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The Interrelationship of Bulk Density, Granule Density, Tablet Weight, and Weight Variation

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THE INTERRELATIONSHIP OF BULK DENSITY,

GRANULE DENSITY, TABLET WEIGHT,

AND WEIGHT VARIATION

BY

AMRITKUMAR BHANDARI

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE

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ABSTRACT

The effects of granule density and bulk density on tablet weight, weight variation, and tablet density were determined for tablets compressed on a Colton Model 216, rotary tablet press. Hardness, thickness, and disintegration times were also determined for the tablets produced. Standardized granulations were made from lactose and mixtures of lactose and bismuth subcarbonate, with gelatin as a binder. Granule density and bulk density of the granulations were varied by changing the concentrations of bismuth subcarbonate in the formula. All tablets were made at a fixed rate of tableting using standardized settings of the fill, pressure, and overload adjustments. The inter-relationship between granule density and bulk density was found to be almost linear, as was also the relationship between granule density, bulk density, and tablet weight.

MASTER OF SCIENCE THESIS

OF

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INTRODUCTION

The compressed tablet has become one of the most widely accepted dosage forms for the administration of orally effective therapeutic agents. It provides a convenient and, if well made, an efficient form of solid dosage for oral administration. The advantages of this type of pharmaceutical preparation are well known and include accuracy of dose, economy, stability, portability, concentration, elegance, and convenience in dispensing and shipping.

The invention of compressed tablets is usually attributed to Brackedon, who in 1843 obtained an English patent on a simple device for compressing dry powders. By 1874 tablets for almost every known disease were being sold on European and American markets. At one time the preparation of tablets was based more on empirical considerations than on sound scientific principles. In recent years, however, there has been a trend to move from the 'art' in making tablets toward the science of tableting.

Tablets first became official in the 9th revision of the United States Pharmacopeia, 1926, and have been official in each succeeding revision.

The National Formulary has included an increasing

number of tablets since their introduction into NF V in 1926.

Both the United States Pharmacopeia and National Formulary set certain standards for the tablets listed therein, including:

      (1) Identity and purity of active ingredients

      (2) Quantitative limits for the active ingredients

      (3) Limits on disintegration time

      (4) Limits on weight variation.

Of these four standards for good tablets, the first two are mainly applicable to the purity and physical-chemical standards of the ingredients to be used for the required therapeutic action from the tablets. The standards for disintegration time limits and those for the variation in the weight of tablets are of great importance in the formulation and compression of granules in the preparation of tablets as dosage forms.

Most materials can not be made into tablets directly, but must be granulated; that is, they must be made into granules before they can be successfully compressed. The characteristics of the granulation such as granule size, bulk density, granule density, and porosity all have a direct effect on the tablets produced.

The qualities of the finished tablets are influenced by the physical and chemical properties of the granulations,

which, in turn, depend upon the physical properties of the ingredients used to make them. These properties, e. g. density, will most likely not be the same for each ingredient being used; and the density of granules prepared from such a variety of ingredients will not be the same for different types of tablet formulations. Therefore, overall granule density of different tablet formulations will change from one to another, and these variations should have some measurable effect on the weight of tablets produced. In addition, the bulk density is related to granule density; therefore, if granule density will vary from one granulation to another, the bulk density will also vary.

The character or qualities of granules are influenced not only by the materials going into the granulation but also by the technique of manufacture of the granulation. A granulation made largely from bismuth subcarbonate (density 6.86 gm/cc) is likely to have a higher bulk density and higher granule density than one containing largely calcium carbonate (density 2.92 gm/cc). In addition, a granulation with a wide range of granule sizes and a large proportion of "fines" is likely to have a higher bulk density than a granulation with a narrow granule size distribution.

Since, during the compression of a particular granulation, the weight of a tablet is adjusted by varying the volume of the die cavity, the packing characteristics of a

granulation are important. If the die cavity in the oper-
ating tablet machine is filled by predominantly large gran-
ules, there will be large void spaces. But if the same die
cavity is filled by smaller granules, the space will be
more compactly filled and there will be less void space.
The tablets compressed from the two granulations will not
have the same weight. Thus variations in the granule size
ultimately may cause variation in the weight of tablets.

The effects on tablet weight of the variables of
granule size, granule fluidity, punch and die size, tab-
let base formula, and tableting speed have all been studied
and reported in the literature. However, there appears to
be no report in the literature concerning the effects of
the variables of bulk density and granule density on tablet
weight. Since the weight or dose of medication in a tablet
ultimately depends on the volume of granulation entering a
die cavity, it is obvious that the density of the volume of
granulations measured out by the machine will influence the
final weight of the tablets produced.

This study is, therefore, primarily concerned with
the relationship of the quality of density, including bulk
density and granule density, to tablet weight. Since bulk
density and granule density are interrelated, and since
tablet weight variation is an important adjunct to tablet
weight, these relationships are also considered.

REVIEW OF PREVIOUS LITERATURE

Variation in the weight of compressed tablets was reported in the pharmaceutical literature as early as 1926; in this study Liverseege (2), an Analyist of Birmingham, England,examined forty-two samples of 5 grain tablets of four different kinds, including sodium salicylate, aspirin, calcium lactate, and sodium citrate. He analysed more than 1700 individual tablets to determine the uniformity in weight of the tablets, uniformity in the amount of medicinally active substance, and uniformity in disintegration time of tablets. He found that the weight of 91.8 per cent of the tablets did not vary more than 5 per cent from the mean weight of the tablets of the sample; 7.3 per cent of the tablets ranged from 5 to 10 per cent from the mean; and 0.9 per cent showed a deviation of greater than 10 per cent from the mean weight of tablets. Based on his observations of the average weight of tablets, he suggested that, "It is necessary that the mixture (i.e. granules mixed with talcum, starch, etc.) should be in a uniform state of division, or equal volumes will not correspond to the equal weights, and therefore some tablets will weigh more than others." In this report he did not pin point any other factors causing weight variation, but stated only that the

granulation should be of uniform size. It has been only
since 1948 that further detailed investigations of tablet
uniformity have been reported. Arambulo and Deardorff (4
and 5) studied weight variation in tablets, using sodium
chloride as a basic granulation. In this study, sodium
chloride granules were separated into narrow size ranges
from 4380 to 81 microns and compressed into tablets on a
single punch tablet press. The press adjustments were set
and remained constant during the compression of all the tab-
lets.

These workers found that, as the particle size de-
creased, the average tablet weight at first increased,
reaching a maximum at 150 - 350 microns, and then decreased.
They also found that, as the particle size decreased, the
percentage of physically perfect tablets increased, the tab-
lets became more glossy, and in general more satisfactory.
This trend also passed through a maximum, followed by pro-
duction of tablets decreasing in quality.

Akoi and Fukuda (9), two Japanese workers, have stud-
ied several factors causing variation in the weight of tab-
lets. In one paper they reported a study of the relation-
ships between both granule size and tablet diameter and tab-
let weight variation. Their conclusion on this aspect of
the investigation was, "In tableting of tablets of a definite
size, the larger the diameter of granules, the larger became

the weight variation, the ratio of its increase being linear
and in tableting of tablets of different sizes with the
granules of the same size, [the] greater the weight of tab-
lets [the] smaller became the weight variation, the ratio of
decrease being linear."

In order to study the relationship between the fluid-
ity of granules and weight variation of tablets during tab-
leting (8;11) these same workers coated the granules with
Vaseline, thereby producing granules of different fluidity.
They found that the greater the coefficient of friction of
the granules, the greater becomes the weight variation. The
coefficient of static friction was found to increase with
increasing amount of powder (including lubricant) in the
granules. From their results they concluded that it seems
advantageous to have the granules as small as possible.
They also studied the influence of a number of different
lubricants, including potato starch, Carbowax 400, stearic
acid, Boric acid, talcum, magnesium stearate, calcium stear-
ate, lycopodium, and Clerosil on the static friction co-
efficient. From this study they concluded that the lubri-
cant powder effects a decrease of the coefficient of static
friction of sticky granules, but such ability differs with
different grades of lubricant. They suggested that it would
be useful to measure the static friction coefficient of
granules in checking the quality of batches of granules in

plant production.

Raff, Arambulo, and Deardorff (10) have also re-
ported weight variation in tablets in their study of in-
ternal flow of granulation during compression. They used
statistical quality control charts for tablet weight,
hardness, and compressional pressure as an aid to study
the internal flow of a granulation in the single punch
tablet press.

In their study they used lactose-starch, sodium
chloride, and aspirin-lactose-starch granulations. The
granulations were prepared by a wet granulation method
using starch paste as a binder. In the case of the lac-
tose-starch granulation, granules were passed through a
U. S. Standard Sieve #10 and retained on a #50. In the
case of the aspirin-lactose-starch granulation, aspirin
was passed through a #70 sieve and retained on a #100,
and it was mixed with lactose-starch granulation. In the
case of sodium chloride, two collections were made; one
granulation was passed through a #10 sieve and retained
on a #12; the other was passed through a #45 sieve and re-
tained on a #50. Talc and magnesium stearate were used as
lubricants for all granulations. Compression was carried
out in the Stokes Model E single punch tablet press,
using 11/32-inch punches. The speed of the machine was
adjusted to produce approximately 100 tablets a minute.

In this study these workers found that, during the first part of the run, the weight of the tablets usually increased, but sometimes decreased, depending upon the nature of the granulation. In the case of the aspirin-lactose-starch granulation a substantial decrease in the weight of the tablets was observed. Results of studies in other fields indicate that, in order to avoid too rapid a flow of fines through coarser particles and consequent variation in weight of tablets, one should not have too wide a disparity in particle size, and further, the active ingredient should be of such a size as to fill substantially the average void space of the basic granulation. They also point out that their experiments confirmed the usual belief that it is important to check the tablet weights most closely during the first and last quarters of the run.

Hasegawa (12) has reported a study on tablet weight variation in which he considered four factors causing weight variation in tablets. The four factors studied were:

(1) the effect of three different tablet bases;

(2) the effect of punch diameter (7 m.m., 10 m.m., and 13 m.m. diameter punches);

(3) the effect of granule size (sieve size No. 12, No. 14, No. 16, No. 18 and No. 20);

(4) the effect of speed of tableting (42 tablets a minute and 76 tablets a minute).

The study was conducted using a Kimura Model KT2 tablet press. Potato starch was used as a binder, and 2% talcum was used as a lubricant.

From the results obtained during this study, he concluded that:

(1) significant differences were not recognized among different tablet bases;

(2) reduction of punch diameter increased weight variation of tablets quadratically;

(3) reduction of granule size decreased weight variation of tablets, and the relationship was linear; the degree of decrease of weight variation was different for each punch;

(4) significant differences were not recognized between the two tableting rates i.e. 42 and 76 tablets a minute.

Uniformity of drug dosage in compressed tablets was studied by Moskalyk, Chatten, and Pernarowski (14), who weighed and assayed individual tablets in order to determine the actual variability in drug dosage. The variations in potency found in a batch of tablets were as a rule greater than those indicated by the uniformity of weight test. Deviations were found greatest in the lightest

weight tablets within a batch. These investigators believe that, should this prove true for all tablets, then a test based on the analysis of a small number of lightest weight tablets or groups of tablets could be adopted as a control procedure to assure uniformity of drug dosage. Used in conjunction with the uniformity of weight test, it would provide a more effective control over excessive dosage variability in tablets.

EXPERIMENTAL PROCEDURE

A. General Order of Experiments

Preliminary experiments were carried out to estab-
lish whether conclusions from previous work could be
applied to the tableting set-up available for testing the
hypothesis that tablet weight and weight variation is re-
lated to granule density and bulk density of granules.
Thus, in the first series of experiments, the effects of
granule size, tableting rate, and die size on tablet
weight and weight variation were studied and the results
compared with those in literature. The results of these
experiments allowed the selection of a normal operating
region for further experiments concerning the main object
of this thesis, i.e., the interrelationship between gran-
ule density, bulk density, tablet weight, and weight var-
iation. In the controlled density experiments density of
a basic granulation was varied by the addition of bismuth
subcarbonate; the size of granules was controlled within
a narrow range; bulk and granule density were determined,
and the relationships among tablet weight, weight vari-
ation, and granule-bulk density were found, by compress-
ing the granules on a rotary tablet machine using the
same machine settings for all the granulations.

B. Preliminary Experiments to Test Applicability of the
   Literature Data

The following preliminary experiments were carried
out to determine the applicability of the literature data.

(1) Granules of three different sieve sizes were
compressed on the tablet machine, maintaining constant
speed of machine, pressure ejection, capacity, etc.

(2) Speed of the tablet machine was increased,
keeping pressure and capacity settings constant.

(3) Two sets of standard concave dies and punches
(3/8" and 3/16") were used on the tablet machine; the
other settings were kept constant during tablet compression.

Granulation. The general formula for preparing
granules was

        Lactose USP . . . . 300.0 gms.
        Starch Soln. 5% 650   ml.

Preparation of Starch Solution. Starch paste was
used as a binding agent to form the granulation. Commer-
cially available corn starch, 50 gms, was put in a suitable
container, one liter of cold water was added to it slowly,
and with continuous stirring to avoid the formation of
lumps. This mixture was slowly heated with continuous
stirring, until the solution began to boil and a translu-
cent paste resulted.

Preparation of Granules. The weighed amount of lactose was placed in a Hobart* mixer and starch paste was added gradually to the contents of the mixer while the mixer was rotating. Starch paste was slowly added and the mixture stirred until the mass readily cohered to a ball but equally readily broke up when rubbed between the fingers. This damp mass was then taken out of the mixer and granulated with an Erweka* wet granulator. The wet granules were collected on brown paper, put on trays, and finally dried in an oven at 70° for four hours.

The dried granules were then reduced to a smaller size using an Erweka dry granulator and separated using U. S. Standard No. 16, 20 and 40 sieves. The granules referred to as #16 mesh were passed through a No. 16 Standard sieve and were retained on a No. 20 sieve. In the case of 20 mesh granules, all granules were passed through a No. 20 and were retained on a No. 40 sieve. In the case of No. 40 granules all granules passed through #40 sieve and were retained on a # 60 sieve. The granule and bulk densities were determined. (See III C - granule and bulk density experiments.)

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*Hobart Manufacturing Company, Troy, Ohio

*Erewka G.M.B.H., Frankfurt. Distributor Chemical and Pharmaceutical Industry Co., Inc., 90 West Broadway, N.Y.C., New York.

Lubrication. All grenules were lubricated with 0.5% magnesium stearate prior to compression.

Tablet Compression. A Colton Model 216[*] rotary tablet press was used for the compression of all of the granulations. The settings and operating conditions for the compression of each granulation lot were varied in order to control certain variables.

Grenule Size Experiments. In order to study the effects of granule size on tablet weight and weight variation, three different sizes of granules prepared and separated were used. Three-eighths inch standard concave dies and punches were set on the tablet machine. The tablet weight was adjusted to 450 mgms. by hand-turning machine when loaded with 16 mesh granules. Pressure roller settings and weight control settings were not changed during the compression of the other two granulations. The tableting rate was kept constant at 582 tab./min. during the compression of all three granulations. To determine the tableting rate, tablets produced during one minute of operation were collected and counted; and the count was repeated three times.

Samples of the tablets used to study the weight and weight variation were collected as follows: ten samples

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[*]Arthur Colton Company, 3529 E. Lafayette Ave., Detroit, Mich.

of ten tablet each were collected during the run of tab-
let machine. Each tablet was weighed individually and the
average weight of each group was calculated.

Tableting Rate Experiments. The effect of speed of
compression on tablet weight variation of the three differ-
ent size of granulations was determined.

Compression of 16 Mesh Granules. The granules
passing through #16 and retained on #20 were lubricated
with 0.5% magnesium stearate. The standard concave 3/8"
dies and punches were used for this compression, and the
weight of tablet was adjusted to 400 mgms. by hand-turning
the machine. The tablets were compressed at five differ-
ent machine speeds:

The tableting rates were increased gradually and
evenly by rotating the speed control wheel six full rota-
tions each time in clockwise direction. Tablets produced
during three 1-minute intervals were counted and the aver-
age speed of compression was computed from the three
counts.

Compression of 20 Mesh Granules. Granules passing
through a #20 and retained on a #40 sieve were lubricated

as before. The tablet weight was adjusted to 450 mgms. by hand-turning the machine, and the tablets were compressed, using exactly the same settings of machine as for the #16 mesh granules. Samples were collected exactly as above.

Effect of Die Size. To determine the effect of die size on tablet weight, the granules, prepared as described, passing through a #20 mesh sieve and retained on #40 mesh were used. The two different die sizes and punches were used (3/8" and 3/16").

First, 3/8" dies were set on tablet press and the #20 mesh lubricated granules, were compressed into tablets at two different speeds. Speed of compression was determined by counting the number of tablets produced in one minute (each three times) and then determining the average. Three samples were collected at each speed and the average weight was determined by calculation from the weight of the individual tablets.

Similarly, 3/16" dies were set on tablet press and same #20 mesh granules were compressed at three different speeds and samples were collected as before, and percentage of weight variation was determined at each speed of compression.

C. Granule and Bulk Density Experiments

Preparation of Granules. For the preparation of

granules, the following ingredients were used:

> Lactose U.S.P. Malincrodt G. 91R
> Bismuth subcarbonate U.S.P. Amend Drug Co.
> Gelatin U.S.P.

Method of Variation of Density of Granules. The density of the basic lactose granulation was increased by the addition of bismuth subcarbonate in concentrations of 10%, 20%, 30%, and 40%. Table I gives the actual formulas used to prepare each of these granulations.

Preparation of the Binder Solution. Gelatin binder solution was prepared by covering 10 gms. of gelatin U.S.P. with 40 ml of water and allowing the mixture to stand until the gelatin became hydrated. The mixture was then heated gently with frequent agitation until the gelatin was dissolved. A sufficient quantity of water was then added to make final volume measure 100 ml.

Mixing. Weighed quantities of lactose and bismuth subcarbonate powders were placed in a Hobart* mixer, and the dry powders were mixed to uniformity, for about 3 - 5 minutes.

Granulation. To the uniform mixture of these powders in Hobart mixer warm gelatin solution was added

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*Hobart Mfg. Co., Troy, Ohio

TABLE I

GRANULATION FORMULAS

Granulation No.	1	2	3	4	5
% Bismuth sub-carbonate	0%	10%	20%	30%	40%
Ingredients					
Lactose	3000gms.	2700gms.	2400gms.	2100gms.	1500gms.
Bismuth sub-carbonate	----	300gms.	600gms.	900gms.	1200gms.
Gelatin Solution	375ml.	390ml.	405ml.	425ml.	460ml.

gradually, while mixer was rotating, and the ingredients mixed until the mass readily cohered to a ball but equally readily broke up when rubbed between the fingers. This damp mass was then taken out of the mixer and granulated with an Erweka wet granulator. The wet granules were collected on brown paper, put on trays, and dried in an oven at 70° for four hours.

Separation into Size Fractions. The dried granules were then reduced to smaller size by hand forcing them first through U. S. Sieve #10 and then through a #16. The granules passed through the #16 sieve and were retained on a #20 sieve.

D. Determination of the Pertinent Characteristics of the Granulations

Size Distribution Determination. A stereo microscope with a calibrated eyepiece and having magnification of twenty times and fixed focal length was used to determine size distribution of the granules. One thousand particles of granules were counted from each lot of granulation. The "mean linear intercept" (1) method was used for the measurement of the granules. In this method the mean length of a line intercept by the profile boundary which approximately bisects the area of the granule profile is taken as the diameter of the granule. The bisecting

line is taken parallel to a fixed direction, irrespective
to the orientation of each particle. This has the effect
of avoiding bias as to the direction in which the profiles
observed are bisected. From this method of diameter count,
reproducible graphs for average size distribution were ob-
tained.

Bulk Density Determinations. For the determination
of bulk density of granules, the method suggested by Butler,
Ransey, and Martin (13) was used. A sample of about 50cc.
of the sized granules was carefully introduced into a
100cc graduated cylinder. The cylinder was then dropped
onto a hard wood surface (table top) three times from a
height of about one inch at approximately two second
intervals. Bulk density was then determined by dividing
the weight of the sample of granules in grams by the final
volume in cc. of the sample contained in the cylinder.

Granule Density Determinations. A mercury displace-
ment method similar to the method suggested by Strickland,
Busse and Higuchi (6) was used to determine granule dens-
ity.

Figure I shows a diagram of apparatus and assembly
used to determine density of the granules. The internal
volume of the glass bulb (labeled "A" in diagram) was de-
termined by calculations from the weighed quantity of merc-
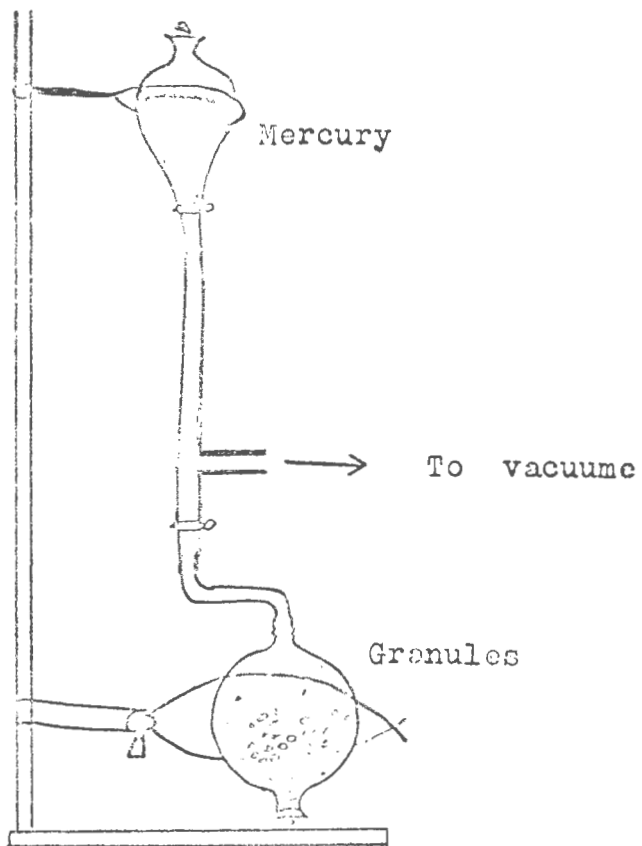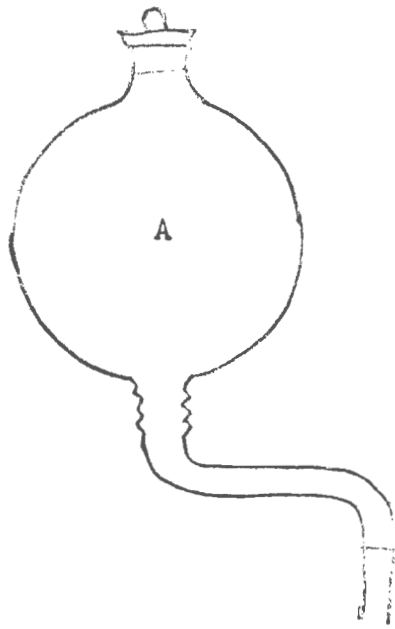
Figure 1   Apparatus to determine Granule Density.

ury required to fill the bulb to the calibration mark. Granule density was determined by placing a known weight of granules in the empty bulb, pumping the air out of the bulb with a vacuum pump, allowing mercury to flow into the bulb to the calibration mark. The bulb containing the mercury and the granules was then removed from the assembly and weighed. From the known weight of the bulb and the granules and the calibrated volume of bulb, the volume displaced by granules was calculated. The granule density was then calculated by dividing the weight of granules by the volume displaced.

E. Compression of Granules

Equipment. A Colton Model 216 rotary tablet machine was used for all tablet compression.

Selection of operating parameters. From the preliminary experimentation some working parameters or conditions were set up for the study of the effects of granule and bulk density on tablet weight variation. In the first place, the No. 16 granulations were selected because the No. 16 granules were the only ones that could be prepared with sufficient yield from the formulas containing the larger proportions of bismuth subcarbonate.

The one-fourth inch dies and standard concave punch-

es were used for tablet compression. The weight of tablet
was adjusted 100 mgms. with the lactose granulation while
turning the machine by hand. The other 'standard' set-
tings of the machine, which were kept constant during com-
pression of all granulations, were: speed of machine or
tableting rate (650 tab/min); overload pressure adjustments;
and flow of granules through hopper.

Lubrication. All granulations were lubricated with
0.5% magnesium stearate; 5% cornstarch powder was added
during lubricating as a disintegrating agent.

F. Determination of Tablet Characteristics

Weight. As the tablets were being produced from
the machine five samples of twenty-five tablets each were
collected in separate boxes, during the compression of the
different granulations (i.e. granules containing 10%, 20%,
30% and 40% bismuth subcarbonate). Each tablet in a group
was weighed individually and the average weight, mean
deviation, and standard deviations were calculated.

Size. Thickness and diameter of each of fifty tab-
lets in each group were measured and the average of thick-
ness and diameter was determined.

Hardness. A Pfizer* hardness tester was used.

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*Pfizer, Chem. Sales Div. Chas. P. Pfizer Co., Inc.
630 Glushing Ave., Brooklyn, N.Y. U.S.Pat. 2975630

Twenty tablets selected at random from each lot of tablets produced, were tested for hardness, and the average hardness was determined for each lot of tablets.

Disintegration Time. The U.S.P. method[*] (basket-rack assembly) was used. One tablet of the sample from the lot of tablets was placed in each of the six tubes of the basket and the apparatus was operated, using distilled water at 37° as the immersion fluid. The time required for the complete disintegration of each tablet was noted and the average of six readings was determined.

_____

[*]U.S.P. Disintegrator. Scientific Glass Apparatus Co., Inc.

RESULTS AND DISCUSSION

PRELIMINARY EXPERIMENTS

Granule Characteristics

The lactose granulations obtained in the first part
of the experiment were pure white. As mentioned before,
in this series of preliminary experiments, granule size
was controlled by passage through U. S. Standard Sieves
Nos. 16, 20 and 40. Detailed studies on these granules
with regard to size distribution, bulk density, and gran-
ule density were not carried out.

Effect of Granule Size

From Table II, which shows the influence of three
different sizes (i.e. Nos. 16, 20 and 40) of granules on
tablet weight and weight variation, it can be seen that
the tablet weight increased as granule size decreased,
and that the weight variation decreased with decreasing
granule size. These results correspond to those obtained
by Arambulo and Deardorff (5) who studied the effects of
granule size from sieve Nos. 4 to 170. Arambulo and Dear-
dorff attributed the increasing weight with decreasing
granule size to a decrease in void space. They reasoned
that large granules gave large proportions of void sapce

TABLE II

TABLET WEIGHT AND COEFFICIENT OF VARIATION OBTAINED
FROM 3 DIFFERENT SIZES OF GRANULATIONS

	Tablet Weight in Mg. From Granulation		
	16 Mesh	20 Mesh	40 Mesh
	424	482	508
	444	485	507
	448	478	509
	439	503	512
	450	508	520
	426	497	524
	449	490	519
	461	499	521
	421	493	518
	431	482	522
Average of tab.	439.3	491.7	516
Max. Deviation	21.7	16.3	9
Coef. of Variation	0.08	0.05	0.03

in the die before compression, resulting in relatively
light weight tablets. As the granule size was reduced,
void space was reduced and the average tablet weight in-
creased.

Effect of Tableting Rate

As shown in Table III and Figure 2, the average
tablet weight decreased as the tableting rate was in-
creased. This trend followed in both sizes of granules
used. As the tableting rate was increased, there was
less time for granules to flow into the die cavity from
the feed shoe. In addition, there was a tendency for the
granules to be thrown outward at higher rotational speeds.
In the case of the No. 16 granulations, at the maximum
rate of tableting a 22.4% drop in the average weight of
tablets was observed, indicating either that the die cav-
ities were incompletely filled by the granules or that
granules were being thrown out of the dies by centrifugal
force. The latter factor would seem to be less important
than the former in view of the later experiments which
showed that, as die size was decreased the weight vari-
ation of tablets was increased. In general, as the speed
of compression was increased the weight of the tablets
produced was decreased, the variation in weight from the
average tablet weight was also found to increase as the

TABLE III

AVERAGE WEIGHT OF TABLETS FROM NO. 16 AND NO. 20

SIEVE GRANULES OBTAINED AT DIFFERENT SPEEDS

Compression of No. 16 Sieve Granules*			Compression of No. 20 Sieve Granules**		
Tab/min	Av. Wt. mg.	Coef. of Variation	Tab/min	Av. Wt. mg.	Coef. of Variation
392	376.6	0.16	-	-	-
508	375	0.19	580	438.0	0.11
632	374.2	0.20	724	428.0	0.12
768	370	0.25	912	409.3	0.14
932	345	0.38	1020	373.0	0.21
1180	290	0.46	1132	344.8	0.29

*hand turned weight 400 mg.   **hand turned weight 450 mg.

tableting rate was increased. These results are shown in
Table III and Figures 2 and 3. As a result of incomplete
fill at higher speeds of compression a drop in the hard-
ness of tablets was also observed. These results do not
parallel those of Hasegawa who studied weight variation
at two rates of tableting - 42 and 76 tab/min, and con-
cluded that significant differences in tablet weight vari-
ation did not result at 76 and 42 tab/min tableting rates.

The difference between his results and the results
reported here can probably be explained by the fact that
Hasegawa used tableting rates of 76 and 42 tab/min which
are very low compared to the 392 - 1180 tab/min rates
used in these experiments. In addition Hasegawa used a
single punch tablet machine (Kimura Model K.T.-2) whereas
results reported here are from a Colton Model 216 rotary
tablet machine.

Effect of Die Size (Diameter)

The effect of two different die sizes on weight
variation at different speeds of compression is shown in
Table IV. In the case of the smaller die diameter the
coefficient of variation is higher and in the case of the
larger die diameter, the coefficient of variation is less
than former. The effect of die size on weight variation
of the tablets is similar to data reported by Hasegawa.
The reason for this type of effect is that larger die
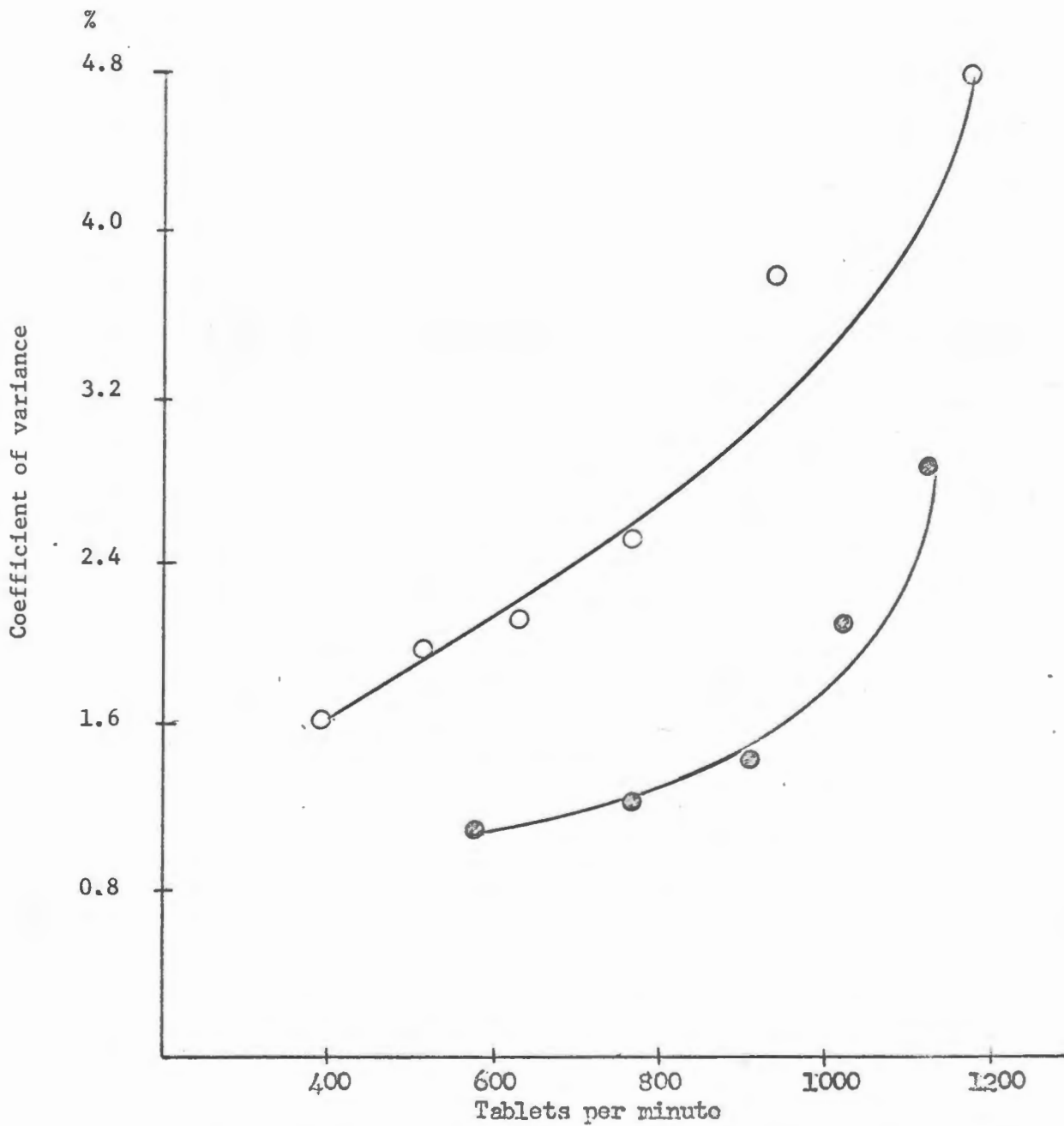
Figure 2 Effect of tableting rate on coefficient of variance.

⊛ Tablets from No. 20 sieve granules.

○ Tablets from No. 16 sieve granules.
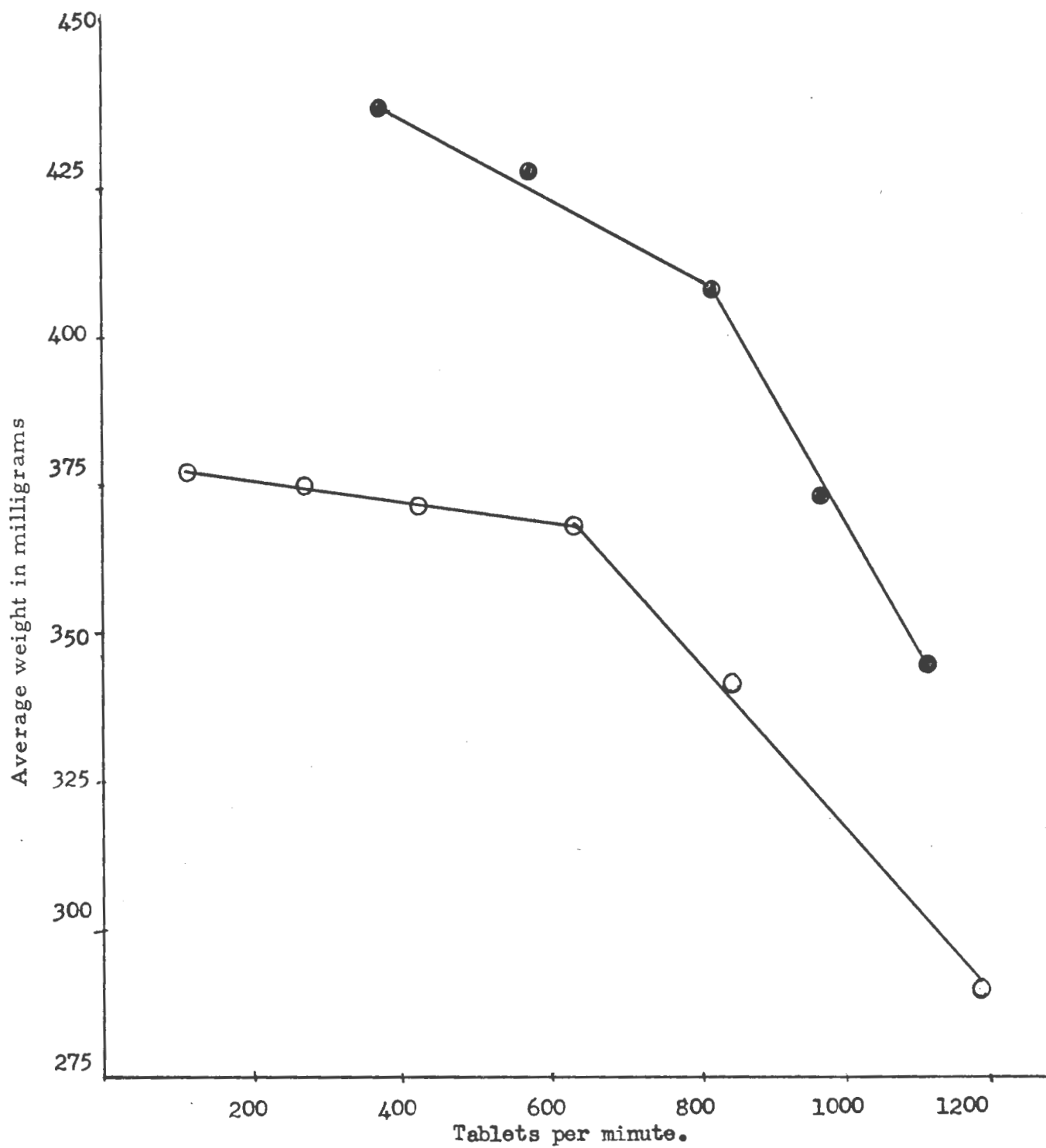
Figure   3   Effect of tableting rate on average weight of tablets.

      ●   Tablets from NO. 20   sieve granules.

      O   Tablets from NO. 16   sieve granules.

cavities are easier to fill and fill evenly during the run of the tablet machine than smaller die cavities.

INTERRELATIONSHIP OF GRANULE DENSITY,
BULK DENSITY, TABLET WEIGHT AND
WEIGHT VARIATION

Characteristics of Granulations

Size Distribution. In these studies the granule size was controlled within a narrow range and size distribution data were obtained to show this distribution. Tables V and VI show the size distribution of the granulations. In Table V only the No. 16 plain lactose granulation was considered, and four counts each of 1,000 granules were made to obtain the plain lactose size distribution plots. The average diameter of the granules in m.m. and the standard deviations in each count show that the results are very close. The reproducibility of these results is also shown by the standard error which is 1.35 ± 0.01. Table VI shows the size distribution of lactose granulations containing various concentrations (10%, 20%, 30%, 40%) of bismuth subcarbonate, compared with plain lactose granulations. It can be seen from these data that all the granulations had similar distributions, but the granulations containing 30% and 40% bismuth subcarbonate apparently contained slightly higher proportions

TABLE IV

EFFECT OF DIE SIZE - AVERAGE WEIGHT AND
COEFFICIENT OF VARIANCE OF TABLETS

Die Size 3/8"			Die Size 3/16		
Tab/min	Av. Wt. Mg.	Coef. of Variance	Tab/min	Av. Wt. Mg.	Coef. of Variance
			912	153	0.061
980	417.0	0.05	1020	140.3	0.092
1130	396.0	0.10	1132	127.0	0.16

TABLE V

PLAIN LACTOSE GRANULATION #16 MESH DIAMETER COUNT

Size in m.m.	.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2	2.1	2.2	2.3	Total Particles	Average Diameter	Standard Deviation
Count No.																		
1	14	42	107	133	226	148	137	80	48	30	14	10	6	3	2	1,000	1.37	0.228
2	14	41	121	136	228	149	130	74	46	29	13	10	4	2	0	1,000	1.36	0.222
3	12	60	105	143	208	141	131	65	43	27	14	10	7	5	3	1,000	1.36	0.229
4	16	59	121	157	230	150	112	62	41	30	10	6	4	2	0	1,000	1.34	0.222

$SE = 1.35 \pm .01$

of granules in the 1.0 to 1.2 m.m. range, resulting in a slightly lower average granule size. Plots of the size distributions of the various granulations are shown in Figures 4 and 5.

Granule Density. Table VII shows that granule density of the five different granulations was increased in proportion to the amount of Bismuth subcarbonate added. The granule density ranged from 1.488 for plain lactose granulations to 2.025 for the granules containing 40% Bismuth subcarbonate.

Bulk Density. The bulk density of the granulation is related to granule density, and when the density of the basic lactose granulation was increased by the addition of Bismuth subcarbonate, the bulk density of the granules was found almost proportionally increased (size distribution was controlled). Table VII shows the increase of bulk density as the concentration of Bismuth subcarbonate was increased. If the size distribution of granules had not been controlled, the bulk density of granules might have shown different a trend, since bulk density is also influenced by shape and size of granules.

Miscellaneous. The granulations prepared from plain lactose and those prepared by adding various con-
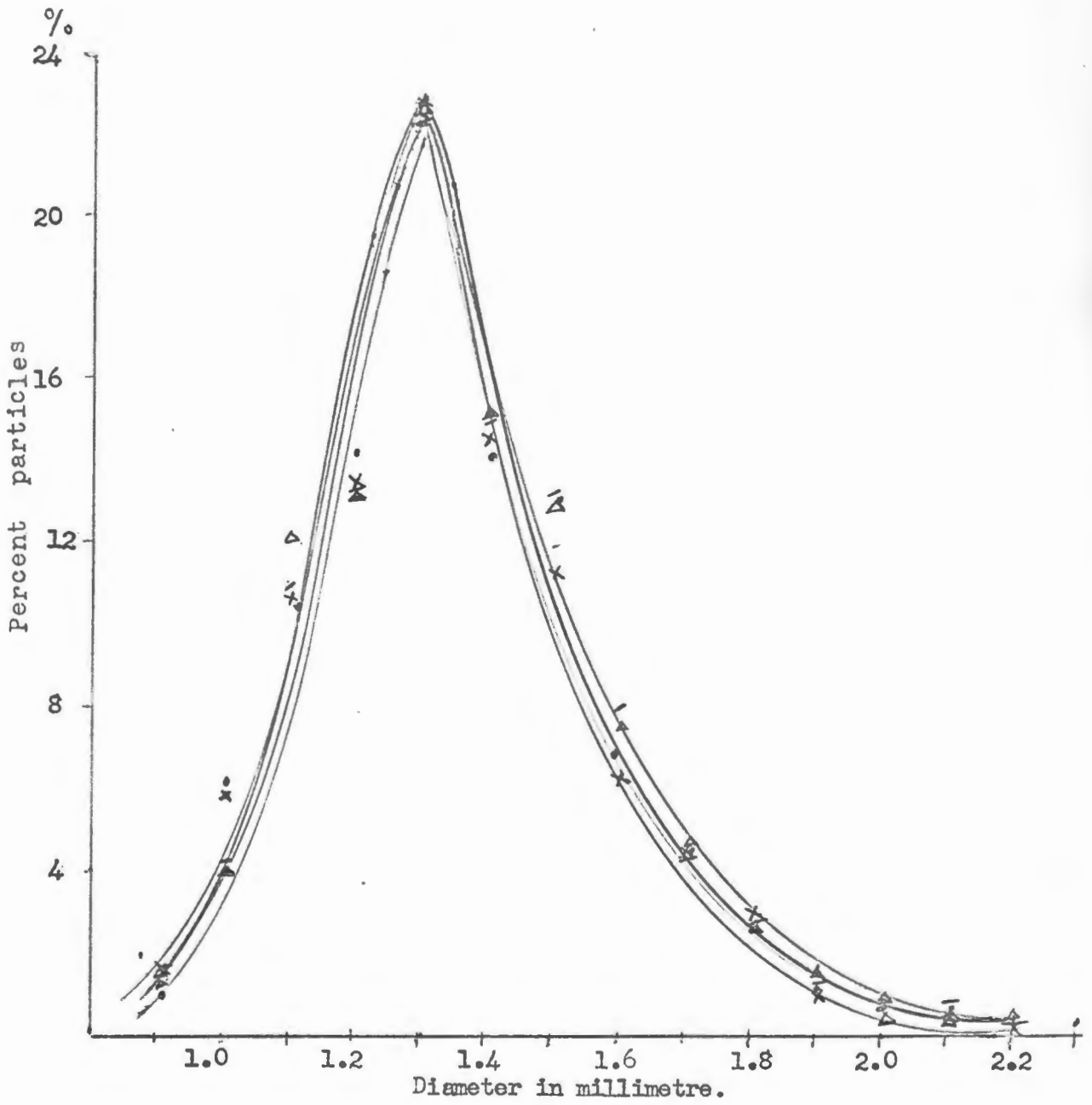
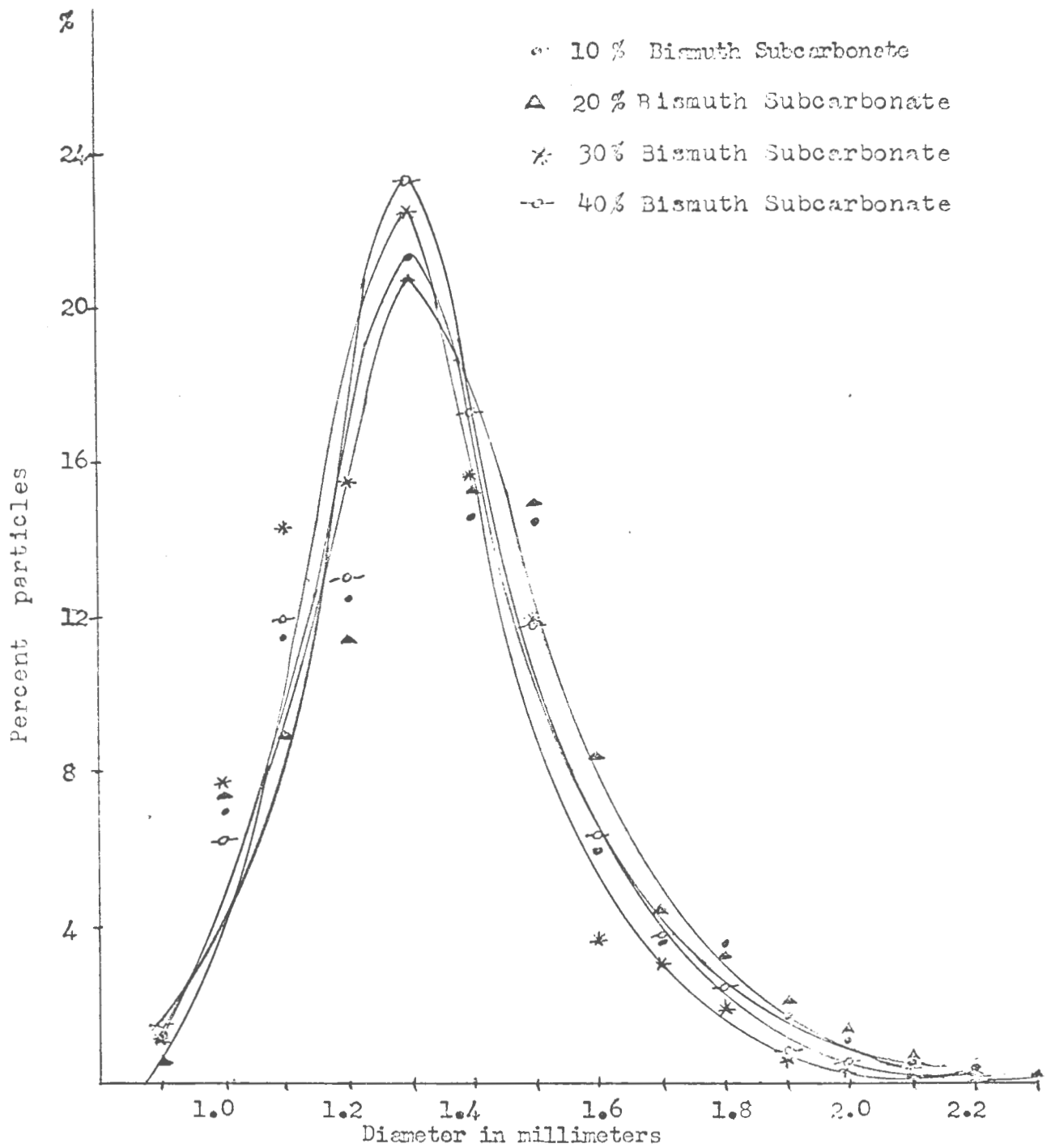Figure 4   Granule size distribution of No. 16 sieve plain lactose granules.

Figure 5   Granule size distribution of No.16 sieve lactose granules
containing various concentrations of Bismuth Subcarbonate.

TABLE VI

GRANULATION OF LACTOSE AND BISMUTH SUBCARBONATE

PARTICLE DIAMETER COUNT

Particle Size in m.m.	.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2	2.1	2.2	2.3	Total Particles	Av.	Standard Deviation
Plain Lactose	14	42	107	133	226	148	137	80	48	30	14	10	6	3	2	1,000	1.37	.228
Lactose + 10% Bismuth Sub-carbonate	12	70	113	126	216	148	128	65	37	34	17	10	3	2	1	1,000	1.36	.232
Lactose + 20% Bis. sub-carbonate	7	75	90	116	208	156	156	84	45	31	21	12	4	1	0	1,000	1.37	.237
Lactose + 30% Bis. sub-carbonate	15	77	145	155	229	157	120	39	30	19	5	4	2	1	0	1,000	1.30	.205
Lactose + 40% Bis. sub-carbonate	7	63	120	130	234	172	120	63	38	25	7	5	3	2	1	1,000	1.33	.217

TABLE VII

GRANULE AND BULK DENSITY OF
DIFFERENT GRANULATIONS

Granulations	Granule Density	Bulk Density
Plain Lactose	1.488	0.432
Lactose + 10% Bismuth subcarbonate	1.564	0.483
Lactose + 20% Bismuth subcarbonate	1.653	0.497
Lactose + 30% Bismuth subcarbonate	1.81	0.582
Lactose + 40% Bismuth subcarbonate	2.02	0.683

centrations of bismuth subcarbonate showed little change
in gross appearance except with respect to color. The
plain lactose granulations were pure white in color, but
as the increasing proportions of bismuth subcarbonate (i.e.
10%, 20%, 30% and 40%) were added the white color was
changed gradually to off white (or pale tan) color. The
granulations containing bismuth subcarbonate were harder,
possibly due to the larger amounts of binder solution re-
quired to prepare the granules. When magnified, it was
observed that the bismuth subcarbonate granules were
somewhat less regular in shape than those of the plain
lactose granulations.

RELATIONSHIP OF BULK DENSITY
TO GRANULE DENSITY

When the size and size distribution of granular
particles are controlled within narrow limits, variations
in other physical characteristics such as porosity and
shape are reflected by changes in the granule density and
bulk density.

Granule density as determined by the mercury dis-
placement method, reflects changes in intraparticle por-
osity (due to totally enclosed air pockets, and micro-

pores too small for the mercury to enter at ordinary pressure) and changes in the average true density of the materials used to make up the granulation. Bulk density reflects the changes in granule density and interparticle void spaces. Since the interparticle void space is dependent upon the packing characteristic of the granulations, shape differences in the granulation will be reflected by the changes in the bulk density. The mathematical relationship as shown below:

In the mercury displacement method granule density

$$Pg = \frac{\text{weight of granules}}{\text{vol. of mercury displaced}} \qquad \text{is given by}$$

the bulk volume, Vb - granule volume, VG.

Now, in the case of bulk density, the mass of the powder is divided by Bulk volume ($\frac{Wg}{Vb}$). Bulk volume includes Void Porosity which is defined as shown below:

$$\text{Void Porosity} = \frac{\overset{Vb}{\text{bulk volume}} - \overset{Vg}{\text{granule volume}}}{\underset{Bv}{\text{Bulk volume}}}$$

$$= 1 - \frac{\text{weight/granule density}}{\text{weight/bulk density}}$$

$$= 1 - \frac{\text{Bulk density}}{\text{granule density}}$$

From this derivation it can be seen that the bulk volume of granules and therefore bulk density is related to granule density. Now, the void porosity or inter

spaces can be controlled by controlling the size and shape
of the granules. And, now if the size of the granules is
controlled and density of the granules is increased, then,
the bulk density should show changes parallel to the
granule densities. Figure 9 shows that this parallel was
obtained experimentally when granule size and size dis-
tribution were very carefully controlled. A nearly
straight line relationship was obtained. As size distrib-
ution data (Figures 5 and 6) shows, all five granulations
had very similar size distributions. It seems probable
that, for a given type of granulation passing through a
No. 16 sieve, the granules would have approximately the
same void spaces, and therefore the bulk density would be
increased as the granule density increased. The small
deviation from linearity that was observed may have been
due either to small differences in granule shape and con-
sequent changes in packing characteristics or to the small
changes in size distributions seen in Figures 5 and 6.

INTERRELATIONSHIPS OF TABLET WEIGHT,
WEIGHT VARIATION AND
GRANULE AND BULK DENSITY

Table VIII shows the interrelationship between gran-
ule and bulk density and tablet weight, weight variation.
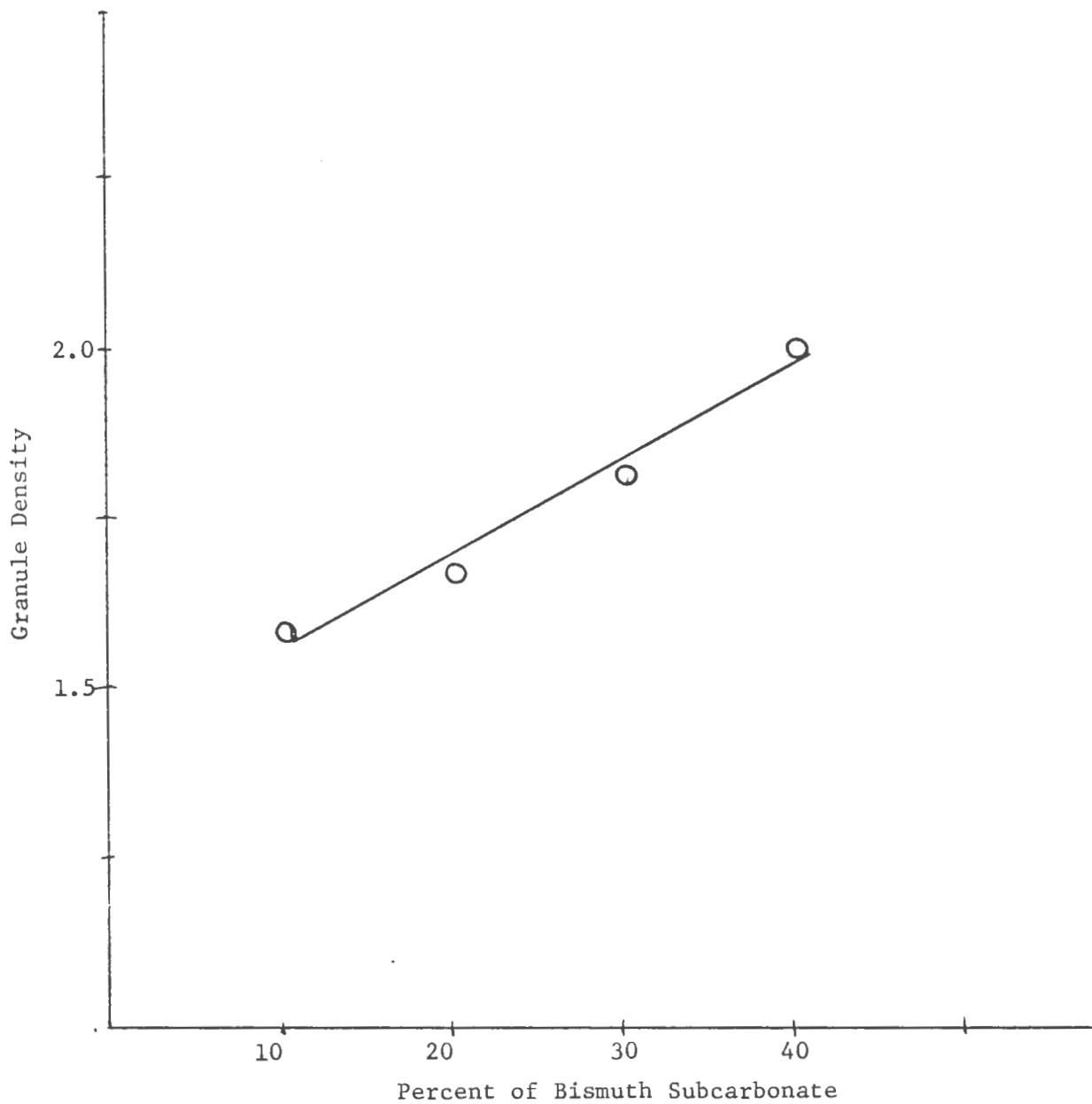Tablet weight was seen to increase linearly, in proportion

Figure 6 Effect of Bismuth Subcarbonate on Granule Density.

TABLE VIII

EFFECTS OF GRANULE AND BULK DENSITY ON

TABLET WEIGHT AND WEIGHT VARIATION

Granulation	Granule Density	Bulk Density	Average Weight	Mean Deviation	Standard Deviation	Coef. of Variance
Plain Lactose	1.488	.432	90.505	2.1154	2.568	0.0284
Lactose + 10% Bismuth subcarbonate	1.564	.483	98.637	2.127	2.627	0.026
Lactose + 20% Bismuth subcarbonate	1.653	.497	102.65	2.0032	2.580	0.025
Lactose + 30% Bismuth subcarbonate	1.81	.582	119.85	1.556	2.428	0.018
Lactose + 40% Bismuth subcarbonate	2.025	.6834	139.81	2.836	3.606	0.026

to the bulk density change. The relationship of tablet
weight to granule density was somewhat more variable (as
might be expected) but with the granulations used, a
fairly close relationship was seen. This relationship
would be expected to vary with particle shape, and with
particle size and size distribution. The bulk density of
plain lactose granules was 0.432 and the average weight
of tablets prepared from these granules was 90.5 mg.,
compared to a bulk density 0.683 of lactose + 40% bismuth
subcarbonate and an average weight of tablets from these
granules of 139.8 mg. The coefficient of variation for
plain lactose tablets was 0.028, and standard deviation
was 2.568, compared to coefficient of variation 0.026 and
standard deviation 3.606 that of lactose + 40% bismuth
subcarbonate tablets. These figures show that bulk dens-
ity of granules affected the average weight and weight
variation of the tablets, and that the variation in
weight within a granulation on a relative basis was pract-
ically identical. These data are shown in Figure 7 in
which the tablet average weight is plotted against gran-
ule density and in Figure 8 in which tablet average weight
is plotted against bulk density. The bulk density of
granules containing 20% bismuth subcarbonate was found
slightly lower than that expected. Although the size of the
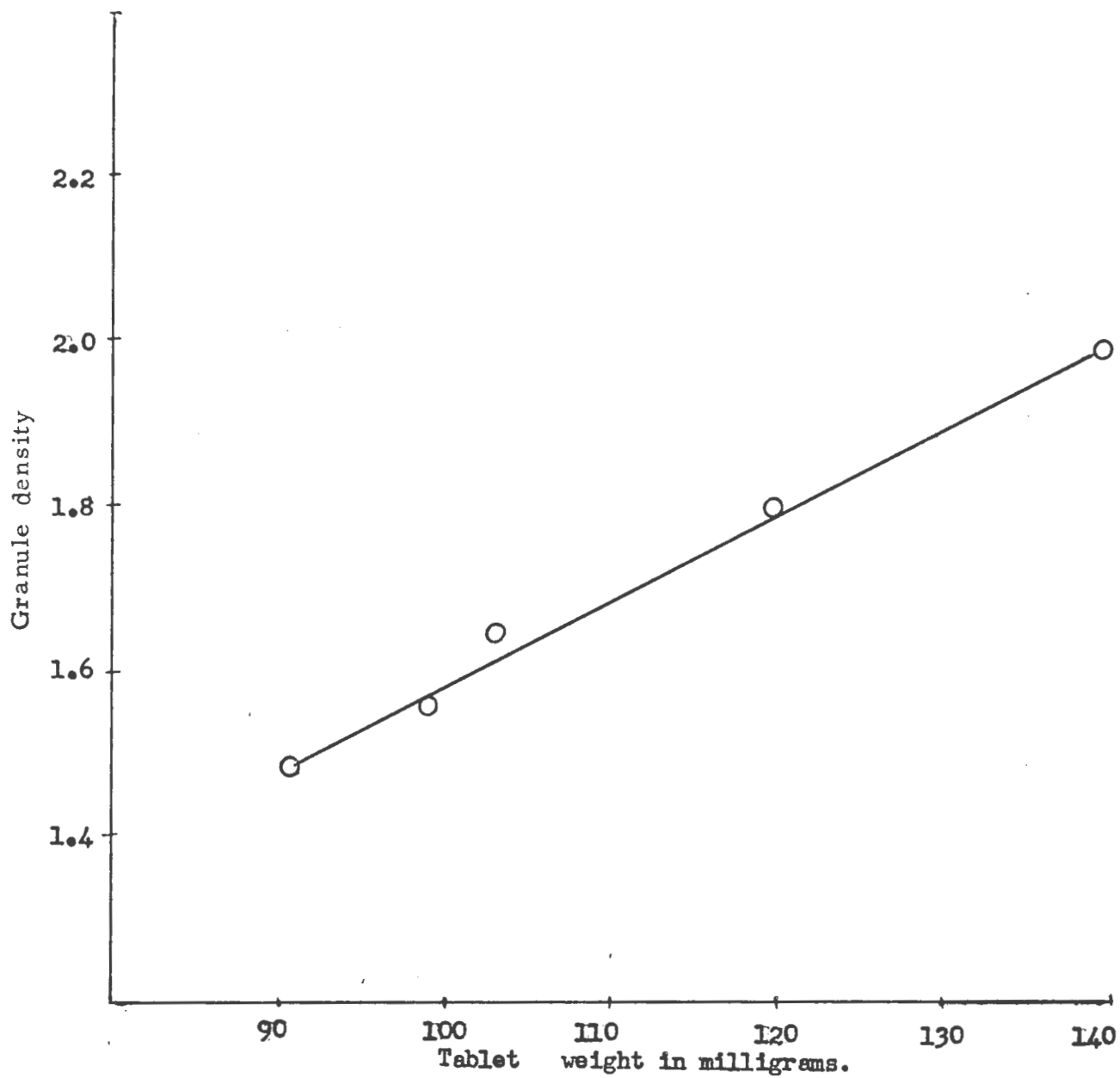granules was controlled to within a narrow range, the size

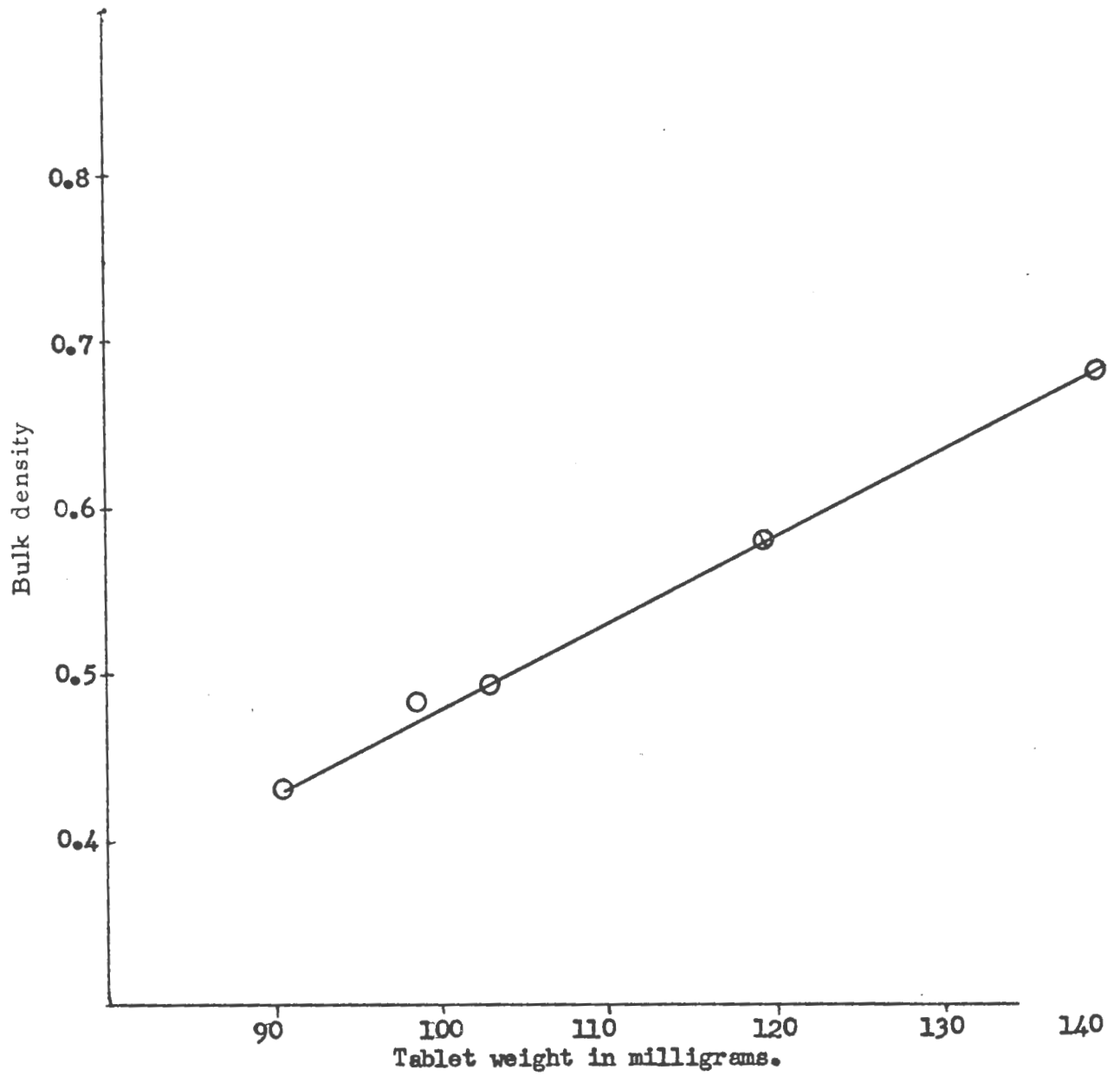Figure 7   Relationship between granule density and average weight of tablets.

Figure 8   Relationship between bulk density and average weight of

tablets.

distribution data (Figures 4 and 5) show a slightly higher proportion of granules in the 1 mm - 1.3 mm region. This variation in distribution could have affected the bulk density of those granules containing 20% bismuth subcarbonate. Another factor affecting the bulk density, could have been shape of the particles and their packing characteristics. When the shapes of different granules were compared under the microscope, the plain lactose granules were found to be smooth and round, but those granules containing bismuth subcarbonate were a little more irregular in shape. The granules containing 20% bismuth subcarbonate had the least smooth surfaces. Both the size distribution and the shape differences could have caused bulk density lower than expected in this granulation.

CHARACTERISTICS OF THE TABLETS PRODUCED
FROM THE DIFFERENT GRANULATIONS

The tablets obtained from the plain lactose granulation were pure white in color, but the tablets containing bismuth subcarbonate were somewhat off white in color, the color darkening as the proportion of the bismuth subcarbonate was increased. The hardness of the tablets was found to increase gradually as the percentage of bismuth subcarbonate added; and therefore, the density of granules
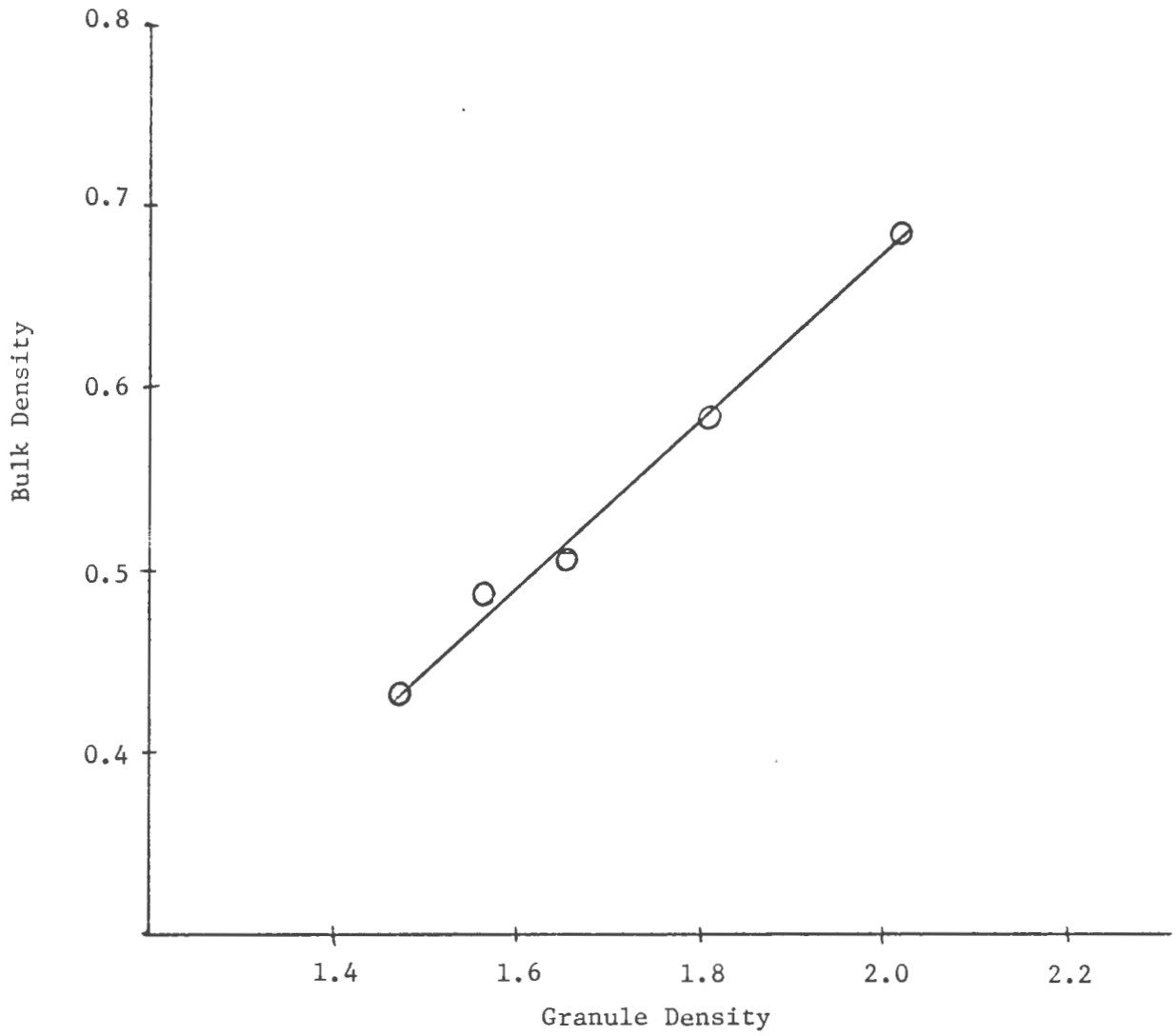
Figure 9 Relationship between Granule Density and Bulk Density.

TABLE IX

TABLE SHOWING OTHER DATA ON TABLETS PRODUCED

Granulation	Granule Density	Bulk Density	Average Weight	D. Time Seconds	Hard-ness Kgs.	Thick-ness Inch	Dia-meter Inch	T. Density	Mois-ture
Plain Lactose	1.488	.432	90.505	34.8	2.24	.1200	.251	1.499	1.61
Lactose + 10% Bismuth sub-carbonate	1.564	.483	98.367	35.5	2.595	.1212	.251	1.576	1.621
Lactose + 20% Bismuth sub-carbonate	1.653	.497	102.65	102.5	2.695	.1205	.251	1.643	1.731
Lactose + 30% Bismuth sub-carbonate	1.81	.582	119.85	135.5	3.105	.122	.2515	1.850	1.681
Lactose + 40% Bismuth sub-carbonate	2.025	.6834	139.81	more than 15 min.	4.90	.124	.2510	2.21	1.701

was increased. This is seen in Table $\overline{IX}$ where hardness
of tablets containing only lactose was 2.24 Kg. and hard-
ness of tablets containing 40% bismuth subcarbonate was
found to be 4.90 Kg.

This table also compares the disintegration time of
tablets from five different granulations. It can be seen
that the disintegration time was gradually increased with
the increasing concentrations of bismuth subcarbonate.
The average disintegration time of plain lactose tablets
was 34.8 seconds and the average disintegration time of
tablets containing 40% bismuth subcarbonate was more than
15 minutes, even though 5% corn starch was added to each
granulation as a disintegrating agent. This gradual in-
crease in disintegration time was probably due to the in-
crease in hardness of the tablets resulting in tablets
less readily penetrated by water.

The tablet diameter in all kinds of tablets was
found to be identical, but the tablet thickness was found
to be slightly increased (0.1200 to 0.1249 inch) as the
density of the granulations increased. The tablet dens-
ity was found to follow the same trend as granule density.

SUMMARY AND CONCLUSIONS

A study of several factors effecting tablet weight and weight variation was carried out. In a preliminary series of experiments, lactose granulations were prepared and effects of granule size, speed of compression, and die diameter were studied, compressing tablets on a Colton Model 216 rotary tables press. Results of these experiments were found to be similar to those reported in the literature. From the data and techniques of these experiments, some optimum conditions, such as granule size, rate of tableting, die diameter, etc., were set up to study the effects of granule and bulk density on tablet weight and weight variation. The density of a basic lactose granulation was increased by the addition of various proportions of bismuth subcarbonate (true density 6.86). Bulk and granule density of these granules was determined. The size of these granulations was controlled to within a narrow range (No. 16 and No. 20 sieves) and the average size distribution was determined by an optical method. All granulations were compressed into tablets on fixed standard settings of a Colton Model 216 rotary press and the following conclusions were drawn:

(1) The density of a lactose granulation can be

successfully increased by the addition of various pro-
portions of heavy substances such as bismuth subcarbonate.

(2) When granule size distribution is carefully
controlled within narrow limits, bulk and granule density
are linearly related.

(3) The increase in the average weight of the tab-
lets was observed to be a linear function of the bulk
density of the granulations.

(4) A similar relationship was found to exist be-
tween granule density and tablet weight, as might be ex-
pected.

(5) The increase in the granule density and in
bulk density also affected other physical properties of
tablets such as hardness, thickness and disintegration
time.

(6) The coefficient of weight variation of tablets
within a granulation was found to be practically identi-
cal for all the different granulations even though bulk
density of the granulations was varied from 0.432 to
0.6834. The standard deviations varied with the average
weight of the tablets produced.

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