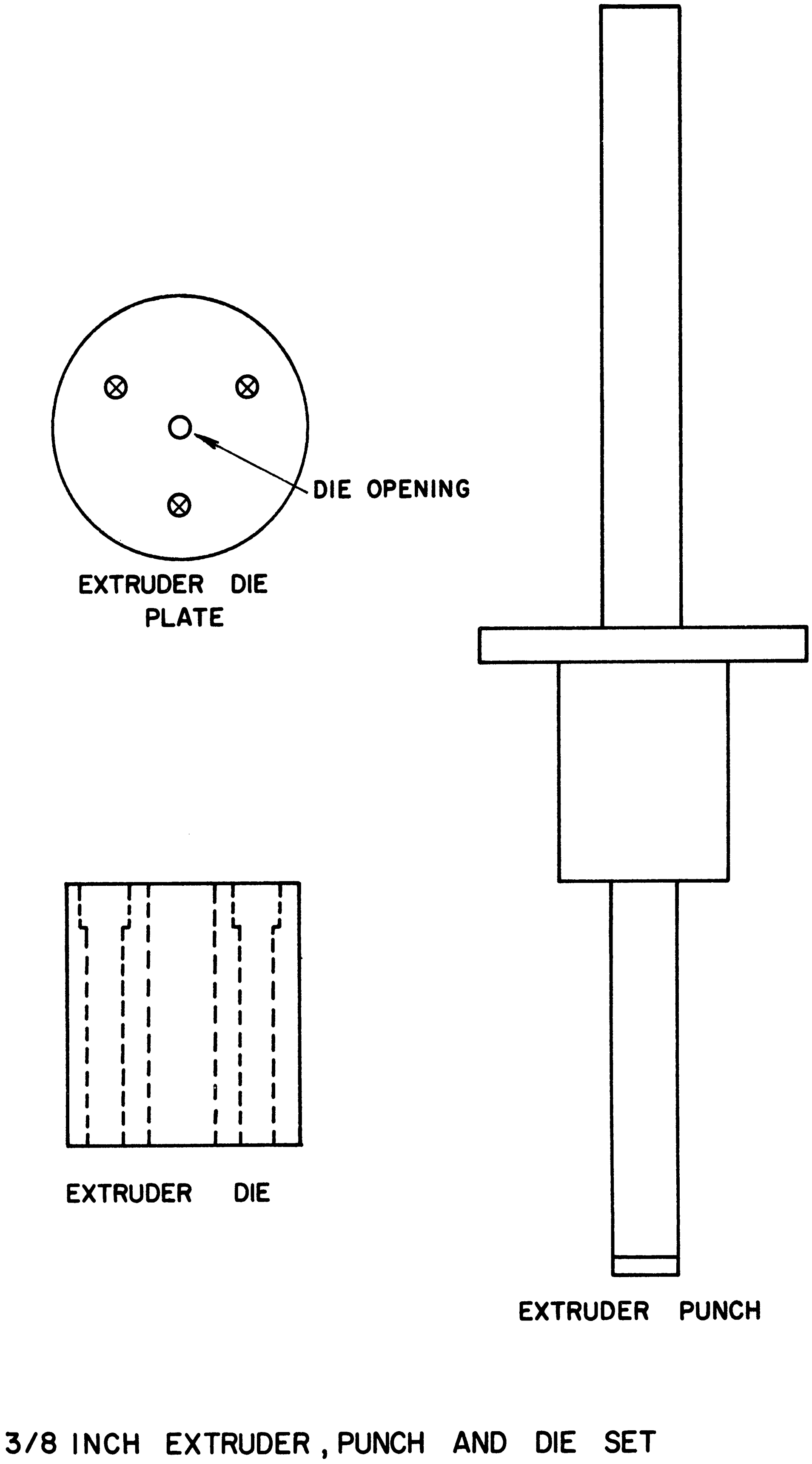
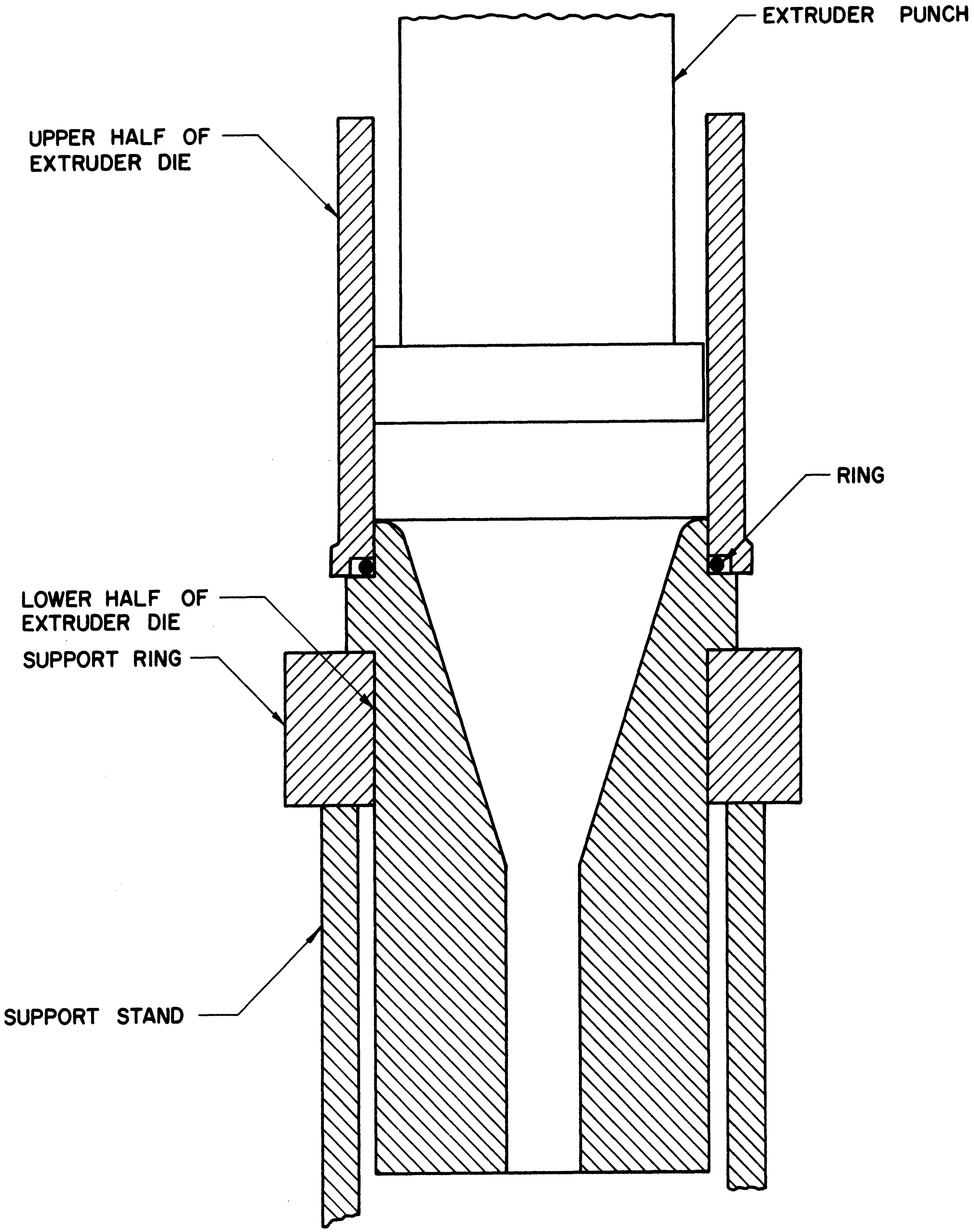


Figure 11. 3/8 Inch Laboratory Extruder.



2 INCH LABORATORY EXTRUDER

FULL SCALE

Figure 12. 2 Inch Laboratory Extruder.

Company) was used. A sketch of the penetrometer and filling device are shown in Figure 13 and a schematic diagram of the hydraulic system of the porosimeter is shown in Figure 14 .

A weighed sample of granules was placed in the chamber of the penetrometer and the ground glass disc was placed in position with a film of silicone grease to aid in sealing. The disc was held in place by means of the screw-type lock ring and an O-ring. The penetrometer was then inserted stem-down in the filling device and evacuated, the pressure in the filling device being reduced to 0.1 mm. of mercury by means of a vacuum pump. Mercury was then allowed to enter the penetrometer, the pressure against the mercury (atmospheric) in the filling device being raised to 6.3 lbs./in.^{2} The excess mercury was then removed, leaving the penetrometer stem and pores in the sample above about 100 microns filled with mercury. Pressure on the mercury was then increased gradually to atmospheric by allowing entry of air, and additional pressure was added by tilting the penetrometer step-wise until it was inverted, the entire column of mercury in the penetrometer furnishing the pressure head. At this point all the pores above about 10 microns would have been filled. To obtain higher pressures, the penetrometer was removed from the filling device and placed in the hydraulic system. Pressure was then increased by means of a hand operated piston pump, and readings were taken up to a maximum of 3,000 lb./in.^{2}, corresponding to about 0.06 micron pore diameter.

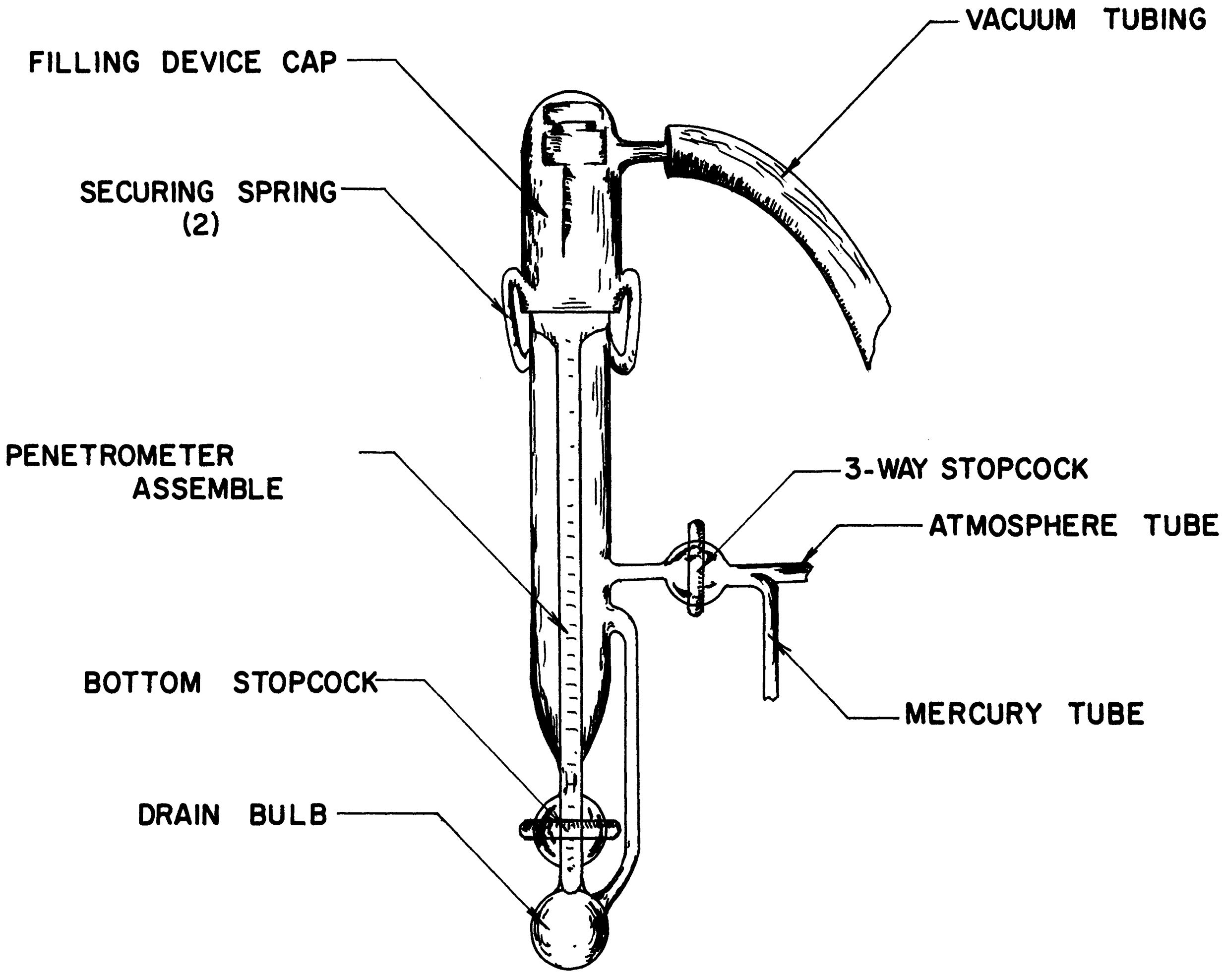


Figure 13. Sketch of the Penetrometer and Filling Device.

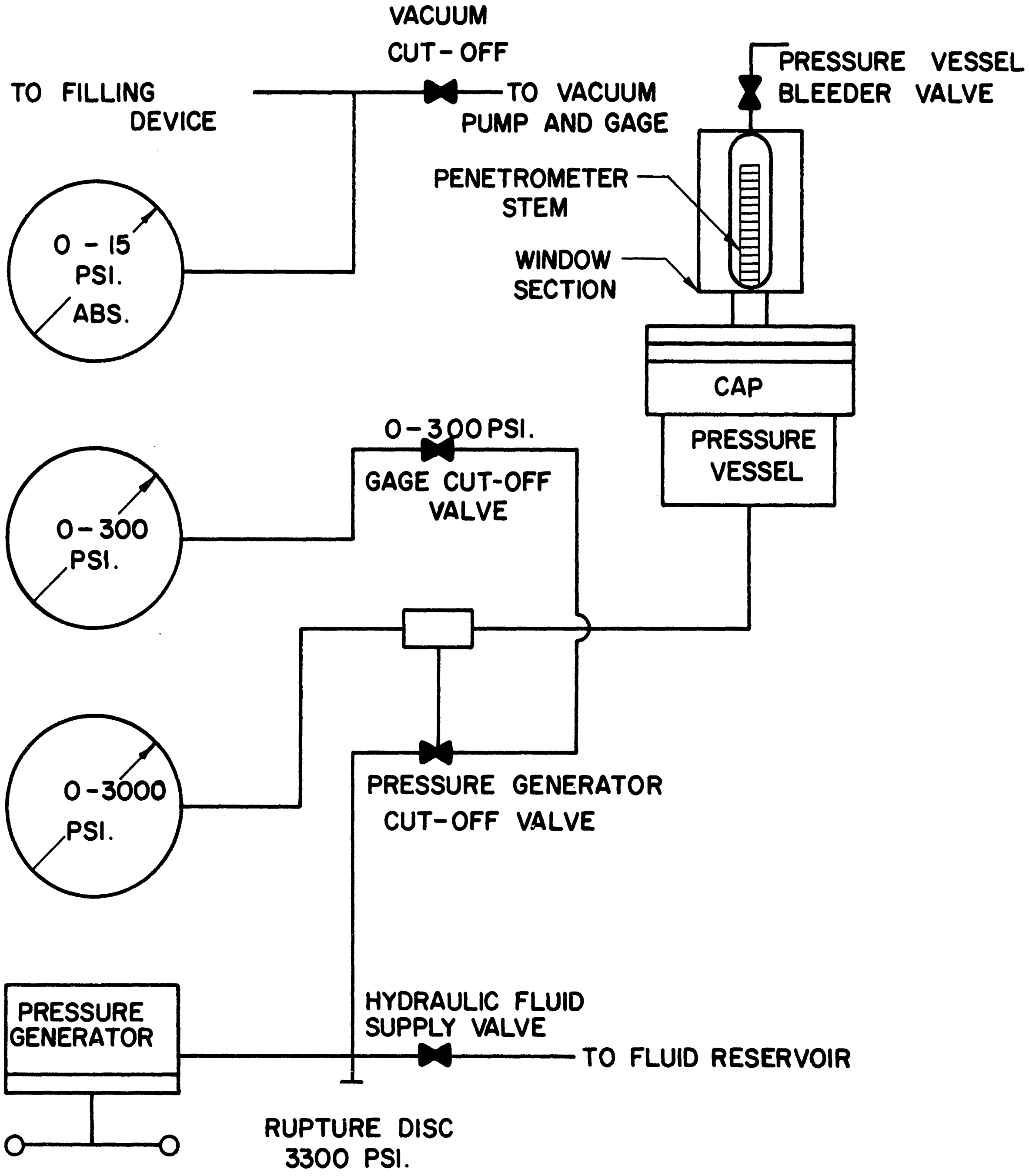


Figure 14. Diagram of the Hydraulic System of the Porosimeter.

Readings of porosity were made at any level of pressure desired simply by reading the level of mercury in the calibrated penetrometer stem. This gave cumulative volume of pores directly, and pressure divided by the factor, 175, gave the pore diameter.

Bulk Density Measurements

Measurements of bulk density were made on the apparatus described by Lowenthal(31), which dropped a 100-ml. graduated cylinder 1 cm. at a rate of 380 times per minute. A sketch of this apparatus is shown in Figure 15. Twenty-five Gm. of the material was placed in the cylinder, and the tapping continued until consecutive readings one minute apart were identical. The volume of the bed was then read on the cylinder. Duplicate readings were taken in all cases.

Friability and Capping Tests

The friability or capping of tablets was measured on the tumbling apparatus described by Lowenthal(23), a sketch of which is shown in Figure 16 . Tablets were placed in the glass cylinders which were revolved at 30 r.p.m.

When tablets had a tendency to split apart or cap the measurement was called a capping test and the time of tumbling required to cause splitting was recorded as capping time.

When tablets did not cap the measurement was called a friability test, and tablets were weighed before being placed in the cylinders and reweighed after tumbling for various periods of time. The result was expressed as loss of weight of individual tablets after tumbling for the

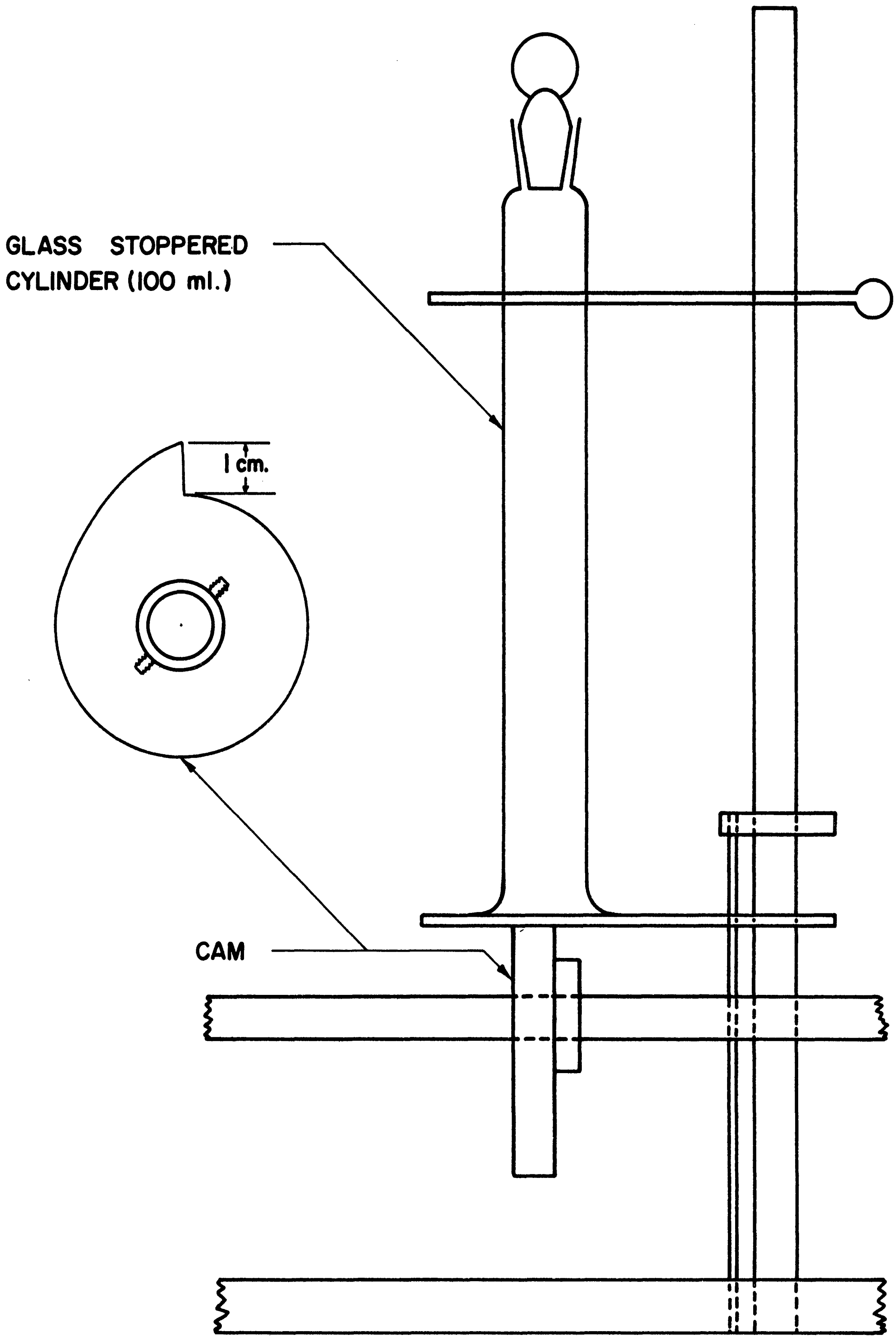
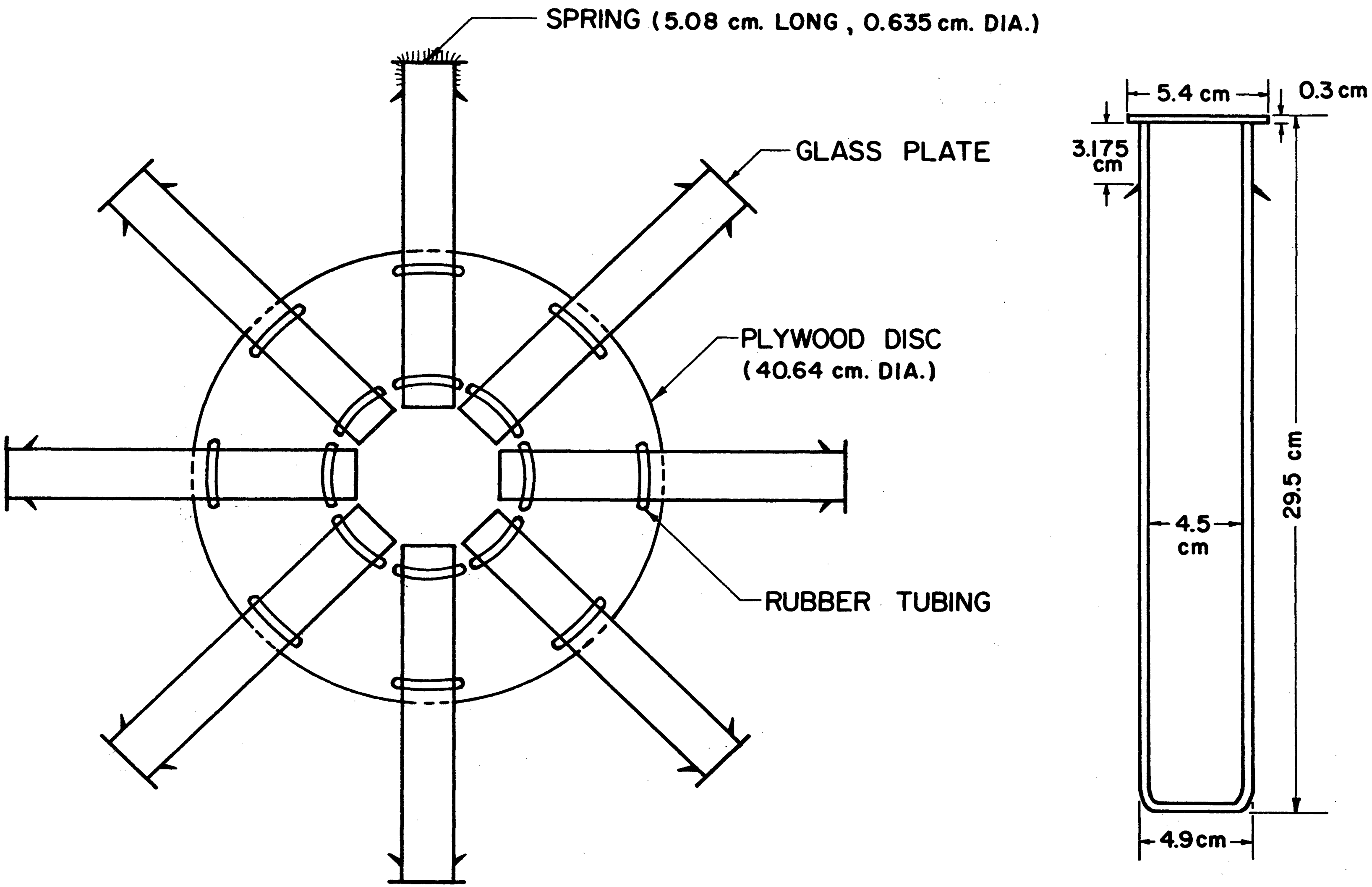


Figure 15. Tapper.



GLASS CYLINDER

DISC AND ATTACHED CYLINDERS

Figure 16. Friability Tester.

given period of time. Graphs of these values were plotted and invariably found to be adequately represented by a straight line upto weight loss of 25-30%. Typical curves of this type are shown in Figure 17. The slopes of these lines, representing average loss in weight per unit time, mg/min., were termed friability.

Size Distribution Measurements

Size distribution of granules was determined by sieving. A set of sieves of the Tyler series was selected and calibrated as suggested by Hatch.(37) Acetophenetidin granules were used as a standard. They were sieved, and the separated fractions were measured microscopically to determine their geometric mean diameter on a count basis. These values were converted to a weight basis by the equation of Hatch and assigned to the screen intervals to be applied to subsequent sieve measurements. The sieve series and calibration values are shown in Table III. For all sieving a vibratory sieve shaker (Syntron^R) was used with an amplitude setting of 50 and a sieving time of 15 minutes.

Results of a sieve analysis were obtained as percent by weight of the sample corresponding to a given geometric diameter assigned by calibration. These results were plotted as cumulative percent <u>versus</u> log size on probability paper, and the log geometric mean diameter was read as the log size corresponding to the 50% point, the standard deviation being determined as the 84.13% point minus the 50% point.

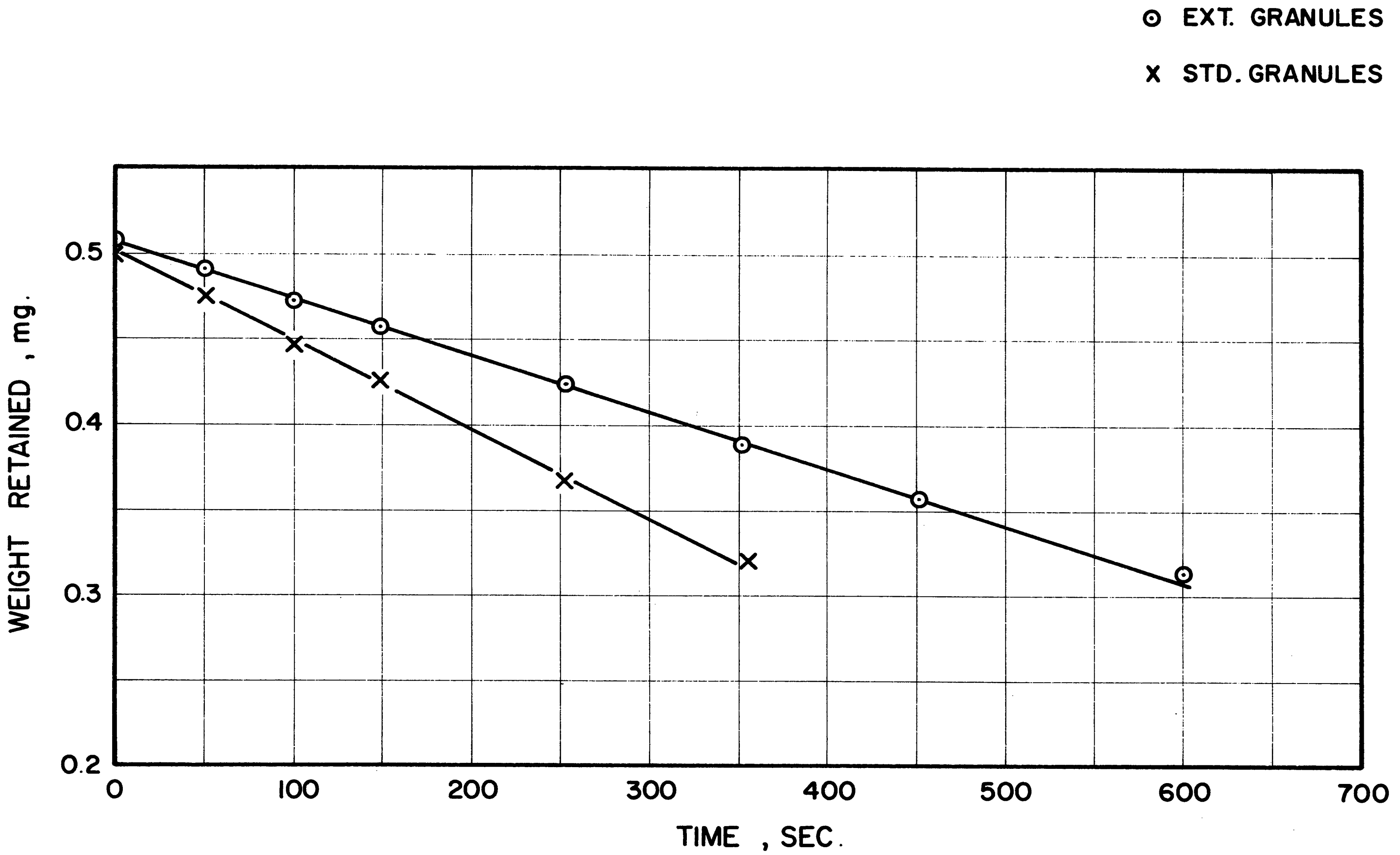


Figure 17. Typical Friability Curves of Acetophenetidin Tablets.

TABLE III

SIEVES AND CALIBRATION VALUES

Tyler Mesh Size	Size of opening microns	Calibration Values		
		Count Basis		Wt. Basis
		Geom. Dia. Microns	Stand. Dev. Microns	Geom. Dia. Microns
16	1190	..	..	..
20	840	1050	1.2	1079
30	590	768	1.2	952
40	420	543	1.2	566
50	297	410	1.2	441
70	210	279	1.3	308
100	149	205	1.2	213
140	105	136	1.3	153
200	74	100	1.3	110
270	53	58	1.4	71

Measurement of Compression Curves

Compression characteristics of granules were determined by means of compression curves. A 1/2 inch punch and die was used on a hydraulic laboratory press fitted with dial micrometers to measure the distance traveled by the punch. This press was set up in the manner described by Huffine(73) with a standpipe and low pressure gauge for reading low ranges of pressure. A diagram of the apparatus is shown in Figure 18. Results were plotted as relative volume, $\underline{V_o}$, which is the volume of the compact divided by the absolute volume of the solid, _versus_ log of pressure. This type of curve exhibits a sharp change in curvature which indicates the point at which distortion or breakage of the granules takes place and may be called a yield value. The curve then becomes linear with a constant change in $\underline{V_o}$ with $\underline{\log P}$, and the slope of this line, $\underline{d(\log P)/dV_o}$, is called the modulus of pressing.

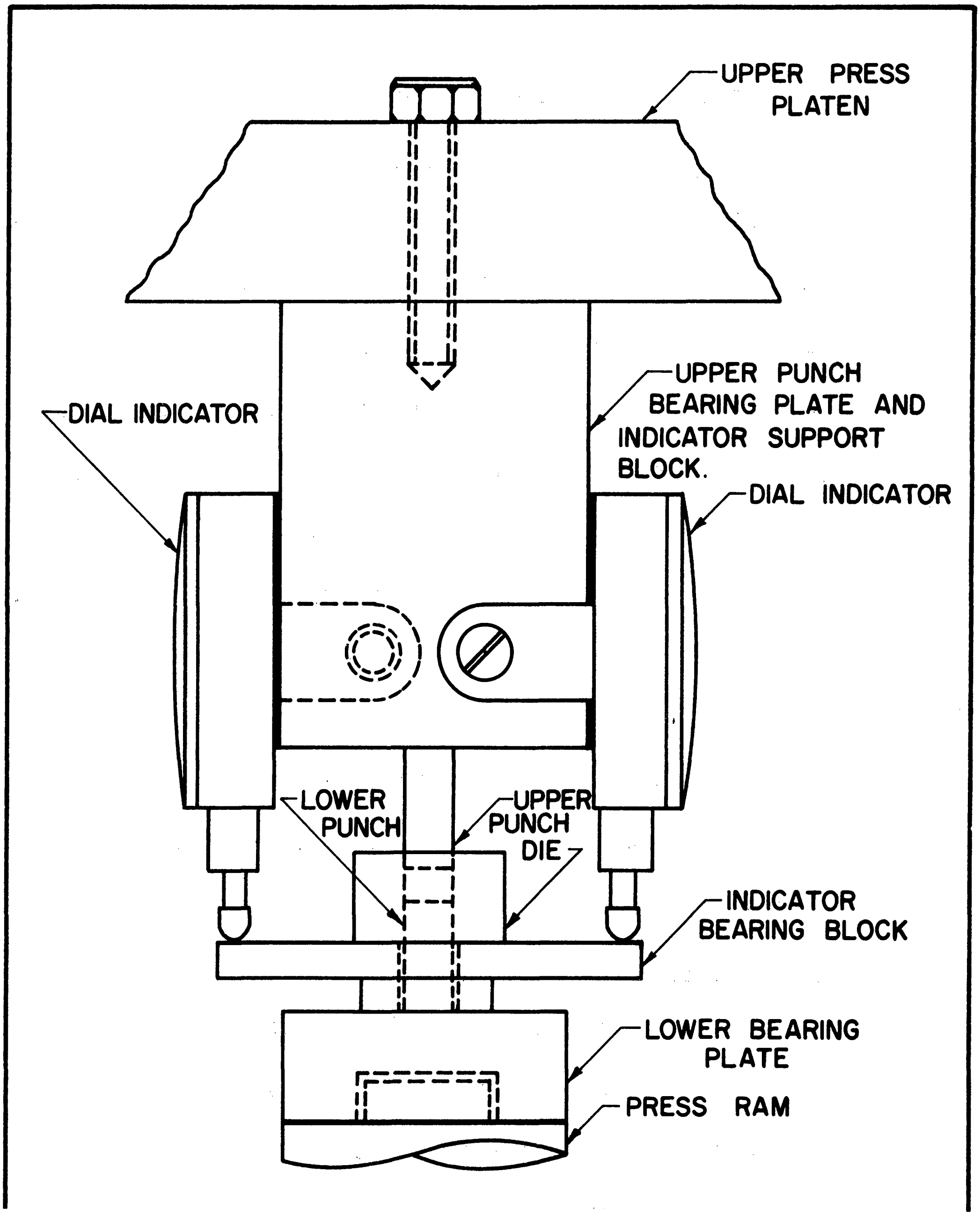


Figure 18. Assembly of Indicators Die and Punches as Used in Compression Study.

Preliminary Experiments

Attempts at Extrusion of Dry Materials

Experiments with 3/8-inch laboratory extruder

Approximately 1 Gm. of powdered material was placed in the 3/8-inch extruder with a solid plate attached. The punch was then inserted, and a pressure of 12,600 lb./in.^{2} was applied for packing. The solid plate was then replaced by one with a 0.1 in. diameter hole, and force was applied to the punch at gradually increasing pressures until extrusion was obtained.

With terra alba the pressure required for extrusion was 251,000 lb./in.^{2} and extrusion was irregular. This level of pressure was considered to be far too high to be practical.

Terra alba with 0.5% calcium stearate as a lubricant also required excessively high pressure for extrusion, little effect of the stearate being noted.

Experiments with 2-inch laboratory extruder

Dry extrusion was attempted with the 2-inch laboratory extruder with the thought that the tapered die might allow extrusion at lower pressures. About 150 Gm. of powdered material was placed in the extruder fitted with a die having an opening of 0.5 in. diameter, the punch was inserted and a solid plate was placed against the die opening. Packing was achieved by application of a pressure of 1,000 lb./in.^{2}. The extruder was then placed in the support and pressure was applied gradually up to a maximum of 7,000 lb./in.^{2}

With terra alba no extrusion was obtained at maximum pressure. It was thought that addition of a waxy substance might increase the plasticity of the powder bed, and Carbowax^R was chosen for this purpose, it being available in various viscosities and acceptable for pharmaceutical use. Carbowax^R 4000 and 6000 were mixed with terra alba in amounts representing 5, 10, 15 and 20% of the weight of terra alba, and extrusion of these mixtures was attempted. In no case was extrusion obtained.

Experiments with the Bonnot extruder

Powdered terra alba, lactose and acetophenetidin containing 2% of calcium stearate were tested in the Bonnot extruder with and without vacuum. These materials could be extruded in large rods without a die plate, although excessive heat was generated at the extruder walls. Extrusion could not be obtained with a die plate, the compacted powders being so resistant as to bend the 1/4 inch steel plates without extruding into the holes of the plates.

From these results it was concluded that extrusion of dry materials commonly used for tablet-making was impractical with the equipment available.

Investigation of Extrusion of Wetted Materials

Use of liquid absorption values

In the investigation of extrusion of wetted materials a method of estimating the amount of liquid required was needed. It was thought that liquid absorption values, as described by Bartell and Hershberger(109) might serve as a guide to the amount of liquid required, since these values represent the amount of liquid which fills the voids of a loosely-packed bed of particles, when wetted with the given liquid.

Liquid absorption values are determined by dropping the liquid from a burette on to a weighed quantity of powder contained in a flask. The powder forms into a ball which continues to absorb liquid until saturated. Saturation is detected as the first appearance of a liquid film on the wall of the flask. Results are expressed as ml. of liquid required to saturate 100 Gm. of powder. Results are generally reproducible to about 2%.

Liquid absorption values were obtained for several liquids on five different solids, and these values were then used as the maximum amounts of liquid to be used in extrusion tests.

Experiments with the 2-inch laboratory extruder

Terra alba, salicylamide, phenobarbital, sulfadiazine and acetophenetidin were selected for wet extrusion tests, and mixtures of these materials with several liquids were prepared. Amounts of liquids corresponding to their liquid absorption values and graded amounts below these levels were used.

Qualitative experiments were conducted with the aim of selecting systems worthy of more thorough study. Extrusion was evaluated on the 2-inch laboratory extruder with a 0.5 inch die and using an initial packing pressure of 1000 lb./in.^{2} Results are shown in Table IV.

These results (Table IV) demonstrated that all of the solids tested could be extruded at reasonable pressures when wetted with sufficient liquid. Further, the amount of liquid required was generally close to that predicted by the liquid absorption value.

TABLE IV

EXTRUSION OF WETTED MATERIALS ON THE 2-INCH LABORATORY EXTRUDER

Solid Material	Liquid	Liquid Absorption Value ml./100Gm.	Amount Liquid Used ml./100Gm.	Pressure Required For Extrusion lb./in.^{2}
Terra alba	Water	21.9	22	2400
			18	max.*
	Water cont. 1% Tween 80	24.2	22	1400
			18	4100
			15	max.
	Water cont. 2% Tween 80	24.1	24	1300
			20	1400
			18	2400
			15	max.
	Isopropyl alcohol	30.5	31	5200
			30	5500
			27	max.
	n-Butyl alcohol	29.6	30	1600
			26	5500
	Polyethylene glycol 300	27.2	27	5000
			22	max.
Salicylamide	Isopropyl alcohol	34.6	34	1400
			29	1400
			24	3100
			20	4600
Phenobarbital	Water	45.4	45	100
			35	3400
			28	4100
	Isopropyl alcohol	28.3	28	1400
			23	5700
			20	max.
Sulfadiazine	Water	88.8	80	300
			70	600
			60	1200
			50	1200
			40	4100

TABLE IV (CONT'D)

EXTRUSION OF WETTED MATERIALS ON THE 2-INCH LABORATORY EXTRUDER

Solid Material	Liquid	Liquid Absorption Value ml./100Gm.	Amount Liquid Used ml./100Gm.	Pressure Required For Extrusion lb./in.^{2}
	Isopropyl alcohol	....	50	1300
			40	3400
			30	max.
Acetophenetidin	Water	43.0	43	300
			30	1400
			25	3000
	Isopropyl alcohol	26.0	26	1900
			20	5000
	Water cont. 10% gelatin	40.5	40	2400
			35	max.
	Water cont. 10% gelatin and 20% sucrose	41.4	40	2200
			35	max.
	Water cont. 2% methylcellulose 1500 cps.	....	40	100
			35	1900
			30	max.

* max. indicates that no extrusion was obtained at the maximum pressure which could be applied (7000 lb./in.^{2})

Experiments with the Bonnot extruder

Calibration of a Bonnot die plate.--In order to avoid damage to the Bonnot extruder it was desired to obtain a die plate from which pressure measurements could be made, thus making it possible to halt the operation before extreme pressure levels were reached. For this purpose a die plate was made with a thickness of 1/2 in. containing 0.315 in. holes. Four strain gauges were bonded into the plate (by Polyphase Instrument Co.) as shown in Figure 19. An auxiliary jig was prepared for holding the plate during calibration and for applying pressure to the face of the die plate by means of a hydraulic laboratory press. The die plate was then subjected to varying pressure applied at its center and corresponding readings of the gauges were recorded with a strain indicator (Model SI-1, Polyphase Instrument Co.). Calibration values so obtained are shown in Table V.

TABLE V

CALIBRATION VALUES OF BONNOT DIE PLATE

Pressure lb./in.^{2}	Gauge Reading
700	2.607
1400	2.635
2100	2.661
2800	2.691
3500	2.719
4200	2.748
4900	2.780
5600	2.812
6300	2.844
7000	2.877

Extrusion of terra alba and acetophenetidin.--Terra alba with 1% stearic acid and acetophenetidin with 2% stearic acid were wetted with several proportions of water, and the mixtures were subjected to extrusion in the Bonnot machine, using the calibrated die plate. Results are shown in Table VI.

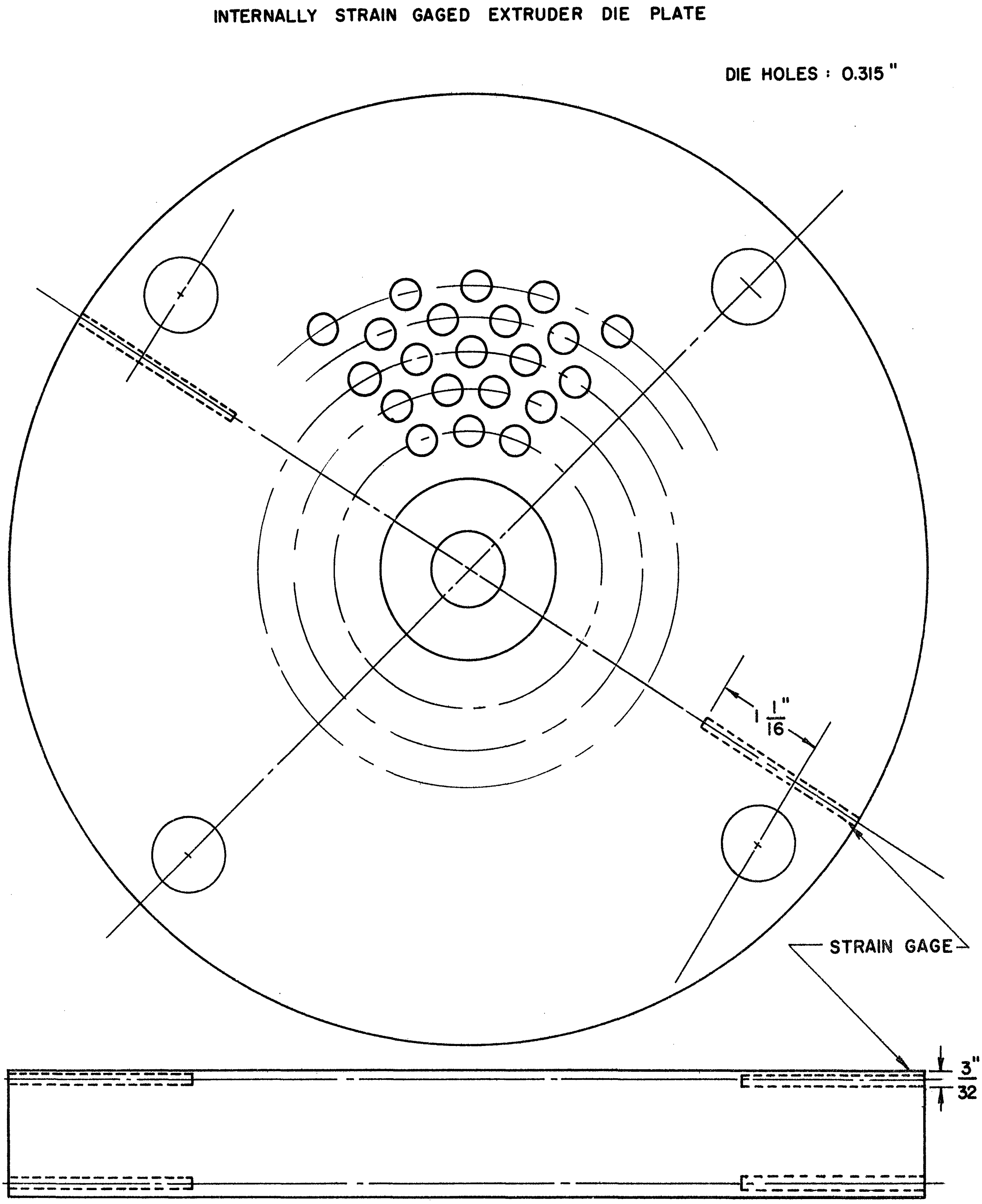


Fig. 19 Internally Strain Gaged Extruder Die Plate.

TABLE VI

EXTRUSION PRESSURES ON BONNOT EXTRUDER FOR TERRA ALBA AND ACETOPHENETIDIN, 0.315 INCH HOLES

Terra Alba with 1% Stearic Acid		Acetophenetidin with 2% Stearic Acid	
% Water	Pressure lb./in.^{2}	% Water	Pressure lb./in.^{2}
25	1100	35	1100
22	1100	32	1100
18	3300	30	2100
		25	No extr.

From the results of Table VI and visual observations made during the tests it was concluded that terra alba with 1% stearic acid and 18% water, and acetophenetidin with 2% stearic acid and 30% water were satisfactory mixtures for extrusion. A die plate was then selected with holes of 0.087 in. diameter, which approximates the size of granules required for tablet-making, and these mixtures were extruded.

The terra alba was extruded without a cutting knife on the extruder, and a portion of the wet mixture was not extruded but passed through a No. 8 screen (0.134 in.) of the oscillating granulator to represent granules which would be obtained by the usual pharmaceutical process. Both types of granules were dried at 120°F. overnight and then sized by passing through a No. 16 screen of the oscillating granulator. The final granules were fractionated on standard sieves for comparison of size distributions. Sieve analyses are shown in Table VII.

TABLE VII

SIZE DISTRIBUTION OF TERRA ALBA GRANULES PREPARED BY EXTRUSION AND STANDARD METHODS - PASSED THROUGH NO.16 SCREEN AFTER DRYING

Calibrated Geom.Diam. Microns	Cumulative Percent by Weight	
	Extruded	Standard
1079	10.8	0.7
952	27.0	2.8
566	40.1	11.8
441	46.4	18.0
308	50.8	25.0
213	54.1	32.2
153	58.8	47.1
110	70.5	64.6
<110	100.0	100.0
Mean Geom. Dia.	263	145
Std. Dev.	6.3	2.6

From Table VII it is seen that larger proportions of coarser particles were obtained with extrusion, even though both types of granules had been forced through the same screen after drying. Whether the difference in size distribution would affect compression properties of the granules was yet to be determined, however, so both types of granules were compressed into tablets. A single-punch tablet machine was used with 7/16 in. standard cup punches, and tablets were made with a weight setting of 400 mg., pressure adjustment being made to produce tablets of maximum hardness. Firm tablets were obtained in both cases with no evidence of difficulty in the compression process. From these results it was concluded that terra alba is so easily tabletted that it is not a satisfactory material for comparing different methods of granulation.

A mixture of acetophenetidin with 2% stearic acid and 30% water was prepared. A portion of the mixture was passed through a No. 8 screen of the oscillating granulator and the rest was extruded through the die plate with 0.087 in. holes. The granules were dried at 120°F. overnight, then sized through a No. 16 screen of the oscillating granulator and subjected to sieve analysis. Results are shown in Table VIII.

TABLE VIII

SIZE DISTRIBUTION OF ACETOPHENETIDIN GRANULES PREPARED BY EXTRUSION AND STANDARD METHODS - PASSED THROUGH NO. 16 SCREEN AFTER DRYING

Calibrated Geom.Diam. Microns	Cumulative Percent by Weight	
	Extruded	Standard
1079	7.7	2.7
952	27.6	12.8
566	40.0	22.3
441	49.2	28.6
308	57.4	37.6
213	61.9	43.9
153	80.7	66.6
110	94.8	91.6
< 110	100.0	100.0
Mean Geom. Dia.	380	240
Std Dev.	2.5	2.4

With acetophenetidin, as well as with terra alba, larger amounts of coarse particles were obtained by extrusion. A tabletting test was made using a single-punch press with 7/16 in. standard cup punches and a weight setting of 400 mg. With both types of granules the tablets obtained were fragile and exhibited capping. The tablets were then compared by a capping test and both gave the same average result of 8 sec. Thus, although the extruded granules appeared to be better from the standpoint of size, neither produced satisfactory tablets. Acetophenetidin is well-known as being difficult to tablet, and it was not surprising that water was not a satisfactory binder, even with extrusion.

Discussion

The preliminary experiments demonstrated that extrusion of dry solids was impractical as a general process. Further, this work showed that liquid absorption values were satisfactory as a first estimate of the amount of liquid needed for extrusion of a given solid. The tests with small extruders indicated that the 2-inch laboratory extruder could be used to predict flow properties of wet mixtures and would make possible the comparison of mixtures with the use of relatively small amounts of material. The calibrated Bonnot die plate was shown to be useful for checking the performance of a mixture on the large extruder without risking damage to the machine. Having thus tested these methods, more detailed experiments were planned to evaluate extrusion as a means of preparing granules for tablet-making.

Extrusion Rate - Pressure Relationships

It was desired to obtain a knowledge of the effect of pressure on extrusion rate which might be used as a guide to extruder operation. Further, it was thought that a meaningful evaluation of the effects of lubricants, binders and other factors would require study at various levels of pressure. An investigation was thus undertaken to determine flow properties of the wetted mixtures and the effects of added substances.

Instrument Constants for the 2-Inch Laboratory Extruder

For rate studies the 2-inch laboratory extruder was used with a 0.1 in. die opening. Since extrusion represents flow of a highly viscous material through an opening of fixed dimensions, this extruder may be treated as a capillary viscometer. It was recognized that the semisolid materials being extruded might not be Newtonian in character and that, theoretically at least, the entire mass may not be in laminar flow. Nevertheless, the errors due to assumption of laminar flow were thought to be small and have little significance in the comparisons to be made.

Since the flow of extruded material might not be linear with respect to pressure it was desired to determine the constants for the laboratory extruder which would convert units of measurement into fundamental stress and shear units. The constants for this purpose are dependent simply on the dimensions of the instrument, and definitions have been presented by Reiner.(110) A convenient expression for rate of shear, S, may be stated as follows:

$$S = 4/\pi R^3 (Q) = K_s Q,$$

where S is rate of shear, R is radius of the capillary, Q is the volume of flow per unit time and K_s may be called the shear constant. The expression for shearing stress is:

$$F = (R/2L)\ P = K_f P,$$

where F is stress, R is the radius of the capillary, L is the capillary length and P the effective pressure.

The radius and length of the laboratory extruder die opening were measured and recorded as: R = 0.127 cm., L = 3.772 cm. Pressure readings were converted from lb./in.^{2} to dynes/cm.^{2} by the factor, 68,948. The stress and shear constants for the extruder were thus:

$$K_s = 4/[\pi(0.127)^3] = 621.55 \text{ cm.}^{-3}$$

and

$$K_f = 0.127/[2(3.772)] = 0.01683 \text{ (dimensionless)}.$$

Direct multiplication of the value of K_s by the volume of flow in ml./sec. gave rate of shear in sec.$^{-1}$, and multiplication of K_f by pressure in dynes/cm.^{2} gave stress in dynes/cm.^{2} Values of stress and shear, so obtained, could be used to plot typical rheograms representing the flow properties of the materials studied.

To test the application of the equation for viscous flow through the extruder a measurement was made of the flow of glycerin through the instrument. A large glass tube (5.6 cm. diam.) was attached to the extruder die by means of plastic tape and filled with glycerin which had been previously measured with a Ubbelohde viscometer. The glycerin was then allowed to flow through the die opening and collected in a tared beaker. The quantity flowing in a given time was determined, and initial and final heights of the glycerin in the glass tube were measured with a cathetometer. The operation was conducted at a room temperature of 28.9°C., and it was thought that no significant change in temperature would occur during the time of the experiment. Triplicate runs were made and results are shown below:

	Run 1	Run 2	Run 3
Init. Ht. of Glycerin-cm.	14.17	13.32	13.97
Final Ht. of Glycerin-cm.	12.98	12.45	12.60
P-dynes/cm.^{2}	16641	15795	16285
F-dynes/cm.^{2}	280.08	265.84	274.09
Time of flow-sec.	211.6	168.3	243.2
Vol. of flow-ml.	27.810	20.626	30.687
Q-ml./sec.	0.1314	0.1225	0.1261
S-sec.$^{-1}$	81.672	76.140	78.377
Viscosity (F/S) -poises	3.429	3.491	3.497
Viscosity by Ubbelohde -poises	3.331		
Viscosity from Lit.(111) -poises	3.375		

From these results it appeared that the values of the stress and shear constants were satisfactory and that the laws for viscous flow could be applied to the extruder.

Measurement of Extrusion Rates at Fixed Pressures

For measurement of extrusion rate the solid was mixed with lubricant and binder and placed in the extruder with the 0.1 in. die attached. Before use the extruder and die were lubricated by wetting with a 1% solution of stearic acid in alcohol and allowing the alcohol to evaporate. The mixture was compacted at 350 lb./in.^{2} by application of pressure with the die pressed against a flat plate. This was done to remove air and thus prevent erratic pressure response. The extruder was then set on the stand for extrusion measurements and pressure was applied. At each point of measurement the pressure was kept constant by maintaining a downward force on the hydraulic pump, and little or no change in pressure was encountered except at extremely high rates of extrusion. No data were recorded except at levels which allowed a constant pressure reading to be maintained.

The rate of extrusion was determined by collecting the material from the die over a measured interval of time and weighing it. From the density of the mixture the volumes were calculated to obtain results in ml./sec.

Data obtained as pressure in lb./in.^{2} and flow in ml./sec. were converted into units of stress in dynes/cm.^{2} and shear in sec.$^{-1}$ by means of the instrument constants for the extruder.

Rate-Pressure Studies of Acetophenetidin, Lactose and Salicylamide with Four Different Binders

In order to select the factors having the greatest influence on flow properties of materials during extrusion as well as to determine the character of the flow curves, three powders were chosen for study, each to be mixed with four different binders. The powders were acetophenetidin, lactose and salicylamide and the binders were aqueous solutions of gelatin, 15%; methylcellulose 1500 cps., 2%; sucrose, 85% and starch paste, 10%. Extrusion with gelatin was performed at 45°C., the entire apparatus being brought to temperature in an oven and maintained at that temperature during operation by means of heating tape. The amount of binder solution was 35% by weight for acetophenetidin, 30% by weight for lactose, except for methylcellulose which was 25%, and 30% for salicylamide. These quantities of binder were selected by preliminary runs with varying quantities. The same lubricant, calcium stearate, was used in a single proportion, 0.5% by weight of the powdered solid, in all cases.

Flow data from this experiment are shown in Tables IX - XI.

TABLE IX

EXTRUSION RATE-PRESSURE DATA FOR ACETOPHENETIDIN WITH FOUR BINDERS

Rate of Shear sec.$^{-1}$

Shearing Stress dynes/cm.^{2}x10^{-4}	Binders			
	Gelatin 15%	Methyl-Cellulose 2%	Sucrose 85%	Starch Paste 10%
16.1	.....	1.298	0.925	2.256
32.2	0.106	1.402	0.795	2.296
56.3	0.110	2.082	0.900	2.969
80.4	0.154	3.498	1.161	3.563
104.0	0.458	6.870	1.112	4.004
129.0	0.482	8.820	1.249	4.927
160.0	0.918	15.488	1.251	5.885
180.0	1.034	17.330	1.229	5.921
201.0	1.244	18.935	1.210	5.588
221.0	1.949	22.319	1.210	5.283
241.0	2.256	26.982	0.884	5.290
261.0	2.360	27.703	0.893	4.856
281.0	2.809	25.174	1.048	4.363
301.0	4.263	.....	1.067	4.221
322.0	4.554	36.020	1.200	3.964
342.0	5.804	.....	1.533	3.629
362.0	7.653	44.789	1.748	2.966

TABLE X

EXTRUSION RATE-PRESSURE DATA FOR LACTOSE WITH FOUR BINDERS

	Rate of Shear sec.$^{-1}$			
Shearing Stress	Binders			
dynes/cm.^{2} x10^{-4}	Gelatin 15%	Methyl-Cellulose 2%	Sucrose 85%	Starch Paste 10%
16.1	.....	0.860	2.052	7.333
40.2	0.110	1.280	2.808	14.590
60.3	0.160	1.523	3.053	27.195
80.4	0.155	2.040	4.438	34.552
100.0	0.210	5.359	4.733	.....
120.0	0.220	8.310	4.733	35.110
141.0	0.224	8.949	3.576	.....
160.0	0.264	11.418	3.995	37.253
180.0	0.288	.....	5.278	.....
201.0	0.347	21.411	5.080	25.148
221.0	0.301	.....	.....	.....
241.0	0.273	28.488	5.303	19.236
261.0	0.201	.....	.....	.....
281.0	0.155	27.528	5.797	17.249
301.0	0.215	.....	.....	.....
322.0	0.238	29.803	5.861	13.410
342.0	0.319	.....	.....	.....
362.0	0.333	32.266	7.132	9.563

TABLE XI

EXTRUSION RATE-PRESSURE DATA FOR SALICYLAMIDE WITH FOUR BINDERS

	Rate of Shear sec.$^{-1}$			
Shearing Stress dynes/cm.^{2} x10^{-4}	Binders			
	Gelatin 15%	Methyl-Cellulose 2%	Sucrose 85%	Starch Paste 10%
20.1	0.347	0.188	0.553	2.106
40.2	2.240	0.342	0.667	2.106
60.3	2.384	0.535	0.815	3.434
80.4	3.384	0.763	0.833	3.667
100.0	4.287	1.006	1.031	4.232
120.0	5.560	1.328	1.118	4.182
141.0	6.546	2.255	1.188	4.435
160.0	7.765	4.381	1.495	4.162
180.0	8.618	5.446	1.588	3.811
201.0	6.590	6.432	1.689	3.667
221.0	6.819	8.186	1.509	3.365
241.0	5.392	8.845	1.634	3.027
261.0	4.064	9.752	1.795	.....
281.0	2.186	7.230	1.570	3.067
301.0	.....	13.003	2.794	.....
322.0	.....	14.911	2.182	2.849
342.0	.....	15.670	2.701	.....
362.0	.....	15.710	3.443	3.509

These data were plotted with shear as a function of stress for purposes of interpretation. With acetophenetidin, starch paste gave a dilatant type of flow curve at low stress, but the curve became irregular at higher stresses. This curve is shown in Figure 20. It was noted during the experiment that separation of liquid occurred at high stresses, and this would account for the irregularity of the flow curve. From these observations it was concluded that acetophenetidin-starch paste is not satisfactory for extrusion.

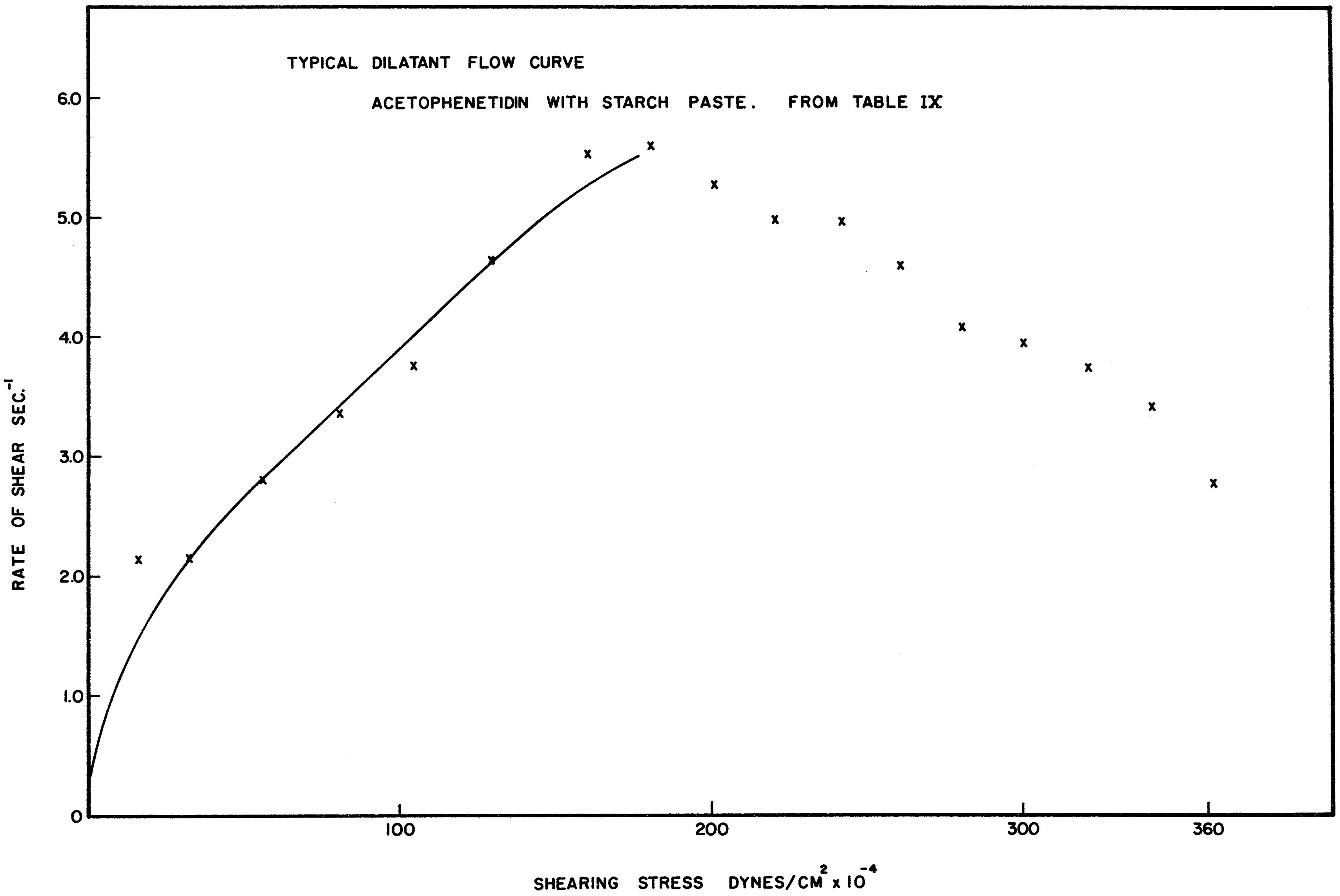


Fig. 20 Typical Dilatant Flow Curve Acetophenetidin with Starch Paste from Table IX.

Acetophenetidin with sucrose binder was found to behave in the same manner as with starch paste and was considered to be unsatisfactory.

Acetophenetidin with gelatin binder exhibited a plastic flow curve which was uniform, indicating homogeneity of the mixture. A yield value was taken from the curve by extrapolation of the linear portion to the stress axis, and a coefficient of plastic viscosity was calculated as the reciprocal of the linear portion.

Uniform plastic flow was also observed with acetophenetidin and methylcellulose binder, and constants were obtained from the curve. This flow curve is shown in Figure 21 to illustrate the general form of plastic curves obtained.

Lactose exhibited dilatant and uneven flow with starch, sucrose and gelatin, separation of liquid being observed visually in the extrusion with starch paste. With methylcellulose, lactose gave a smooth plastic flow curve.

Salicylamide also gave uneven curves with starch, sucrose and gelatin and a smooth plastic curve with methylcellulose.

Thus, the three solids exhibited essentially the same type of flow curves with a given binder, uniform flow being exhibited by all three only with methylcellulose binder. The resistance to flow of the solids may be compared by means of the yield values and plastic viscosities obtained with one binder, as is shown in Table XII.

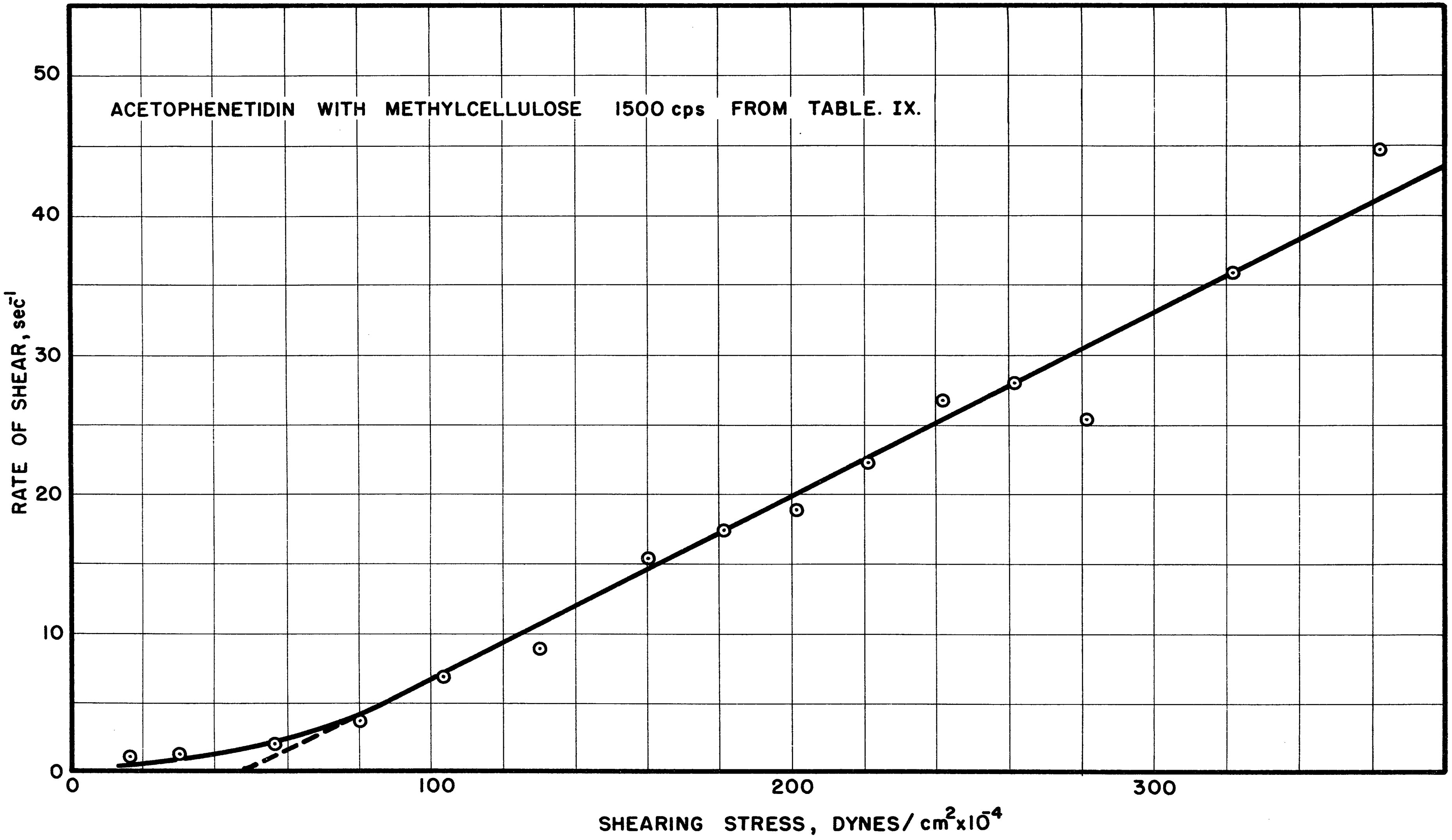


Fig. 21 Typical Plastic Flow Curve.

TABLE XII

FLOW CONSTANTS FOR ACETOPHENETIDIN, LACTOSE AND SALICYLAMIDE WITH METHYLCELLULOSE 1500 CPS.

Solid	Amount Binder %	Yield Value dynes/cm.^{2}	Plastic Viscosity Poises
Acetophenetidin	35	0.47×10^6	0.076×10^6
Lactose	25	0.65×10^6	0.071×10^6
Salicylamide	30	1.02×10^6	0.186×10^6

Effects of Varying Concentrations of Methylcellulose Binder on Extrusion of Acetophenetidin

Since methylcellulose binder gave satisfactory extrusion with all of the solids tested, it was decided to select a single solid, acetophenetidin, and evaluate the effect of change in concentration of methylcellulose binder solution and determine whether the flow properties of the mixture might be related to the viscosity of the binder solution. Since methylcellulose is available in several grades of different viscosity it was possible to use methylcellulose 400 cps., 1500 cps. and 4000 cps. and have solutions of different concentration but the same viscosity. It should be noted that viscosity of methylcellulose solutions is variable with shear and that the term viscosity in this instance is used as an apparent viscosity at the arbitrary shear rate prescribed in the U.S.P. test.

Aqueous solutions of methylcellulose of the three types were prepared as binder solutions to represent five different viscosities as shown in Table XIII . Solutions of methylcellulose 1500 cps. were prepared in concentrations of 1, 2, 3, 4, and 5%, and concentrations of types 400 and 4000 required to give the same viscosity were selected from the literature.(12)

Mixtures of acetophenetidin with $\frac{1}{2}$% calcium stearate and 35% of the appropriate binder solutions were prepared and extruded through the 2-inch laboratory extruder with 0.1 in. diameter die. Flow rates and pressures were measured in the manner previously described. Results in terms of shear and stress are shown in Tables XIV - XVI.

TABLE XIII

VISCOSITY AND CONCENTRATION OF METHYLCELLULOSE BINDERS

Viscosity Poises	Concentration - % w/w		
	Type 400	Type 1500	Type 4000
3.0	1.3	1	0.8
15.0	3.0	2	1.5
100.0	4.2	3	2.5
1400.0	6.0	4	3.5
39800.0	7.4	5	4.5

TABLE XIV

EXTRUSION RATE-PRESSURE DATA FOR ACETOPHENETIDIN WITH METHYCELLULOSE 400 CPS.

Rate of Shear sec.$^{-1}$

Shearing Stress dynes/cm.^{2} x10^{-4}	Concentration of Methylcellulose				
	1.3%	3.0%	4.2%	6.0%	7.4%
16.1	5.489	1.357	0.239	0.035	0.025
32.2	8.310	1.417	0.268	0.042	0.016
56.3	9.636	1.626	0.309	0.025	0.026
80.4	12.016	1.284	0.294	0.065	0.037
104.0	14.779	2.873	0.640	0.048	0.048
129.0	15.765	3.940	0.756	0.089	0.124
160.0	17.115	8.361	1.975	0.102	0.271
180.0	14.441	10.935	2.730	0.205	0.517
201.0	14.946	11.806	2.782	0.345	0.421
221.0	14.297	13.645	4.069	0.400	0.553
241.0	15.469	14.201	4.731	0.623	0.585
261.0	11.496	14.011	5.929	0.827	0.747
281.0	12.272	13.321	6.659	0.935	0.862
301.0	13.502	.....	8.884	1.051	1.052
322.0	11.933	15.650	10.186	1.172	1.027
342.0	10.065	......	......	1.245	1.037
362.0	8.198	17.382	11.100	1.530	1.585

TABLE XV

EXTRUSION RATE-PRESSURE DATA FOR ACETOPHENETIDIN WITH METHYLCELLULOSE 1500 CPS.

Rate of Shear sec.$^{-1}$

Shearing Stress Dynes/cm.^{2} x10^{-4}	Concentration of Methylcellulose				
	1%	2%	3%	4%	5%
16.1	13.965	1.298	.....	.....	.....
32.2	13.668	1.402	.....	.....	.....
56.3	15.381	2.082	.....	.....	.....
80.4	15.437	3.498	.....	.....	.....
104.0	16.721	6.870	.....	.....	.....
129.0	16.627	8.820	.....	.....	.....
161.0	16.141	15.488	.....	.....	0.359
180.0	15.050	17.333	0.876	.....	0.295
201.0	12.619	18.935	2.277	0.547	0.389
221.0	14.069	22.319	2.973	0.448	0.744
241.0	14.556	26.982	4.627	0.465	0.709
261.0	13.093	27.703	4.984	0.825	0.701
281.0	11.446	25.174	7.614	0.782	0.968
301.0	.....	.....	8.239	0.923	1.255
322.0	11.324	36.020	10.281	0.703	1.574
342.0	.....	.....	14.066	1.416	1.252
362.0	10.692	44.789	12.947	1.518	1.898

TABLE XVI

EXTRUSION RATE-PRESSURE DATA FOR ACETOPHENETIDIN WITH METHYLCELLULOSE 4000 CPS.

Rate of Shear sec.$^{-1}$

Shearing Stress dynes/cm.^{2} x10^{-4}	Concentration of Methylcellulose				
	0.8%	1.5%	2.5%	3.5%	4.5%
16.1	12.961	0.470	0.498	.....	0.041
32.2	13.102	0.889	0.396	.....	0.038
56.3	12.048	1.556	0.383	.....	0.064
80.4	12.320	3.356	0.412	.....	0.098
104.0	11.148	6.610	0.296	0.324	0.141
129.0	10.697	9.403	0.826	0.226	0.310
160.0	10.022	13.892	1.771	0.207	0.438
180.0	9.710	15.993	1.949	0.446	0.511
201.0	9.612	19.954	3.256	0.632	0.687
221.0	10.007	19.984	4.096	0.820	1.013
241.0	8.568	20.463	5.173	1.154	1.034
261.0	6.945	20.900	6.273	1.341	1.437
281.0	8.920	23.350	6.328	1.503	1.916
301.0	9.201	.....	7.479	1.913	2.345
322.0	10.293	26.547	7.849	2.630	2.092
342.0	9.333	.....	8.840	3.046	2.122
362.0	7.884	28.872	11.109	3.779	2.356

With the lowest concentration of each type of methylcellulose extrusion was uneven and showed separation of liquid. Above this concentration the flow was plastic, and flow curves were plotted to determine the yield values and coefficients of plastic viscosity. These constants are shown in Table XVII. From these results it appears that the binder solution must have a minimum viscosity to allow extrusion without separation. Above this minimum increase in viscosity of the binder appears to cause a general increase in plastic viscosity and yield value of the mixture. The change due to viscosity was much greater than that due to change in type of methylcellulose, and it appears that viscosity is the major factor influencing flow properties during extrusion.

TABLE XVII

YIELD VALUES AND PLASTIC VISCOSITIES OF MIXTURES
OF ACETOPHENETIDIN WITH METHYLCELLULOSE

Viscosity	Type 400		Type 1500		Type 4000	
Poises	f*x10^{-6}	U#x10^{-6}	f x10^{-6}	U x10^{-6}	f x10^{-6}	U x10^{-6}
15	0.52	0.148	0.47	0.076	0.14	0.112
100	1.26	0.208	1.62	0.157	1.36	0.221
1400	1.56	1.378	1.74	1.332	1.71	0.686
39800	1.06	1.780	1.44	1.220	1.18	0.959

* -f is yield value in dynes/cm.^{2}
\# -U is coefficient of plastic viscosity in poises

Effects of Different Lubricants on Extrusion of Acetophenetidin

Up to this point flow curves had been made using only one lubricant at a single concentration, calcium stearate at 0.5%. It was desired to determine how the flow curves might be influenced by different concentrations of calcium stearate and by other lubricants. To determine these effects acetophenetidin was mixed with 35% of a 4% solution of methylcellulose 1500 cps.. and the following lubricants: calcium stearate 0.25%, 0.5% and 1%, stearic acid 1% and 2%, talc 5% and mineral oil 3%. A control with no lubricant was also tested.

In this experiment the mixtures were prepared and passed through the 2-inch laboratory extruder with the 0.5 in. die attached in an effort to obtain uniform packing and removal of air, thus to obtain better-defined flow curves. The mixtures were then extruded through the 0.1 in. die, measurements of shear and stress being made.

Stress and shear data are shown in Tables XVIII and XIX. Flow constants obtained from the curves are shown in Table XX . The mixtures with no lubricant, stearic acid 1%, and mineral oil did not exhibit typical flow curves but showed no increase in shear with increased stress except at the lower portions of the curves; thus, flow constants could not be obtained in these cases. Failure of the control to show any even flow, indicated a need for satisfactory lubricant.

TABLE XVIII

EXTRUSION RATE-PRESSURE DATA FOR ACETOPHENETIDIN WITH METHYLCELLULOSE 1500 CPS. AND WITH DIFFERENT AMOUNTS OF CALCIUM STEARATE LUBRICANT

Rate of Shear sec.$^{-1}$

Shearing Stress dynes/cm.^{2} x10^{-4}	Amount Calcium Stearate None	0.25%	0.5%	1.0%
20.1	3.933	1.111	0.887	1.283
40.2	4.548	2.186	0.700	1.500
60.3	6.375	3.019	1.133	2.292
80.4	10.873	6.204	1.186	4.451
100.0	12.108	6.951	2.180	7.993
120.0	14.278	11.179	3.217	12.600
141.0	20.518	16.132	5.200	16.879
160.0	23.254	21.186	6.477	16.222
180.0	23.046	25.723	8.239	16.014
201.0	26.317	25.071	10.399	21.075
221.0	25.376	.....	8.747	19.327
241.0	22.549	25.424	13.572	23.511
261.0	25.697	.....	14.705	24.233
281.0	26.108	31.013	18.311	27.550
322.0	21.309	43.624	22.260	25.638
362.0	24.531	48.214	23.437	34.877

TABLE XIX

EXTRUSION RATE-PRESSURE DATA FOR ACETOPHENETIDIN WITH METHYLCELLULOSE 1500 CPS. AND WITH STEARIC ACID, TALC, AND MINERAL OIL LUBRICANTS

Rate of Shear sec.$^{-1}$

Shearing Stress dynes/cm.^{2} x10^{-4}	Stearic Acid 1.0%	Stearic Acid 2.0%	Talc 5%	Mineral Oil 3%
20.1	2.917	1.218	1.619	1.309
40.2	3.537	1.351	2.089	2.629
60.3	3.372	1.320	2.699	4.152
80.4	7.016	2.783	4.205	7.037
100.0	9.608	4.226	6.935	8.111
120.0	13.899	7.385	9.752	10.852
141.0	20.657	11.125	13.792	12.627
160.0	23.175	12.065	14.497	12.941
180.0	25.841	13.332	18.290	13.731
201.0	28.304	14.443	19.376	13.519
221.0	29.362	14.475	21.908	14.395
241.0	30.859	16.036	22.303	16.222
261.0	.....	16.260	.....	13.486
281.0	32.451	17.232	34.214	11.590
301.0	.....	21.748	.....	12.637
322.0	35.486	23.142	32.670	11.718
362.0	31.601	25.183	29.244	11.050

TABLE XX

EFFECTS OF LUBRICANTS ON EXTRUSION OF ACETOPHENETIDIN WITH 35% OF A 4% SOLUTION OF METHYLCELLULOSE 1500 CPS.

Lubricant		f dynes/cm.^{2} x10^{-6}	U Poises x10^{-6}
0.25%	Calcium stearate	0.32	0.070
0.5%	Calcium stearate	0.70	0.123
1%	Calcium stearate	0.38	0.084
2%	Stearic acid	0.40	0.120
5%	Talc	0.44	0.081

From Table XX it is seen that the change in plastic viscosity was greater with different levels of the same lubricant than with change in kind of lubricant. Thus, this experiment cannot be used as a basis for comparison of types of lubricant. Also, the plastic viscosity appeared to pass through a maximum as the concentration of calcium stearate changed from 0.25% to 1%, making it difficult to select an optimum concentration without a detailed study of different levels of lubricant. On the other hand, the fact that mineral oil and stearic acid 1% did not allow satisfactory extrusion is sufficient evidence to eliminate them as a suitable lubricants for extrusion.

The effect on the flow constants caused by a preliminary passage of the material through the extruder was quite large, as can be seen by comparison of values for mixtures containing 0.5% calcium stearate from Tables XVII and XX. This indicated that large differences might be due to uncontrolled variations in packing of the mixtures. To investigate this effect further, a mixture of acetophenetidin with 35% of a 4% solution of methylcellulose 1500 cps. and 0.5% calcium stearate was prepared and subjected to varying treatment preliminary to measurement in the laboratory extruder. One portion was passed through the 0.5 in. die three times, a second sample was extruded completely through the 0.1 in. die, and a third sample was repeatedly subjected to the range of stress prior to measurement. Results are shown in Table XXI.

TABLE XXI

VARIATIONS IN FLOW CONSTANTS DUE TO TREATMENT PRIOR TO MEASUREMENT

Treatment Before Measurement	f dynes/cm.^{2} x10^{-6}	U Poises x10^{-6}
Passed through 0.5 in. extruder 3 times	0.52	0.116
Passed through 0.1 in. extruder completely	0.60	0.097
Subjected to range of stress repeatedly	0.84	0.103

The variations in flow constants due to preliminary treatment (Table XXI) were quite large, thus, it appeared that carefully controlled treatment of the mixtures would be required for comparisons to be made.

Another experiment was planned in an effort to compare different concentrations of methylcellulose binder and effects of two lubricants, stearic acid 2% and talc 5%, on flow constants. Acetophenetidin mixtures were made with 35% of methylcellulose 1500 cps. in solutions of 2, 3 and 4%, and with the appropriate lubricant. Mixtures were made as uniform as possible by thorough mixing but were not subjected to other preliminary treatment. Each mixture was measured twice to determine the errors of measurement. Results are shown in Table XXII.

TABLE XXII

COMPARISON OF STEARIC ACID AND TALC AND THREE CONCENTRATIONS OF METHYLCELLULOSE BINDER SOLUTION

Concentration of Binder Solution %	Stearic Acid 2%				Talc 5%			
	f_1	f_2	U_1	U_2	f_1	f_2	U_1	U_2
	dynes/cm.^{2}x10^{-6}		Poises		dynes/cm.^{2}x10^{-6}		Poises	
2	0	0	0.145	0.126	0.351	0.481	0.146	0.126
3	1.340	1.320	0.068	0.067	1.779	1.717	0.172	0.147
4	1.638	1.630	0.044	0.044	2.075	2.145	0.183	0.174

From these data (Table XXII) standard errors for yield value and for plastic viscosity were found to be 0.051 and 0.011 respectively. These were used to compare means. It could thus be concluded that increasing the concentration of binder solution gave increase in yield value but no consistent change in plastic viscosity. Also, it can be stated that stearic acid 2% gave lower yield values and lower plastic viscosities than talc 5%. This indicated that stearic acid is superior as a lubricant for extrusion.

Effect of Particle Size on Extrusion of Acetophenetidin

Before applying the findings with the laboratory extruder to the Bonnot machine it was desired to know what effect size of the powder particles might have on extrusion. To investigate this acetophenetidin powder was sieved and 70/100, 100/120, 120/140, and 140/200 fractions were separated. These fractions and the original powder were mixed with 0.5% calcium stearate and 35% of a 2% solution of methylcellulose 1500 cps. and measured in the usual manner. Results are shown in Table XXIII.

TABLE XXIII

EFFECT OF PARTICLE SIZE ON EXTRUSION OF ACETOPHENETIDIN

Sieve Fraction	f dynes/cm.^{2} x10^{-6}	U Poises x10^{-6}
70/100	0.35	0.092
100/120	0.44	0.109
120/140	0.54	0.133
140/200	0.68	0.185
Orig. Powd.	0.47	0.076

From these data (Table XXIII) it was concluded that the difference due to change in particle size was small and that flow rate was greater at a given pressure with the coarser fraction and the original powder than with finer particles.

Evaluation of Granules Prepared by Extrusion

Since it was found that extrusion can be used to prepare granules of pharmaceutical substances, it became important to learn whether this process might have some advantages over the commonly used methods. Extrusion of granules prepared with aqueous binders might offer some mechanical advantages, such as requiring less handling of materials, less floor space, etc., but these might be of minor importance. The most significant gain would be some improvement in quality of granules produced. It was undertaken, therefore, to compare extruded granules with those produced by conventional methods to determine whether a difference in quality might be found. Further, it was planned to examine the physical properties of the granules in order to explain any differences which might be detected.

Comparison of Acetophenetidin Granules Made by Extrusion and Standard Process Using Starch Paste Binder

Preparation of granules

Acetophenetidin was mixed with 2% stearic acid and 30% of a 10% starch paste. A portion of the mixture was broken into granules by means of an oscillating granulator to represent granules prepared by the process in common use today (called standard process or standard granules). A No. 8 screen with 0.134 in. diameter openings was used in the granulator. The rest of the mixture was passed through the Bonnot extruder using a plate with 0.087 in. die holes and an eight-blade cutting knife. Both types of granules were dried in an oven at 120°F. overnight.

Comparison of tablets from extruded and standard granules

The dried granules, both standard and extruded, were ground to pass through a No. 12 screen by means of an oscillating granulator in order to have their size suitable for tablet-making. They were then compressed on a single-punch press with 7/16 in. standard cup punches, tablets being made at the highest pressure judged possible on the machine, the lowest pressure at which intact tablets could be obtained and at a pressure judged to be midway between the two extremes, thus furnishing six groups of tablets.

Ten tablets of each group were measured and weighed, and their densities were calculated. Capping times for the same tablets were determined. Results are shown in Table XXIV.

TABLE XXIV

DENSITY AND CAPPING TIME FOR ACETOPHENETIDIN TABLETS PREPARED FROM EXTRUDED AND STANDARD GRANULES

Averages for 10 tablets.

Compression	From extruded granules		From standard granules	
	Density Gm./ml.	Capping time sec.	Density Gm./ml.	Capping time sec.
High	1.115	24.0	1.098	8.9
Medium	1.067	93.1	1.097	8.7
Low	1.049	66.1	0.957	4.5

From the data of Table XXIV it was concluded that much firmer tablets were obtained at all degrees of compression with extruded granules. It was thought at the beginning of the experiment that a difference in density of tablets from the two types of granules would be found and that this might indicate the firmness of the compacts. As can be seen from Table XXIV, no correlation seemed to exist between density and capping time, and the tablets from extruded granules were not uniformly more dense than those from standard granules.

Comparison of physical properties of granules

Porosity of granules.--The porosity of the two types of granules was measured on the granules as obtained from the drier. Results are shown in Table XXV , and curves of cumulative pore volume *vs.* pore diameter are shown in Figure 22. From these measurements it is seen that the extruded granules were much less porous, the difference being due primarily to the presence of fewer pores of large diameter in extruded granules.

In order to eliminate any effect of size distribution of the granules on porosity values 8/12 fractions of the granules of both types were isolated by sieving and measured for porosity. The values of total porosity were 50.07 for standard granules and 26.98 for extruded, these being quite similar to the values for unsized granules. The porosity curves were similiar throughout, indicating that the size distributions had little effect on porosities.

Size distribution of granules.--The granules were subjected to sieve analysis as obtained from the dried and again after being passed through the oscillating granulator with a No. 10 screen (0.065 in. diam. openings). Data are shown in Table XXVI.

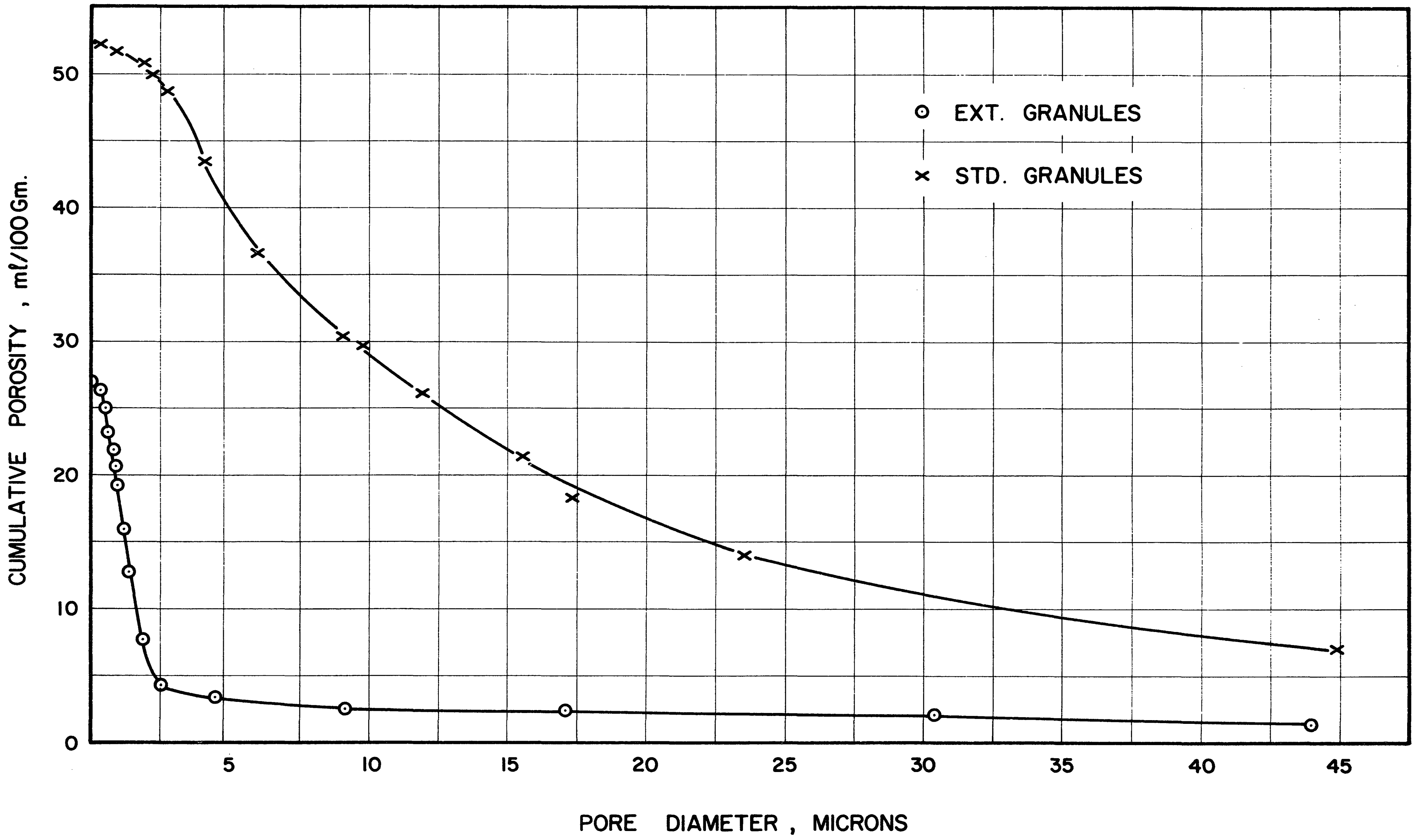


Fig. 22 Typical Porosity Curve for Granules of Acetophenetidin with Starch Paste.

TABLE XXV

POROSITY OF GRANULES OF ACETOPHENETID IN WITH STARCH PASTE

Extruded Granules		Standard Granules	
Pore Diameter Microns	Cumulative Porosity ml./100 Gm.	Pore Diameter Microns	Cumulative Porosity ml./100 Gm.
70.9	0.71	59.9	4.41
44.1	1.42	44.9	7.01
30.4	2.13	23.4	14.02
17.2	2.31	17.2	18.40
9.1	2.49	15.5	21.46
4.5	3.45	11.9	26.28
2.5	4.27	9.7	29.78
1.86	7.82	9.1	30.66
1.47	12.80	6.0	36.79
1.26	16.00	4.0	43.36
1.03	19.20	2.72	48.62
0.90	20.62	2.20	49.93
0.80	21.87	1.86	50.81
0.65	23.01	0.80	51.68
0.55	24.89	0.23	52.12
0.23	26.31	0.16	52.34
0.06	26.67	0.06	52.56

TABLE XXVI

SIZE DISTRIBUTION OF STANDARD AND EXTRUDED ACETOPHENETIDIN GRANULES PREPARED WITH STARCH PASTE

	Cumulative Percent by Weight			
Calibrated Geom. Dia.	Dried Granules		Granules Passed Through No. 10 Screen of Oscillating Granulator	
Microns	Standard	Extruded	Standard	Extruded
1892	0.7	36.5	...	...
1429	59.0	93.2	7.0	19.9
1079	73.9	96.7	34.1	62.4
952	78.3	97.4	51.9	73.4
566	79.7	97.8	61.3	78.0
441	83.0	98.1	68.1	80.7
308	84.4	98.4	72.7	82.2
213	86.3	98.7	77.7	84.1
153	88.2	99.0	81.2	85.5
110	91.0	99.2	86.9	88.1
71	94.7	99.5	92.0	93.0
< 71	100.0	100.0	100.0	100.0
Geom. Mean Diameter	1450	1780	790	1180

These results demonstrate that the extruded granules were generally much larger in size, thus that they did not break down as much when passed through the No. 10 screen.

Compression curves of granules.--Compression curves were made for standard and extruded granules which had been passed through a No. 12 screen after drying. These are shown in Figure 23 and data in Table XXVII. Curves were also made for 8/12 sized fractions and found to be essentially the same as for those not sized. Yield values and compression moduli taken from the curves are shown below:

	Standard granules	Extruded granules
Yield value -lb./in.^{2}	15,850	12,300
Modulus of pressing	5.21	3.90.

From these data the bed of extruded granules appears to yield at slightly lower pressure and to undergo more rapid change in volume for a given increment in pressure above the yield value.

Bulk density of granules.--Granules which had been passed through the No. 12 screen of the oscillating granulator were examined for bulk density. The value for standard granules was 0.444 Gm./ml., and for extruded granules was 0.547 Gm./ml.

Discussion

These measurements on granules can be used to estimate the distribution of void space within the granule bed, a long-sought goal which has not been possible before the use of the porosimeter. A summary of the calculations is shown below:

	Standard granules	Extruded granules
Internal voids	0.230	0.145
External voids	0.410	0.411
Total voids	0.640	0.556
Granule density	0.748	0.928.

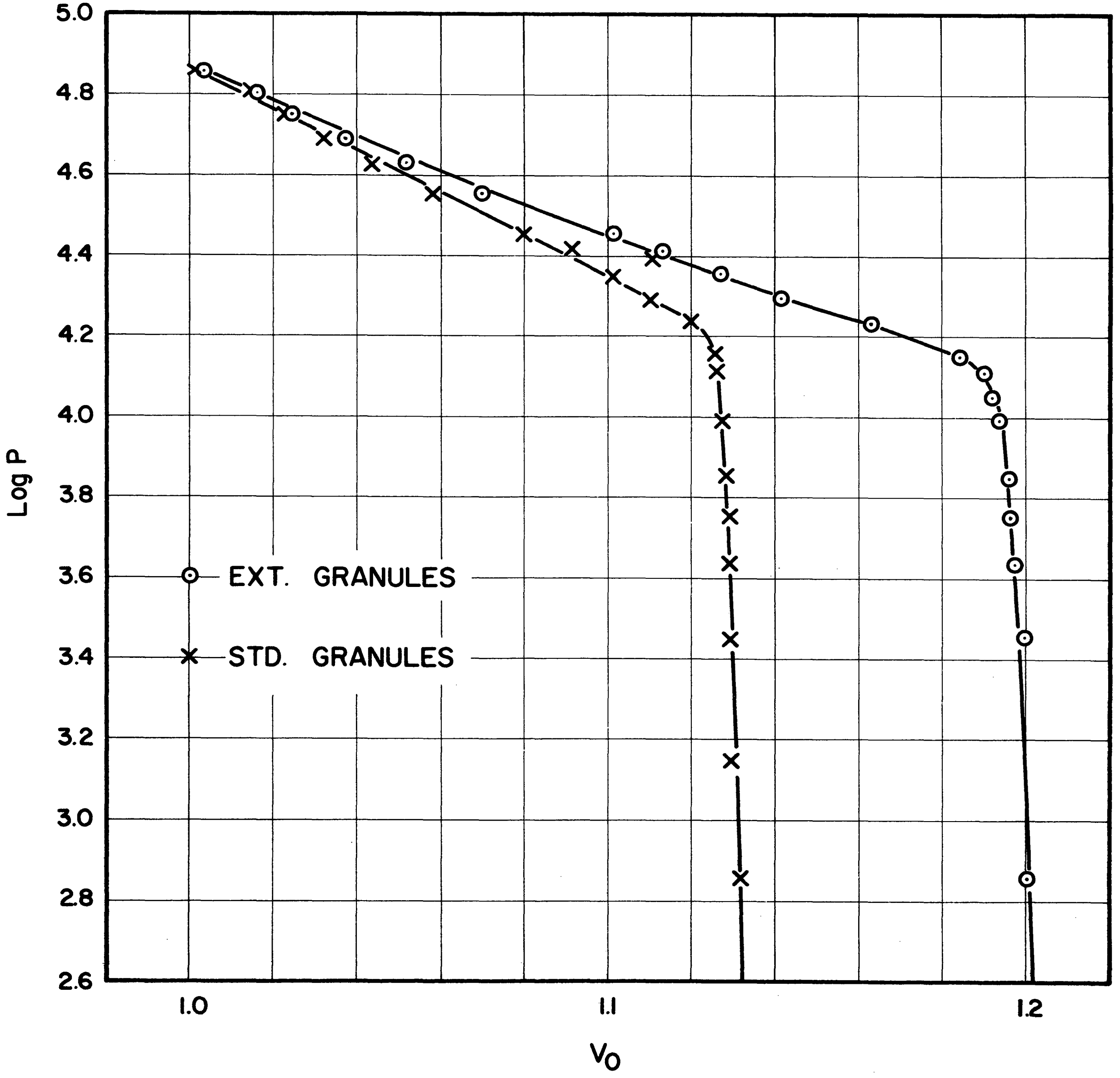


Fig. 23 Compression Curve for Acetophenetidin with Starch Paste.

TABLE XXVII

COMPRESSION CHARACTERISTICS OF ACETOPHENETIDIN GRANULES
LOG PRESSURE *VERSUS* RELATIVE VOLUME

Log p	Std. V_o	Ext. V_o
2.849	1.1326	1.1997
3.150	1.1292	1.1996
3.451	1.1290	1.1978
3.627	1.1287	1.1974
3.752	1.1296	1.1970
3.849	1.1291	1.1963
3.928	1.1289	1.1959
3.995	1.1278	1.1940
4.053	1.1271	1.1925
4.104	1.1263	1.1899
4.150	1.1248	1.1841
4.229	1.1203	1.1629
4.296	1.1110	1.1415
4.354	1.1008	1.1268
4.405	1.0906	1.1131
4.451	1.0805	1.1010
4.548	1.0585	1.0700
4.627	1.0437	1.0521
4.694	1.0316	1.0369
4.752	1.0217	1.0240
4.803	1.0137	1.0149
4.849	1.0073	1.0030

From this it is seen that the individual powder particles are brought closer together in the extrusion process. This would promote more contact between particles imparting greater strength to the wet mass and causing the formation of larger granules. The dried granules prepared by extrusion would also be stronger and would break down to a lesser degree when passed through a size-reduction screen.

Since the compression curves do not differentiate between plastic flow and fracture of granules, one cannot demonstrate from these why the stronger granules form less fragile tablets. The differences cannot be explained on the basis of the number of granule-to-granule point contacts, since the same effects are shown with sized granules. It may be speculated that the stronger granules undergo less fracture and more plastic distortion and thus form a compact with more interlocking of particles, and at the moment this appears to be the best interpretation of the data.

Evaluation of Extruded Granules Prepared with Different Binders

Previous evaluations were limited to granules prepared with only one binder, starch paste, and it was important to learn whether similar advantages would be found with extruded granules regardless of the type of binder used. An experiment was planned, therefore, to compare standard and extruded granules prepared with several types of binders. Binders selected for this study were: aqueous solutions of methylcellulose 1500 cps., 2%; acacia, 15%; starch paste, 10%; sucrose, 85% and tragacanth, 5%. All binders were used as 25% by weight of the powder mixture.

Acetophenetidin was used as the solid, being mixed with 2% of stearic acid before addition of the binder solution. The mixtures were divided into two portions, one to be passed through the No. 6 screen of the oscillating granulator, the other to be passed through the extruder. The conical die of the extruder was used with a No. 6 screen attached, thus both types of granules were passed through openings of the same size and shape. Granules were dried at 120°F. overnight, and a portion of each batch of dried granules was passed through a No. 14 screen for size reduction.

Comparison of Tablets

In order to obtain tablets made under the same conditions a hydraulic laboratory press was used. Five hundred mg. of each type of granule (passed through No. 14 screen) was compressed on a 1/2 in. die with flat-faced punches at six different pressures. Tablets were made and tested in duplicate. Friability measurements were made and are shown in Table XXVIII.

These results show that friability of tablets decreased with increased compressive force. Further, those made from extruded granules were markedly less friable when prepared at the first four pressure levels, the differences being less marked at the two highest pressures. From these data it can be said that extruded granules of acetophenetidin form less friable tablets with each of the binders used.

These data show an interesting relationship between type of binder and pressure of compression. Methylcellulose furnished less friable tablets than the other binders at all pressures, but the other binders can be compared only at specific pressures, since their relative positions changed with pressure.

Comparison of Granules

The granules passed through the No. 14 screen after drying were measured for size distribution, bulk density and compression characteristics. Since porosity measurements on granule beds containing fine particles would yield values representing internal voids and an undetermined fraction of the external voids, porosity measurements on the original dried granules were used to indicate internal voids. Results are shown in Table XXX.

From the data on Table XXIX it is seen that the particle size of extruded granules was larger in every case. Also, the extruded granules were less porous and the bulk density of extruded granules was slightly lower in each case. No uniform differences were noted in compression curves.

The distribution of voids in the granule beds was estimated, making the assumption that granules of all sizes have equal porosity, and these values are shown in Table XXX.

From these data it is seen that the friability of tablets produced from a given set of granules can be correlated with the porosity of the granules. This is illustrated in Figure 24 where friability of tablets made at 11,300 lb./in.^{2} (approximately the maximum range of the usual tablet press) *versus* porosity of the granules is plotted.

TABLE XXVIII

FRIABILITY OF TABLETS PREPARED BY STANDARD PROCESS AND EXTRUSION

Binder	Process	Compression Pressure Lbs./sq.in.					
		5650	8480	11300	14100	21200	28300
Acacia 15%	Std.	--	--	34	31	16	14
	Ext.	40	34	29	22	13	11
Methocel 2%	Std.	35	19	15	12	9	8
	Ext.	15	11	10	9	8	6
Starch 10%	Std.	--	60	47	33	20	15
	Ext.	48	32	21	17	13	11
Sucrose 85%	Std.	--	--	37	32	22	19
	Ext.	--	41	24	20	15	14
Tragac. 5%	Std.	--	67	38	38	18	17
	Ext.	48	46	30	22	15	13

TABLE XXIX

MEASUREMENTS ON GRANULES PREPARED BY STANDARD PROCESS AND EXTRUSION

Binder	Process	Mean Geom. Diam. Microns	Porosity ml./100 Gm.	Bulk Density Gm./ml.	Compression Constants	
					Yield Val. lb./in.^{2}	Pressing Modulus
Acacia 15%	Std.	371	42.6	0.642	3800	4.12
	Ext.	490	31.2	0.601	4750	4.20
Methocel 2%	Std.	380	33.4	0.617	3950	3.69
	Ext.	813	27.2	0.602	4550	3.38
Starch 10%	Std.	229	42.2	0.627	6600	4.21
	Ext.	459	32.9	0.606	3950	3.84
Sucrose 85%	Std.	269	38.9	0.676	3300	4.35
	Ext.	468	29.3	0.641	3000	3.14
Tragac. 5%	Std.	240	39.1	0.653	2850	4.30
	Ext.	479	31.4	0.629	3700	3.92

TABLE XXX

DISTRIBUTION OF VOIDS IN BEDS OF STANDARD AND EXTRUDED GRANULES

Binder	Process	Internal voids	External voids	Total voids	Granule density Gm./ml.
Methylcellulose	Std.	0.207	0.292	0.499	0.872
	Extr.	0.164	0.347	0.511	0.922
Acacia	Std.	0.273	0.206	0.479	0.808
	Extr.	0.188	0.324	0.512	0.889
Starch	Std.	0.264	0.227	0.491	0.811
	Extr.	0.200	0.308	0.508	0.876
Sucrose	Std.	0.263	0.188	0.451	0.836
	Extr.	0.188	0.292	0.480	0.905
Tragacanth	Std.	0.256	0.214	0.470	0.831
	Extr.	0.198	0.292	0.490	0.888

These data also show that extrusion produces granules of lower porosity regardless of the binder used. It should be noted that the results of this experiment are not identical with the previous one using starch paste binder, and this is hardly to be expected, since a different extruder die and oscillating granulator screen were used in preparation of the granules and a different quantity of binder was used.

The different binders may be compared on the basis of porosity. Methylcellulose gave granules of lowest porosity, sucrose and acacia were next (for extruded granules), and starch paste and tragacanth gave granules of highest porosity.

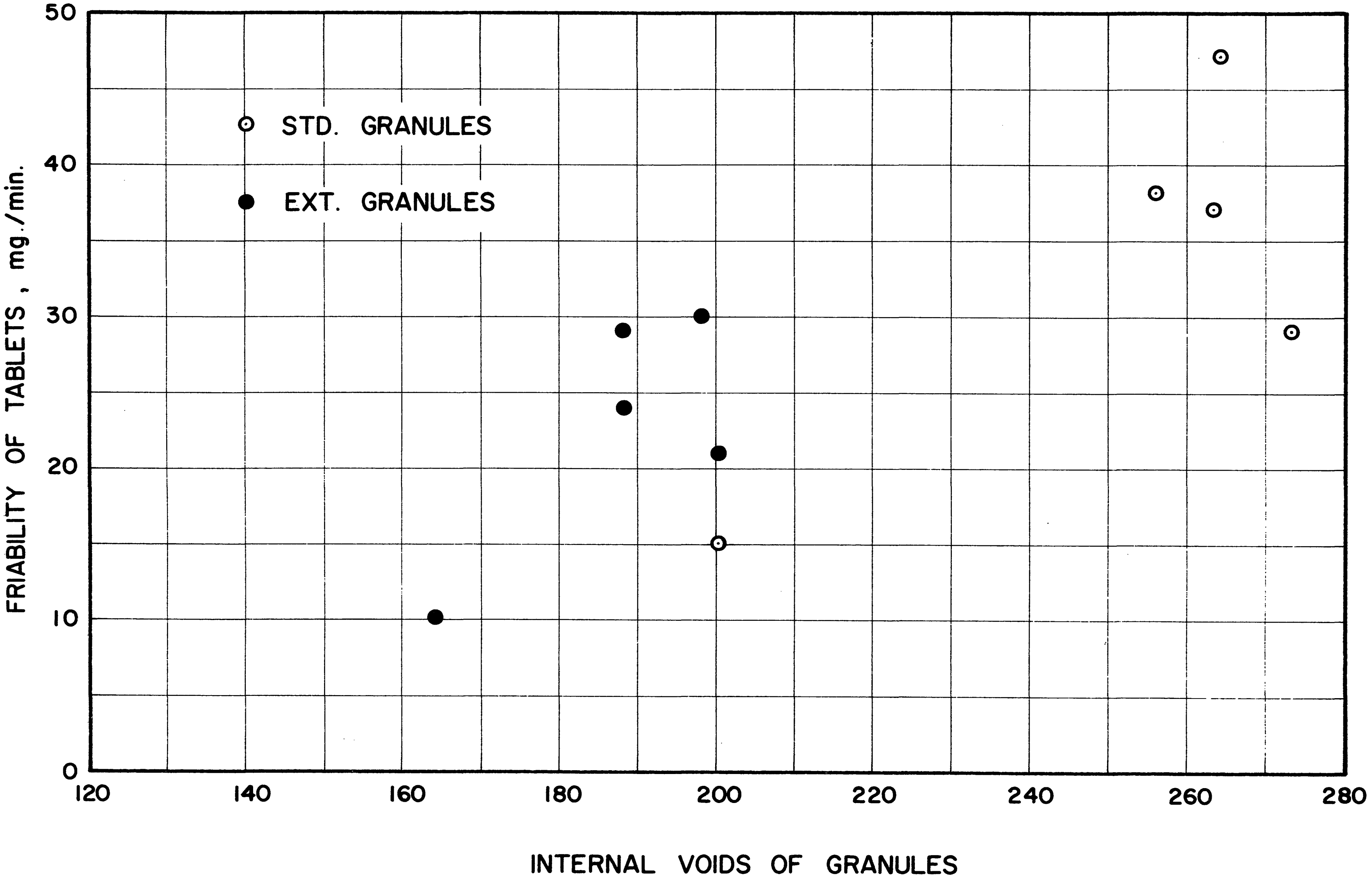


Figure 24. Relationship Between Internal Voids of Granules and Friability.

Extrusion with Non-aqueous Binders

It was believed that an important advantage in the preparation of granules might be gained if a binder solution could be used which would contain a volatile solvent instead of water. Experiments were planned, therefore, to determine if a non-aqueous solution might be found which would yield granules suitable for tablet-making.

Selection of a Binder

Although preliminary experiments with the laboratory extruder had indicated that isopropyl alcohol did not perform well as a binder for extrusion, this solvent was tested with acetophenetidin and lactose in the Bonnot machine. In both cases extrusion could be achieved but the granules were so soft as to be obviously unsatisfactory. Methylene chloride was also tested with acetophenetidin and lactose and found to yield soft granules.

Methylcellulose 60-HG, being relatively soluble in organic solvents, was evaluated as a binder in methylene chloride solution. It was tested in 2.2% solution with acetophenetidin and lactose but gave poor extrusion. Believing that a higher concentration of methylcellulose might improve the flow properties, propylene glycol was added to increase the solubility of methylcellulose 60-HG in methylene chloride. The amount of propylene glycol needed to insure solution of 5 Gm. of methylcellulose in 100 ml. of methylene chloride was determined, and the following formula for binder solution was evolved: methylcellulose 60-HG, 3.4% w/w; propylene glycol 4.8% w/w; methylene chloride, 91.8% w/w. In preliminary tests this binder was found to yield mixtures which could be extruded readily, and it was selected for further study.

Preparation of Granules

Acetophenetidin was mixed with 2% stearic acid and 25% of methylcellulose-methylene chloride binder, and the mixture was extruded in the Bonnot machine, using a die plate with 0.087 inch holes. The granules obtained were compressed into tablets without reduction of size. The tablets were firm but were observed to stick to the punches of the press. Addition of 2% talc to the granules eliminated this difficulty. It was thought that stearic acid might be the cause of the sticking, and calcium stearate was selected as the lubricant for subsequent tests. The formula with calcium stearate was found to yield satisfactory tablets, but additional lubricant (0.5%) had to be added to the granules just prior to compression.

The granules obtained with the 0.087 inch die holes were judged to be a bit too large for most sizes of tablets, and it was conceivable that if smaller die holes were used along with a suitable cutting knife no size reduction of granules would be needed and the material might be ready for tabletting as received from the extruder. This had not been possible with aqueous binder, since the mixtures had to be so wet with binder solution in order to be extruded through the small holes that the granules would coalesce on emergence from the die plate. With non-aqueous binder the solvent evaporated so rapidly that coalescence did not occur. Consequently, a die plate with 0.062 inch holes was used in subsequent tests. To facilitate extrusion through holes of this size a 4-bladed knife was mounted on the extruder worm at the inside face of the die plate. A 4-bladed cutting knife was used on the outside of the plate. Unfortunately, the cutting knife speed was not great enough and the granules were too long to be suitable for direct tabletting. Thus, they still had to be passed through a size-reduction screen to break them into suitable lengths.

The amount of binder solution to be used with a solid was arbitrarily limited to 30% as a maximum for fear that more propylene glycol would make the granules sticky. When more liquid was needed for extrusion the balance was added as methylene chloride.

Five materials were selected for test. Wet mixes were divided into two portions, one being passed through a No. 8 screen of the oscillating granulator, the other being extruded. Portions of the granules were reduced in size by means of a No. 14 screen of the oscillating granulator. The formulas for the granulations are shown in Table XXXI.

TABLE XXXI

FORMULAS FOR GRANULATIONS WITH NON-AQUEOUS BINDERS

Solid	Amt. Binder %w/w	Amt. Methylene chloride %w/w
Acetophenetidin with 0.5% calcium stearate	30	7.5
Lactose with 0.5% calcium stearate	30	15.0
Sodium p-aminosalicylate with 0.5% calcium stearate	30	15.0
Sodium bicarbonate with 0.5% calcium stearate	30	7.5
Sodium salicylate with 0.5% calcium stearate	30	15.0

Comparison of Tablets

To obtain tablets for comparison from the granules prepared with non-aqueous binder it was decided to compress the granules on the hydraulic laboratory press at a pressure of 11,300 lb./in.^{2}, this being estimated as the maximum of most commercial tablet presses. Tablets were formed on a 1/2 in. die with flat-faced punches from 500 mg. of granules which had been passed through a No. 14 screen. The tablets were then tested for friability. Results are shown in Table XXXII.

TABLE XXXII

FRIABILITY OF TABLETS FROM STANDARD AND EXTRUDED GRANULES MADE WITH NON-AQUEOUS BINDER

Material	Process	Friability mg./min.
Acetophenetidin	Std.	25
	Extr.	16
Lactose	Std.	14
	Extr.	10
Sodium bicarbonate	Std.	36
	Extr.	24
Sodium p-amino salicylate	Std.	14
	Extr.	10
Sodium salicylate	Std.	26
	Extr.	16

From these results it is seen that extruded granules yielded less fragile tablets in every instance.

Comparison of Granules

The granules obtained with non-aqueous binder were tested for size distribution, porosity and bulk density. The coarse granules were used for porosity measurement, and those which had been passed through a No. 14 screen were used for size distribution and bulk density measurements. Results are shown in Tables XXXIII and XXXIV.

TABLE XXXIII

VOIDS OF EXTRUDED AND STANDARD GRANULES PREPARED WITH NON-AQUEOUS BINDER

Material	Process	Bulk Density Gm./ml.	Total Porosity ml./100Gm.	Void Fractions		
				Internal	External	Total
Acetophenetidin	Std.	0.500	45.2	0.226	0.368	0.594
	Extr.	0.588	28.8	0.169	0.354	0.523
Lactose	Std.	0.611	47.0	0.287	0.312	0.599
	Extr.	0.735	24.1	0.177	0.342	0.519
Sodium bicarbonate	Std.	0.781	44.3	0.346	0.296	0.642
	Extr.	0.862	31.8	0.274	0.331	0.605
Sodium p-amino salicylate	Std.	0.543	49.7	0.270	0.239	0.509
	Extr.	0.641	33.1	0.212	0.208	0.420
Sodium salicylate	Std.	0.602	47.4	0.285	0.233	0.518
	Extr.	0.731	31.2	0.228	0.186	0.414

These data show that extruded granules were less porous in every instance, indicating greater strength of granules. Also, as would be expected, the extruded granules broke down to a lesser extent on size reduction yielding granules with larger mean diameters.

Discussion

From the work done with the non-aqueous binder it can be concluded that satisfactory granules for tablet-making can be made by extrusion using a binder which contains no water but an organic solvent

TABLE XXXIV

SIZE DISTRIBUTION OF EXTRUDED AND STANDARD GRANULES PREPARED WITH NON-AQUEOUS BINDER

Calibrated Geom. Diam. Microns	Cumulative Percentage by Weight									
	Acetophenetidin		Lactose		Sodium Bicarbonate		Sodium p-amino Salicylate		Sodium Salicylate	
	Std.	Ext.	Std.	Ext.	Std.	Ext.	Std.	Ext.	Std.	Ext.
1079	18.9	38.3	5.8	22.2	7.3	30.0	7.8	16.9	13.2	18.4
952	44.0	63.0	7.9	48.5	21.0	54.0	24.4	42.7	34.4	40.9
566	62.3	74.0	32.2	59.4	36.8	63.2	40.6	67.5	50.3	53.9
441	72.9	79.5	45.4	65.0	49.0	68.2	56.8	76.1	61.6	63.5
308	81.0	84.0	59.4	70.3	60.7	72.3	69.4	83.5	70.7	73.3
213	86.2	87.0	72.2	73.6	69.8	75.7	79.1	88.0	77.3	78.4
153	90.5	90.0	87.3	80.6	81.5	80.8	86.0	92.4	82.8	84.3
110	92.6	93.6	94.5	85.7	90.5	83.7	91.8	97.9	87.2	89.2
71	97.2	97.0	98.2	92.4	96.4	92.2	95.8	99.0	93.3	94.0
< 71	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Mean Geom. Diameter	630	870	360	590	360	790	460	720	500	560
Std. Deviation	1.9	2.2	2.1	3.9	2.4	5.9	2.6	2.6	3.1	3.4

which can be removed rapidly. The process appears to be quite practical, and extrusion with the non-aqueous binder is more easily conducted than with the aqueous binders tested. In several cases the standard process using the non-aqueous binder produced tablets with satisfactory qualities, but generally the friability was markedly reduced by the use of granules prepared by extrusion.

PRACTICAL APPLICATIONS OF THIS RESEARCH

The use of extrusion for preparation of tablet granulations has been shown to be useful in producing granules of less porosity which, in turn, yield less friable tablets. Also, the use of a non-aqueous binder has been shown to produce satisfactory granulations. Non-aqueous extrusion is of particular interest to the pharmaceutical industry, since it offers an opportunity to eliminate the costly step of drying now present in the commercial process. Further, it makes possible the preparation of granules of water-sensitive materials such as vitamins and antibiotics which cannot be granulated with the usual binders. Yet another advantage is gained, that of having granules properly sized as they emerge from the extruder, and in this way the extruder fits well into a continuous and automatic tablet-making process.

As a result of the work reported in this thesis, pharmaceutical manufacturers are examining multivitamin formulas prepared by extrusion for chemical stability and a manufacturer of pharmaceutical machinery is planning the development of a machine specifically designed for extrusion of pharmaceuticals.

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