ANALYSIS OF THE VARIABLES ENCOUNTERED IN COMPRESSED TABLETS

by

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INTRODUCTION

Object: To collect and correlate physical data on some of the variables in compressed tablets and compressed tablet manufacture; to review some of the existing information; and to summarize possible sources of variations.

Purpose: To make a statistical analysis of the quantitative data obtained, by graphic methods, averages and measures of frequency; to characterize the analysis to determine significant correlations between variables and the different distributions; and to correlate some of the variables in manufacturing with observed properties of compressed tablets.

In other instances where physical data were accumulated in order to correlate variables which influence properties of compressed tablets, the weight and compressional force were carefully controlled and regulated by weighing the granulation for each fill of the die and by the use of a special force machine specially adapted for compressing tablets. (1) But in this project, the tablets were compressed on indust-type tablet machines, as they would be in routine production and, therefore, the weights varied and it was expected that the varying amounts of granulation in the die would influence the hardness and

other associated physical properties of the compressed tablets, since the length of the compressional stroke was not regulated during the production of the tablets.

However, it was thought that by sorting the tablets into groups, according to weight, and conducting tests on the tablets within each weight group, that the results gained from this study might be indicative and, perhaps, correspond with some of the facts already available. The tablets were arranged in this way, also, in order that the frequency of weights could be graphed and a comparison made with the normal probability curve.

GENERAL DISCUSSION

Historical

The modern history of compressed tablets dates back to 1843 when the Englishman, Brockedon, invented and patented a machine for compressing tablets. (2) Brockedon termed his products "compressed pills." Kebler states (3) that the term, compressed tablets, more than likely was originated in the United States by John Wyeth and brother in 1877. The manufacture of tablets in the United States was inaugurated at Philadelphia in 1875 when Dunton built the first tablet machine in America and obtained the first American process patent for the preparation of tableting substances. By 1897 tablets for almost every known disease were being sold on both continents, and writers of the time referred to the wide popularity of tablets as the "Tablet Pad." (4)

The compressed tablet of today is the most popular doseage form for medicines and it also has wide useage in other fields where uniform amounts of substances are required. Food and drug legislation, the raising of ethical standards, and improvements in manufacturing technique have all served to improve the compressed tablet to the extent that, unlike its counterpart of the "Tablet Pad" era with all its attendant evils, the compressed tablet of today is highly regarded as a predictable and reliable doseage form for medicines.

The Official Acceptance of Compressed Tablets as a Development of Modern Pharmacy

It is evident that compressed tablets are a development of modern Pharmacy when it is noted that the U.S.P.X., official in 1926, contained only one tablet, a tablet of 0.5 gram of mercuric chloride with a method of assay and a prescribed tolerance. The N.F.V., official in 1926, contained only 8 tablets all with specified composition and size, but there were no assay methods or tolerance statements. At the present time there is a total of 113 tablets in the official compendia, in contrast to the 9 mentioned above, and this indicates very clearly that the development and official acceptance of compressed tablets are recent achievements. At the present time assay methods, prescribed tolerances, and weight variation are prescribed for all tablets in both the compendia. There is no requirement for hardness, but disintegration times are given for many tablets.

REVIEW OF THE LITERATURE

According to Silver and Clarkson (5) great skill is not necessary in compressing the majority of formulae, the main requirement being a knowledge of the simple characteristics of the different drugs and chemicals. Other authorities are not entirely of this opinion but it is difficult to take strong issue with this assertion if the implication is merely conformity to present day standards. However, the raising of official requirements or standards has always coincided with development and improvement within the industry, therefore, it is logical to anticipate that the trend toward improvement will continue, present standards will be raised and then, perhaps, the assertion above may not be apropos.

Despite the general acceptability of the compressed tablet of today, as has often been observed, its manufacture is still an empirical process and the bulk of the literature is also largely empirical. The substance of most of the usual empirical literature on tablet manufacture consists of a description and discussion of the tableting equipment and of general procedures for granulating by the "wet" and "dry" methods replete with such indefinite stock phrases as, "moisten the powders to be granulated with the binder until it assumes approximately the consistency of brown sugar." The quantities of the auxiliary agents to be used are usually stated in very approximate amounts. The relative

merits of the many materials used as binders, fillers and lubricants are listed. The information that the most important attributes of a good granulation are uniformity, ability to flow freely and compressibility is always stressed. Rule of the thumb procedures for hardness and tablet disintegration are described and, finally, a list of difficulties commonly encountered, i.e. capping, picking, etc., are given with suggested causes for these conditions.

It has only been of late that experimental data, resulting from basic research on physical factors, have been available. In the light of very recent investigations on the quantitative correlation of variables in compressed tablets it appears that, if tablet manufacture is to be put on a more rational basis, certain physical factors or variables heretofore ignored should be considered. Higuchi et al, (6) have studied the influence of compressional force on density, porosity, hardness and disintegration of sulfathiazole tablets and have observed certain quantitative relationships among these variables. Further work is being done (7) on other formulations in this connection.

Definition and Composition of Compressed Tablets

The following might suffice for a terse definition of a compressed tablet and a summary of its composition and manufacture. A compressed tablet is a medicated or non-medicated mass, usually in the shape of a disk or flat

square, which is made by compressing dry gramular powders in specially constructed dies under a high force, approximately 2,500 pounds. If the principal medicinal ingredient is insoluble, an additional agent, e.g. starch, should be added which will make the tablet capable of disintegration in an aqueous medium. The granules must be compressible and if the material to be tableted does not possess this property, a suitable agent, e.g. starch paste, which will impart cohesiveness to the granules, should be used. After the substance to be compressed has been converted into uniform granules of suitable size by either the "wet" or "dry" granulating process and appropriate sieving, it is imperative that they flow freely and uniformly from the feed hopper into the die and not adhere to the punches or die during compression. If the granulation does not possess this property, a suitable lubricating agent must be added, e.g. talcum and/or magnesium stearate. The amount of force to be used for compression of the tablet should be such that the tablet will be hard enough to withstand the handling of its processing for market but not so extremely hard that porosity is reduced to the extent that ready permeation or solution by water is unduly delayed.

SUMMARY OF THE VARIABLES IN MANUFACTURING

When the tableting process is viewed for possible sources of variation, it might be well to begin by considering that this process is actually a series of mutually dependent operations. The ultimate properties of a given tablet would then be dependent upon the variables introduced by each operation in the series. Therefore, by adding or omitting an operation or ingredient, the sources of variation would be increased or decreased respectively. It follows that, aside from the chemical and physical properties of aspirin which play an important role in its behavior, the very uniform disintegration and hardness data for aspirin tablets can be partly related to the relatively few operations required for preparation of the granulation and the fact that only two ingredients are involved.

Another possible source of variation during manufacturing involves the method of incorporation of the ingredients into the granulation. For example, it is practically impossible to obtain a homogeneous granulation by adding starch to the formed granules. In the case of aspirin granulations, however, the starch and aspirin are combined as powders before precompression and, by so doing, an extremely high degree of homogeneity is attainable. This is a contributing factor to the uniform behavior of aspirin tablets with respect to hardness and rate of

disintegration tests. Another possible source of variation, also involving the method of incorporating ingredients, concerns the exact order in which several auxiliary agents, i.e. lubricants and disintegrants, are added to a granulation.

In view of the preceding discussion and the fact that the following information has wide acceptance, it may be stated: if the compressional force is relatively constant, as in routine tablet manufacture, or the compressional force is held exactly constant, as with a special force machine, the degree of uniformity of the granulation will largely determine the extent of variations in the compressed tablets. Therefore, any factor or condition of the granulating process, or the constituents of the granulation, would have to be considered as a potential variable in a summary of possible causes of variations in compressed tablets.

Some of the variables, then, which might influence the degree of uniformity of the granulation are: the previously mentioned method of incorporation and number of the ingredients; the number of unit operations used in the granulating process; and such physical properties of the granulation as moisture content, hardness and density of the particles and, the adsorptive powers of fine powders (1 μ - 250 μ). (8)

Other sources of variation in compressed tablets,

but not directly referrable to the granulating process, are: variance of compressional force, stratifying of the particles of the granulation in the hopper and the collecting of powders under the feed-shoe, as these conditions will cause weight variance. The machine, although constructed within close tolerances, is a potential source of variation because of the necessary amount of play between moving parts and bearing surfaces. Finally, the degree of atmospheric moisture has to be considered.

PLAN OF STUDY

The following is the plan that was carried out to study the effect of tablet machine feed variance on the various physical properties of tablets and the frequency of weight distribution.

Four thousand aspirin tablets, sulfathiazole tablets and sodium bicarbonate tablets, as well as 500 sodium bicarbonate and mint tablets, were weighed on a projection type analytical balance. The entire group of weights for each of the first three type tablets were partitioned into subgroups (see general procedure) of a 5 mg. range in order to show the frequency of weight in each range.

The height of approximately 12% of the tablets in each range was measured. Hardness data, for approximately 12%, and disintegration data, for approximately 20% of the tablets, were collected for the tablets in each range, or subgroup. Data for the effect of three different pH levels on the disintegration rates of sodium bicarbonate tablets were collected.

The tablets were compressed on industrial type tablet machines. The only variable that was relatively constant was the length of the compressional stroke. Therefore, the compressional force varied proportionally with weight variance. The work reported in this thesis concerns the influence of weight variance on other variables such as: hardness, disintegration time, and density.

Also described is a statistical analysis of the mass of data obtained for the weights of the different type tablets studied. Ranges, graphic methods, averages, standard deviations and percentage deviations are used. A comparison of the three distributions is also made.

Preparation of the Tablets Used

Since one of objectives of this work was to observe tablet machine performance, tablets were not collected for weighing and testing until it was determined that the machine had been closely set up for the weight required and that the variation in weight for any ten tablets was less than 5%. Ten tablets were weighed periodically after that as a check, approximately 15 minutes apart, but the machine was not regulated or changed in any way thereafter. The weight variation at each check was not found to exceed 5%. A summary of the preparation of each tablet is given below.

The aspirin tablets were prepared by compressing a commercial granulation, containing 10% starch and obtained from the Dow Chemical Co., with a Stokes Rotary tablet machine type R-D_3 and 3/8" punches and die.

Three pounds of sodium bicarbonate USP grade were granulated with 0.9 pound of a 10% starch paste using a Colton rotary wet granulator type 3 WG . After drying for 4 hours at 50°C., the granules were cooled and ground

to a no. 16 mesh in a Stokes Hance type drug mill. The granulation, after addition of 1% magnesium stearate, was compressed into tablets using the Stokes rotary machine with 3/8" punches and die.

The sodium bicarbonate and mint tablets were prepared similarly with the preceding except for two modifications: 0.05% oil of peppermint was incorporated by spraying the granulation with an alcoholic solution prior to the addition of the magnesium stearate and considerably more force was used for compressing the tablets.

The sulfathiazole tablets were prepared by granulating 7.67 pounds of sulfathiazole USP grade with 2.45 pounds of a 10% starch paste using the Colton rotary wet granulator. After drying for 4 hours at 60°C., the granules were cooled and ground to a no. 20 mesh. Ten per cent of starch and 1% of magnesium stearate, by weight, were added to the granulation before compressing the tablets on a Colton single punch tablet machine (type 3 ET) with 7/16" punches and die. The machine was set up to compress tablets weighing 8.9 grains.

EXPERIMENTAL

General Procedure:

Four thousand of each of the following: sulfathiazole tablets, aspirin tablets and sodium bicarbonate tablets; and 500 sodium bicarbonate and mint tablets were weighed individually on a projection type analytical balance. The heights of approximately (See Table X) 12% of the total of the numbers above were measured with a micrometer caliper; approximately 12% of the total number were tested for Strong Cobb hardness; and approximately 20% were disintegrated by various methods. In the selection of a tablet to be measured, or tested, a simple sampling procedure was followed, whereby, the same set of circumstances essential to drawing a random sample existed throughout the whole series of drawings.

After each tablet was weighed, it was placed in one of a consecutive series of labelled, stoppered bottles according to the weight of the tablet. Each bottle represented a 5 mg. differential and contained tablets, therefore, that were heavier by 5 mg. on the average than the tablets in the preceding bottle and lighter by the same amount than the tablets in the succeeding bottle. This arrangement was followed in order to determine the frequency of weights in each differential and plot the frequency distribution. Another purpose of the progressive arrangement of the tablets by weight was to enable

measurement of height, hardness data and disintegration data to be collected for each group of tablets in the series. The purpose of this was to determine the effect of weight deviation on these variables, and possibly, other correlations.

Sodium bicarbonate tablets were disintegrated at three different pH levels to study the possible effect of pH on the rate of disintegration of these tablets.

Method for Hardness Determination

A Strong Cobb hardness tester was used to determine the hardness of the tablets and the values were expressed in Strong Cobb units. Rao (9) has sketched the apparatus and described the procedure. However, because of the large number of tablets to be tested and the relatively small differences in hardness, modification of the apparatus and procedure was found to be necessary.

Instead of using the pump of the instrument to build up pneumatic pressure, the pump was disconnected and the instrument was connected to a compressed air line with a needle valve placed between the two. A long handle was attached to the valve and a stop was provided in order that the handle could be swung quickly to the same point each time. The position of the stop was so situated that after the handle was brought against it, the compressed air flowed slowly and uniformly from the line into the

instrument. The time required for sufficient pressure to build up in the instrument varied from about 10 to 30 or more seconds depending upon the degree of hardness of the tablets.

It was possible to obtain very close approximations with this arrangement and the utilization of the rider type pointer. The rider pointer was forced up each time by the bottom pointer, or index pointer, of the gauge as the pressure in the cylinder increased and, although the index pointer dropped to the zero mark after each tablet broke, the rider pointer remained at the position on the dial which indicated the amount of pressure that had been required to break the tablet.

By using this arrangement, the operation was fairly well standardized and, in view of the large number of tablets tested, it was far less arduous than would have been the case with the unmodified procedure. Another advantage involved the fact that the slow flow of air into the hardness tester prevented the rider pointer, the position of which indicated the degree of hardness on the dial, from being bounced to a higher position by the recoil of the bottom or gauge indicator after a tablet broke. The latter occurred when air was introduced fairly rapidly. If this factor of the index pointer recoiling and bumping the rider pointer had been disregarded, it is doubtful in the case of the softer tablets, particularly the sodium

bicarbonate tablets, if reproducible data would have been obtained, since the differences in hardness between the various weight groups were relatively small.

Disintegration and Discussion of Methods Used

It was necessary to explore a number of methods for determining rates of disintegration before sufficiently sensitive ones, enabling reproducible data to be obtained, were discovered. This was to be expected since the variations in weight and hardness of the tablets were relatively small and it followed that the effect of these variables on the rate of disintegration would be proportionally small. Several methods were eventually devised and found to give indicative results but one was sought which could be simply standardized and involve an apparatus and procedure suitable for disintegration tests on all the tablets studied. This was ultimately accomplished.

The first method tried was essentially the method of the USP with a few minor changes. (10) The results, see Table VI, obtained indicated plainly that the method was not adaptable for qualitative or quantitative studies on disintegration rates of tablets manufactured as these were. The method has been used successfully where the difference in the compressional force applied to tablets was 500 or more pounds. But, when the compressional force varies only slightly, as is the case when tablets are

compressed as these were on an industrial type tablet machine with mechanical regularity, the USP procedure is suitable only as a limit test.

The rapid rate of disintegration of the aspirin tablets made it impossible to conclude anything except the fact that they had disintegrated when the USP method was used. But with a method employing a stationary, vertical tube and water highly reproducible results were obtained, to the extent that it was found possible to distinguish between two groups of nine tablets each, differing in weight by 10 mg., simply on the basis of a comparison of the different rates of disintegration. The possibility of prejudicial errors in the preceding was obviated by concealing the weights of the tablets from the operator until they were disintegrated. The procedure merely involved the dropping of the tablet into the column of water in the tube with one hand and the simultaneous starting of the timing device with the other hand; and, when disintegration was complete, the stopping of the timing device. The tube was 1.2 cm. in diameter and had an effective length of 57.5 cm. See Table VI and Figure 2.

Another method, used for the disintegration of some of the sulfa tablets and sodium bicarbonate tablets, here involved the following equipment and procedure. A glass tube, stoppered at both ends, with an effective length of 130 cm. and a diameter of 1.7 cm., was filled with water

except for 1.9 cm. The latter air space was responsible for a bubble coursing up through the column of water, striking the tablet and, thereby, aiding disintegration each time the tube was inverted. The tube was fastened at the mid-point with a swivel type clamp to a fixed, vertical iron bar in order that the tube could be inverted each time the partially disintegrated tablet settled to the bottom, until disintegration was complete.

The data obtained by this method were reproducible and appeared indicative, as shown in Tables VII and VIII. However, since the temperature was not held exactly constant, the results were not used as a basis for the conclusions drawn in this paper. The effect of temperature on the rate of disintegration was determined only for the aspirin tablets and is shown in Figure 2.

The method which was eventually devised to meet the previously stated requirements of ready standardization and adaptability for disintegrating all the tablets studied, involved the following. The apparatus consisted essentially of a 20L Pyrex glass jar to hold the disintegration fluid (water), an electric heating element to maintain the temperature of the water at 37°C., an electric motor, rheostats for suitable speed reduction of the motor and regulation of the heating element and, a tube-basket assembly which was attached to the shaft at a distance of approximately 2.5 cm. from the motor.

The tube-basket assembly consisted of a rubber stoppered glass tube, with an effective length of 7.8 cm. and a diameter of 2.15 cm., provided with a round opening, approximately 2 cm. in diameter, closely adjacent to the stoppered end. The rubber stopper had a single, centric hole by means of which the proximal end of the tube-basket was tightly fitted to the shaft of the motor. A circular 10-mesh wire cloth basket was secured snugly around the distal end of the tube in such a fashion as to allow the mesh basket to extend 2.5 cm. below the end of the tube and 3.5 cm. below the surface of the water in the glass jar. The portion of the basket that protruded below the tube was the functional part of the apparatus.

The following procedure was used with this apparatus. The speed of the motor was adjusted to 520 r.p.m. for the sulfathiazole tablets and sodium bicarbonate tablets and 172 r.p.m. for the aspirin tablets, since these rates led to good reproducibility. The adjustments were made with the rheostat and the use of a tachometer. The motor was not stopped each time a tablet was to be disintegrated, since it was conveniently possible to reduce the speed to about 1 r.p.m. by pressure of a finger against the shaft. The tablet to be disintegrated was inserted through the opening in the side of the tube-basket assembly with one hand and the timing device was started simultaneously with the other hand. Disintegration was considered complete after the last fragment of the tablet had been impelled through the screen.

Certain Advantages of the Method; Comparison with the USP Procedure

As a limit test for the rate of disintegration the previous method offers no advantage over the USP procedure since preciseness would not be indicated in this type of determination. Its principle advantage in this experiment was the fact it proved to be a method whereby reproducible, indicative data could be obtained on tablets that differed only slightly with respect to weight, hardness and rate of disintegration. The USP method is suitable for obtaining similar data only where differences in compressional force, hardness and rate of disintegration are relatively large.

Some of the reasons why the method devised in this experiment is more sensitive become evident when a comparison is made between the essential features of each procedure. In the USP procedure the basket-rack must be withdrawn from the bath in order to place a tablet in each tube and difficulty was experienced in wetting the tablets, since the basket-rack and tablets had to be returned slowly to the bath in order to avoid splashing. On the other hand in the method developed here the tube and basket need not be withdrawn from the bath since the tablet is inserted through the opening in the side of the tube and drops to the bottom. The momentum of the falling tablet plunges it into the water and, consequently, facilitates rapid wetting and permits prompt starting of the timing device. This is in direct contrast

to the slower wetting and immersion of the tablets in the USP method; with the resulting variation or error caused by not starting the timing device until all the tablets are sufficiently wetted to be immersed, even though one or several of the tablets begin to disintegrate in the intervening time.

The revolving basket arrangement has a centrifugal action and the resultant force tends to impel the granules of the disintegrating tablet outward from the center of rotation through the mesh, whereas in the USP procedure, gravity is largely relied on to cause the granules to pass through the mesh. Frequently, in the use of the USP procedure, several granules of apparent equal dimensions were observed to require vastly different periods of time to drop through the mesh, apparently for the following reasons: adherence to the wire of the mesh, or the long dimension of the granule happened to be perpendicular to the mesh, thereby enabling it to pass through, whereas another granule would seemingly fail to drop through the mesh only because its long dimension happened to be horizontal to the mesh. These conditions were not encountered in the method developed and used in this work.

In the determination of disintegration rates of tablets prepared without a disintegrating agent, i.e. sodium bicarbonate tablets, solubilizing of the principle ingredient is an important factor in the disintegrating process. The effect of solution is to cause the tablet to gradually become

smaller and, at the same time, the solvent appears to slowly permeate the tablet until many small perforations are formed. The tablet finally breaks up into fragments of granule size which pass thru the wire mesh. The method involving the rotating basket provided for more rapid displacement of the solvent around the tablet and, therefore, quicker solution and disintegration. The results indicated good reproducibility.

Calculations involved the following formula:
Obtaining the average or mean value of a series of data:

$$\text{Average} = \bar{x} = \frac{\Sigma X}{N}$$

where Σ denotes summation of all the N values of the variable X, where N is the number of observations. Mean values are used in this paper unless otherwise stated.

The standard deviation was used as a measure of variation and precision.

$$\text{Standard deviation} = \sigma = \sqrt{\frac{\Sigma (x-\bar{x})^2}{N-1}}$$

where the average is subtracted from the value for each individual observation and this difference is squared. The squares are then added as denoted by Σ and this sum is divided by N-1, one less than the number of values used. Then the square root of this quotient is the standard deviation.

$D = \frac{W}{h}$ was used as a measure of density, where D varies as the density and W equals mass and h equals the height of a tablet. The formula was used because it includes the three

variables in the formulas that would be used to determine the geometric volume of a concave tablet. The other values involved were treated as constants. It is actually a measure of the tablet density multiplied by a constant, volume/height.

DATA

The graphs were plotted from the values in Tables I - VI and are arranged as follows for convenience of discussion. The values used are mean values, unless indicated otherwise.

1. Figure 1: Weight variance vs. disintegration time of aspirin tablets using rotating tube-basket at 172 r.p.m. and at 37°C.

2. Figure 2: Weight variance vs. disintegration time of aspirin tablets using stationary, vertical tube at 35°C., also at 24.8°C.

3. Figure 3: Weight variance vs. disintegration time of sodium bicarbonate tablets at three different pH levels. The rotating tube-basket was used at 37°C. and 520 r.p.m.

4. Figure 4: Weight variance vs. disintegration time of sodium bicarbonate and mint tablets at two different pH levels and the same conditions as in preceding figure.

5. Figure 5: Weight variance vs. disintegration time of sulfathiazole tablets with the rotating tube-basket at 520 r.p.m. and at 37°C.

6. Figures 6-9: Weight variance vs. hardness of the tablets. "S-C units" are used as an abbreviation for "Strong-Cobb units".

7. Figures 10-13: Weight variance vs. height of the tablets.

8. Figures 14-16: Weight variance vs. the quotient of weight over height. The quotient of weight over height is

used as a measure of the approximate density.

9. Figures 17-19: Frequency of weight distribution curves

10. Figure 20: Hardness of aspirin tablets vs. disintegration time by plotting the mean values for each in Table I.

11. Figure 21: Hardness of aspirin tablets vs. weight over height, as a measure of density, by using values in Table I.

12. Figure 22: Disintegration time of aspirin tablets vs. weight over height utilizing the data in Table I.

The tables are arranged as follows:

1. Tables I-VI: Contain values for the above plots.

2. Tables VII-VIII: Disintegration times for sodium bicarbonate and mint tablets and sulfathiazole tablets using a tube with vertical rotation.

3. Table IX: Total numbers of tablets measured and tested, and referred to in the procedure as approximate percentage amounts.

4. Tables X-XI: Determination of the degree of reproducibility of the various methods used for disintegration times of sulfathiazole tablets and aspirin tablets.

5. Table XII: Range of deviation and percentage deviation of 4,000 aspirin tablets, sodium bicarbonate tablets, and sulfathiazole tablets. Standard deviations and the mean weights are also included for comparisons.

TABLE I

Physical Properties of Aspirin Tablets

Weight in grams	0.350-0.355	0.355-0.360	0.360-0.365	0.365-0.370	0.370-0.375	0.375-0.380
Mean Weight	0.1919	0.1929	0.1937	0.1948	0.1957	0.1965
Mean Disintegration (tube)	6.9	7.5	8.5	9.3	10.4	11.0
Mean Hardness	4.8	6.1	7.6	8.3	9.8	11.1
Weight/Height	1.824	1.843	1.859	1.874	1.891	1.908
Mean Disintegration (tube-basket)	4.6	5.4	6.2	6.8	7.7	8.6

The approximate number of tests for each range are: rate of disintegration 20%, hardness 12% of total and height 12% of total. (See Table V for total in each range.) In the above ranges where the indicated % amounts were less than 60, the heights of one half of the total tablets were measured and tested for hardness; the other half was tested for disintegration time.

Hardness is expressed in Strong-Cobb units.

Disintegration times are expressed in seconds.

Heights of the tablets are expressed in inches.

Weight over height, used as a measure of approximate density, is computed from the values in the above table.

TABLE II

Physical Properties of Sodium Bicarbonate Tablets

Weight in grams	0.330-0.335	0.335-0.340	0.340-0.345	0.345-0.350	0.350-0.355	0.355-0.360
Mean Height	0.1462	0.1469	0.1477	0.1484	0.1490	0.1498
Mean Disintegration (pH 2.0)	48	54	64	72	83	89
Mean Disintegration (pH 8.0)	49	54	67	74	80	87
Mean Disintegration (pH 7.0)	50	52	65	75	79	93
Mean Hardness	2.5	2.8	3.3	3.6	4.3	4.8
Weight/Height	2.257	2.281	2.302	2.325	2.346	2.369

The approximate number of tablets tested in each range are: disintegration 20% of total in the range, hardness 12% of the total and height 12% of the total. (See Table V for total in each range.) Where the indicated percentage amounts were less than 60, the heights of one half of the total in the range were measured and tested for hardness; the other half was tested for disintegration time.

Hardness is expressed in Strong-Cobb units.

Disintegration times are expressed in seconds (obtained with tube-basket).

Heights of the tablets are expressed in inches.

Weight over height, used as a measure of approximate density, is computed from the values in the above table.

S.C.

TABLE III

Physical Properties of Sodium Bicarbonate and Mint Tablets

Weight in grams	0.330-0.335	0.335-0.340	0.340-0.345	0.345-0.350	0.350-0.355	0.355-0.360
Mean Height	0.1293	0.1302	0.1307	0.1317	0.1328	0.1336
Mean Disintegration (pH 2.0)	282	340	360	417	510	575
Mean Disintegration (pH 8.0)	285	338	375	425	490	572
Weight/Height	2.552	2.573	2.601	2.620	2.636	2.655
Mean Hardness	12.4	13.0	13.7	14.8	15.3	16.4

Tests were conducted on 30 tablets in each weight range for each physical property.

Hardness is expressed in Strong-Cobb units.

Disintegration times were obtained using the rotating tube-basket and are expressed in seconds.

Heights of the tablets are expressed in inches.

Weight over height, used as a measure of approximate density, is computed from the values in the above table.

TABLE IV

Physical Properties of Sulfathiazole Tablets

Weight in grams	0.565-0.570	0.570-0.575	0.575-0.580	0.580-0.585	0.585-0.590	0.590-0.595
Mean Height	0.2038	0.2044	0.2058	0.2072	0.2081	0.2090
Mean Disintegration	190	224	250	264	282	286
Mean Hardness	14.2	14.5	14.6	14.6	14.8	15.0
Weight/Height	2.772	2.788	2.794	2.799	2.811	2.823

The approximate number of tablets tested in each range are: disintegration 20% of total number in the range, hardness 12% of the total and height 12% of the total. (See Table V for total number in each range).

Hardness is expressed in Strong-Cobb units.

Disintegration times are expressed in seconds (obtained with tube-basket).

Heights of the tablets are expressed in inches.

Weight over height, used as a measure of approximate density, is computed from the values in the above table.

TABLE V

Frequency Distribution of Weights of Tablets

Aspirin		Sodium Bicarbonate		Sulfathiazole	
Weight range 5 mg.	Frequency	Weight range 5 mg.	Frequency	Weight range 5 mg.	Frequency
0.350 - 0.355 grm	135	0.320 - 0.325 grm	127	0.555 - 0.560 grm	37
0.355 - 0.360 "	577	0.325 - 0.330 "	657	0.560 - 0.565 "	202
0.360 - 0.365 "	1390	0.330 - 0.335 "	839	0.565 - 0.570 "	468
0.365 - 0.370 "	1323	0.335 - 0.340 "	908	0.570 - 0.575 "	717
0.370 - 0.375 "	78	0.340 - 0.345 "	812	0.575 - 0.580 "	786
		0.345 - 0.350 "	492	0.580 - 0.585 "	754
		0.350 - 0.355 "	119	0.585 - 0.590 "	620
		0.355 - 0.360 "	46	0.590 - 0.595 "	338
				0.595 - 0.600 "	89
				0.600 - 0.605 "	20

Weights in grams	0.565	0.570	0.575	0.580	0.585	0.590
	319	484	315	215	283	444
	223	598	118	746	376	294
	497	403	410	424	437	503
	286	419	696	347	278	386
	461	310	395	462	464	131
	352	159	340	310	325	312
	339	885	142	253	195	208
	937	272	485	654	1200	337
	554	235	355	292	702	653
Median Value	352	419	355	347	376	337

Table VI. Disintegration times in seconds are given for sulfathiazole tablets. Each column represents a range of the weight given plus 0.00_5 gram. The times were obtained with the modified USP procedure.

Weights in grams	0.330	0.335	0.340	0.345	0.350	0.355
	250	330	305	390	470	540
	280	310	335	450	490	470
	288	222	324	438	502	482
	232	294	422	450	513	598
	220	305	342	462	485	674
	270	210	210	400	345	620
	292	298	203	414	334	612
	250	275	350	420	495	480
	205	342	365	408	504	492
	270	315	410	440	525	610
	259	327	330	472	496	687
Median Value	259	305	335	420	495	610

Table VII. Disintegration times in seconds for sodium bicarbonate and mint tablets using tube and vertical rotation. Each column represents a range of the weight given plus 0.005 gm.

Weights in grams	0.565	0.570	0.575	0.580	0.585	0.590
	132	185	216	188	136	130
	112	182	170	162	145	150
	146	220	218	192	151	147
	144	165	164	190	131	138
	183	165	166	207	149	151
	111	130	144	144	152	158
	135	160	142	160	170	162
	192	170	148	179	175	131
	206	198	152	202	180	220
	140	183	155	184	138	117
	160	197	173	186	160	181
	179	165	188	185	173	136
	191	175	222	190	112	160
	138	150	200	158	125	143
	145	170	280	144	177	163
	135	215	182	148	160	120
	154	138	140	198	176	131
	164	142	108	202	186	140
	174	162	142	200	165	180
	189	172	112	150	194	200
	142	162	155	175	138	132
	158	171	165	162	160	150
	148	160	160	188	149	141
	156	164	182	180	166	136

	165	182	172	185	174	161
	160	195	168	192	171	148
	155	170	176	186	159	145
Median Value	155	170	166	184	160	148

Table VIII. Disintegration times in seconds for sulfathiazole tablets with tube and vertical rotation.

	Aspirin	Sulfathiazole	Sodium Bicarbonate
Weight	570	590	275
Hardness	428	444	502
Disintegration	842	1121	588

Table IX. Total numbers of tablets measured and tested and referred to approximately as percentage amounts in the description of the general experimental procedure.

Reading	Deviation	Square of deviation
188 sec.	6	36
192	10	100
190	8	64
207	25	625
164	18	324
160	22	484
179	3	9
202	20	400
184	2	4
186	4	16
185	3	9
190	8	64
162	20	400
184	2	4
162	20	400
158	24	576
184	2	4
198	16	256
200	18	324
		4099

$$\sigma = \sqrt{\frac{\Sigma(x-\bar{x})^2}{N-1}} = \sqrt{\frac{4099}{18}} = 15.1$$

Reading	Deviation	Square of deviation
319 sec.	109	11881
223	205	42025
497	69	4761
286	142	20164
461	33	1089
352	76	5776
339	89	7921
937	509	259081
554	126	15876
484	56	3136
598	170	28900
403	25	625
419	9	81
310	118	13924
159	269	72361
885	457	208849
272	156	24336
235	193	37249
418	10	100
		758135

$$\sigma = \sqrt{\frac{\Sigma(x-\bar{x})^2}{N-1}} = \sqrt{\frac{758135}{18}} = 205$$

Table X. Use of the standard deviation as a measure of precision of the methods used in disintegrating sulfathiazole tablets. The modified USP procedure was used for disintegration times in the righthand column; the rotating basket was used for those in the lefthand column.

Reading	Deviation	Square of deviation
5.5 sec.	0.1	0.01
4.6	0.8	0.64
6.4	1.0	1.00
5.9	0.5	0.25
5.8	0.4	0.16
5.6	0.2	0.04
5.4	0.0	0.00
5.2	0.2	0.04
5.4	0.0	0.00
5.1	0.3	0.09
5.3	0.1	0.01
5.9	0.5	0.25
5.4	0.0	0.00
4.8	0.6	0.36
5.5	0.1	0.01
5.1	0.3	0.09
5.0	0.4	0.16
4.9	0.5	0.25
4.8	0.6	0.36
5.4	0.0	0.00
4.8	0.6	0.36
5.8	0.4	0.16
5.5	0.1	0.01
5.4	0.0	0.00
5.9	0.5	0.25
5.8	0.4	0.16
5.5	0.1	0.01
4.6	0.8	0.64
		5.31

$$\sigma = \sqrt{\frac{\Sigma (x-\bar{x})^2}{N-1}} = \sqrt{\frac{5.31}{27}} = 0.44$$

Reading	Deviation	Square of deviation
6.7 sec.	0.6	0.36
6.8	0.5	0.25
7.0	0.3	0.09
7.4	0.1	0.01
6.8	0.5	0.25
7.3	0.0	0.00
7.1	0.2	0.04
6.8	0.5	0.25
7.7	0.4	0.16
7.6	0.3	0.09
6.7	0.6	0.36
7.1	0.2	0.04
7.6	0.3	0.09
7.4	0.1	0.01
7.4	0.1	0.01
7.5	0.2	0.04
6.8	0.5	0.25
7.3	0.0	0.00
7.4	0.1	0.01
7.4	0.1	0.01
6.8	0.5	0.25
7.7	0.4	0.16
7.0	0.3	0.09
7.5	0.2	0.04
7.5	0.2	0.04
7.0	0.3	0.09
8.0	0.7	0.49
8.0	0.7	0.49
		3.97

$$\sigma = \sqrt{\frac{\Sigma (x-\bar{x})^2}{N-1}} = \sqrt{\frac{5.31}{27}} = 0.38$$

Table XI. Use of the standard deviation as a measure of precision of the methods used in disintegrating aspirin tablets. The tube method was used for times in the righthand column; the rotating basket for those in the lefthand column.

VARIATIONS IN WEIGHTS OF TABLETS

	Aspirin	Sodium Bicarbonate	Sulfathiazole
Mean	0.362	0.334	0.576
Standard deviation	0.0053	0.0073	0.0088

Percentage of total	Range of deviation from mean	Percentage deviation	Percentage of total	Range of deviation from mean	Percentage deviation	Percentage of total	Range of deviation from mean	Percentage deviation
67%	LT 0.005	2.8%	43.7%	LT 0.005	3%	36.4%	LT 0.005	1.8%
28%	MT 0.010 & LT 0.015	5.5%	36.7%	MT 0.010 & LT 0.015	6%	33.3%	MT 0.010 & LT 0.015	3.5%
5%	MT 0.015 & LT 0.020	8.3%	18.5%	MT 0.015 & LT 0.020	9%	20.1%	MT 0.015 & LT 0.020	5.2%
	Weighted Average of total	3.6%	1.1%	MT 0.020 & LT 0.025	12%	7.2%	MT 0.020 & LT 0.025	6.9%
				Weighted Average of total	5.3%	1.3%	MT 0.025 & LT 0.030	8.7%
							Weighted Average of total	3.5%

Table XII. The tablets in each range are expressed as percentages of the total weighed, 4000. The deviation is from the average weight, or mean, and is expressed in grams. "LT" and "MT" are abbreviations for "less than" and "more than" respectively.

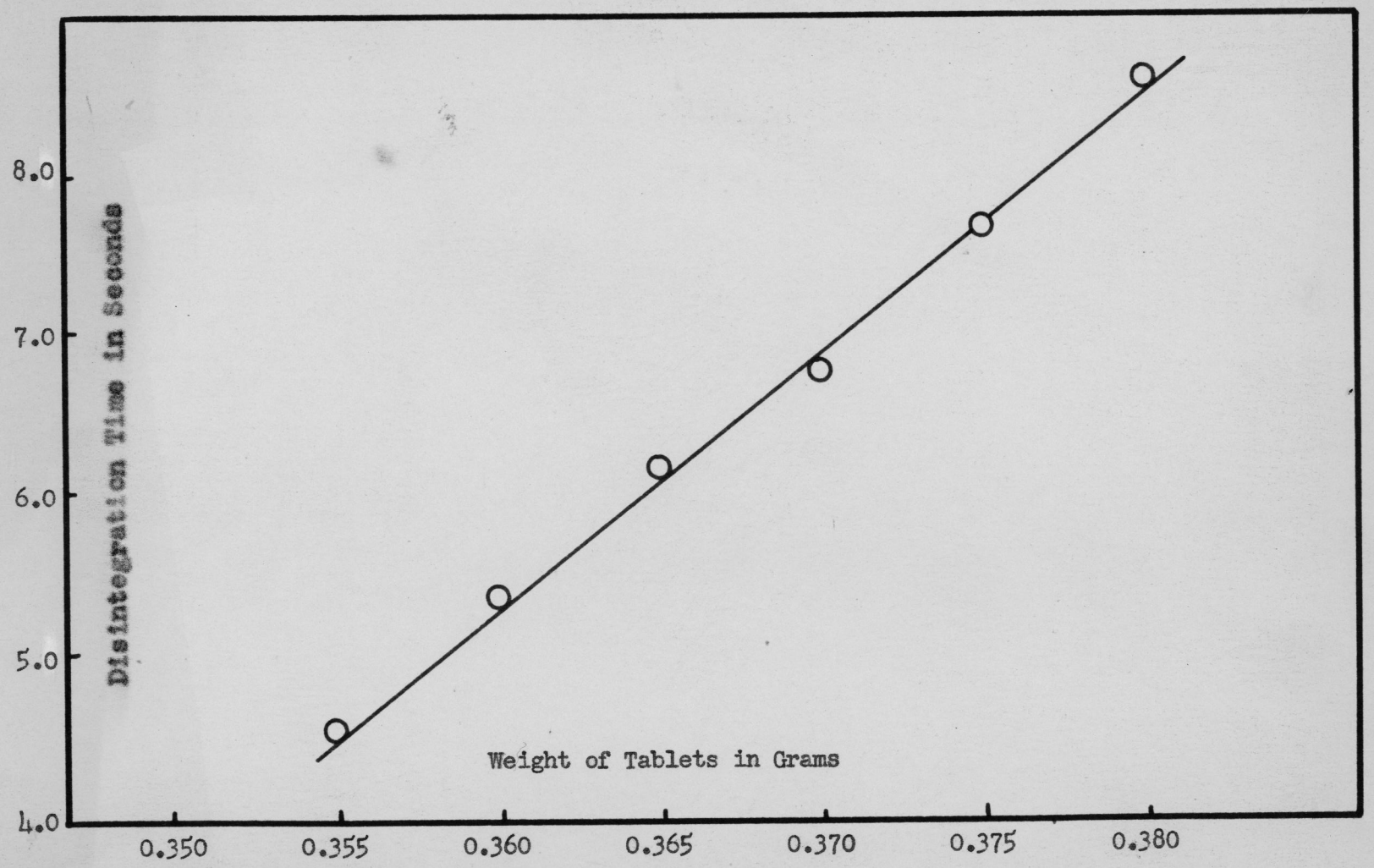

Fig. 1. Disintegration Time vs. the Weight of Aspirin Tablets.

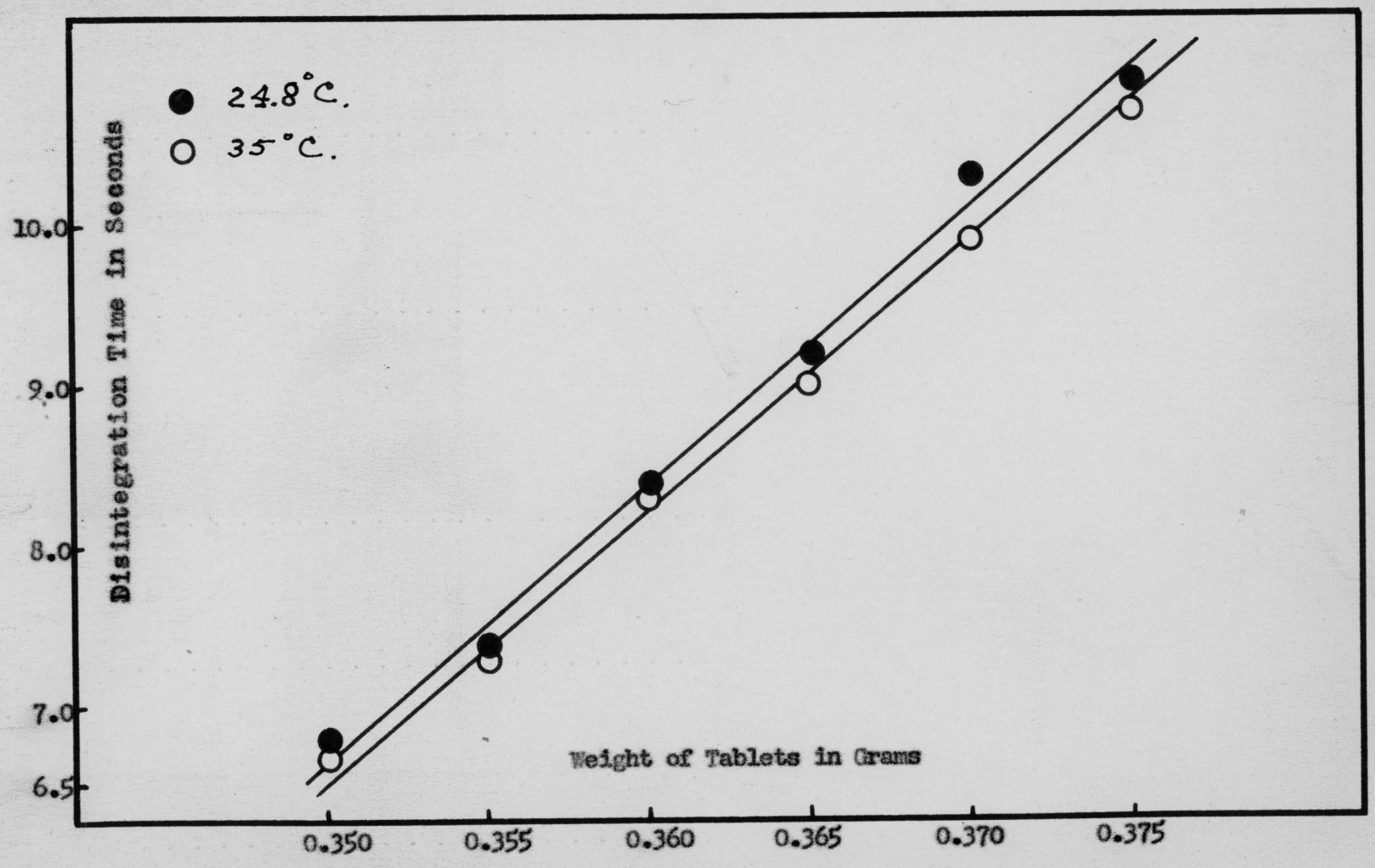

Fig. 2. The Influence of Temperature on the Disintegration Time of Aspirin Tablets.

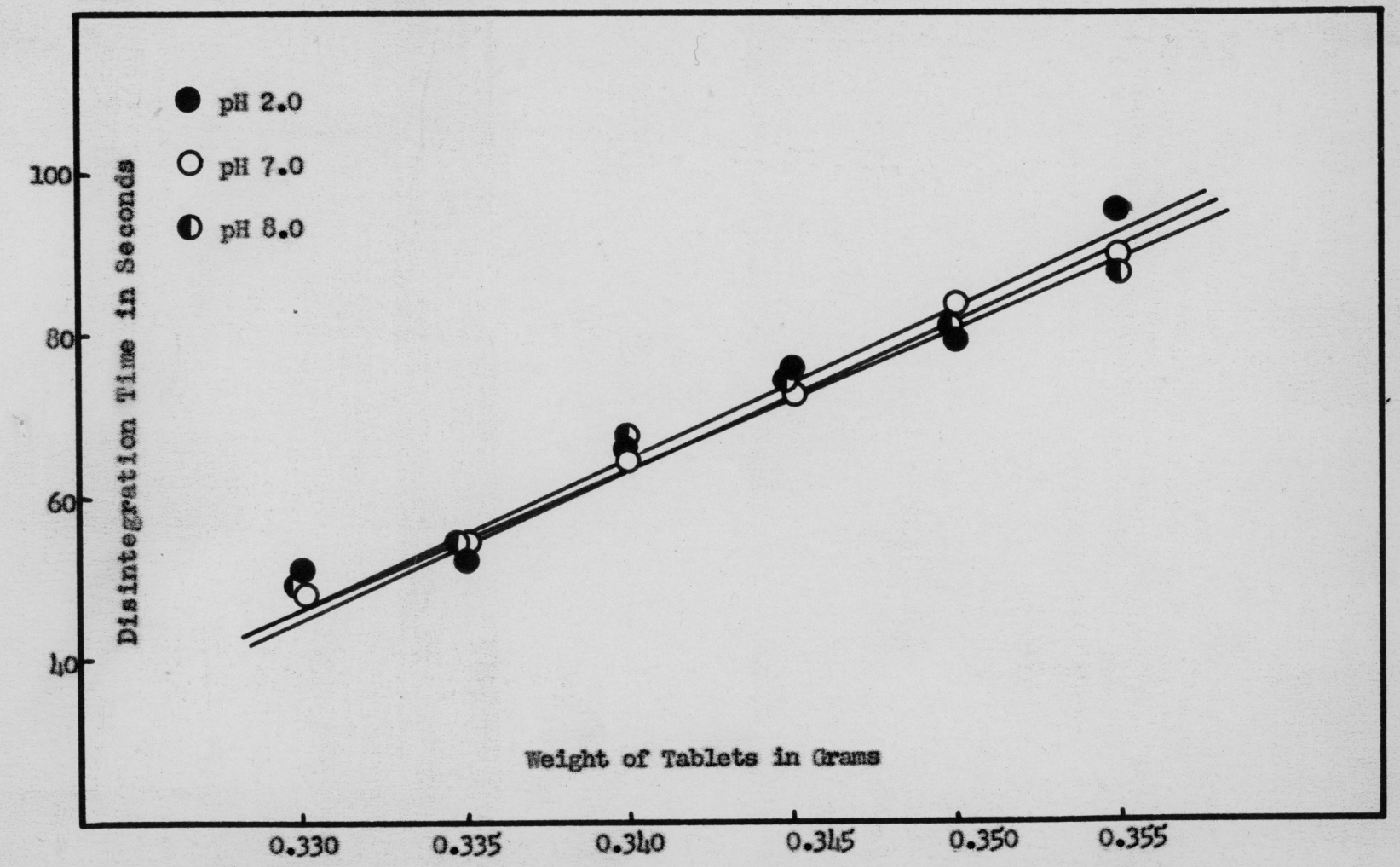

Fig. 3. The Influence of pH on the Disintegration Time of Sodium Bicarbonate Tablets.

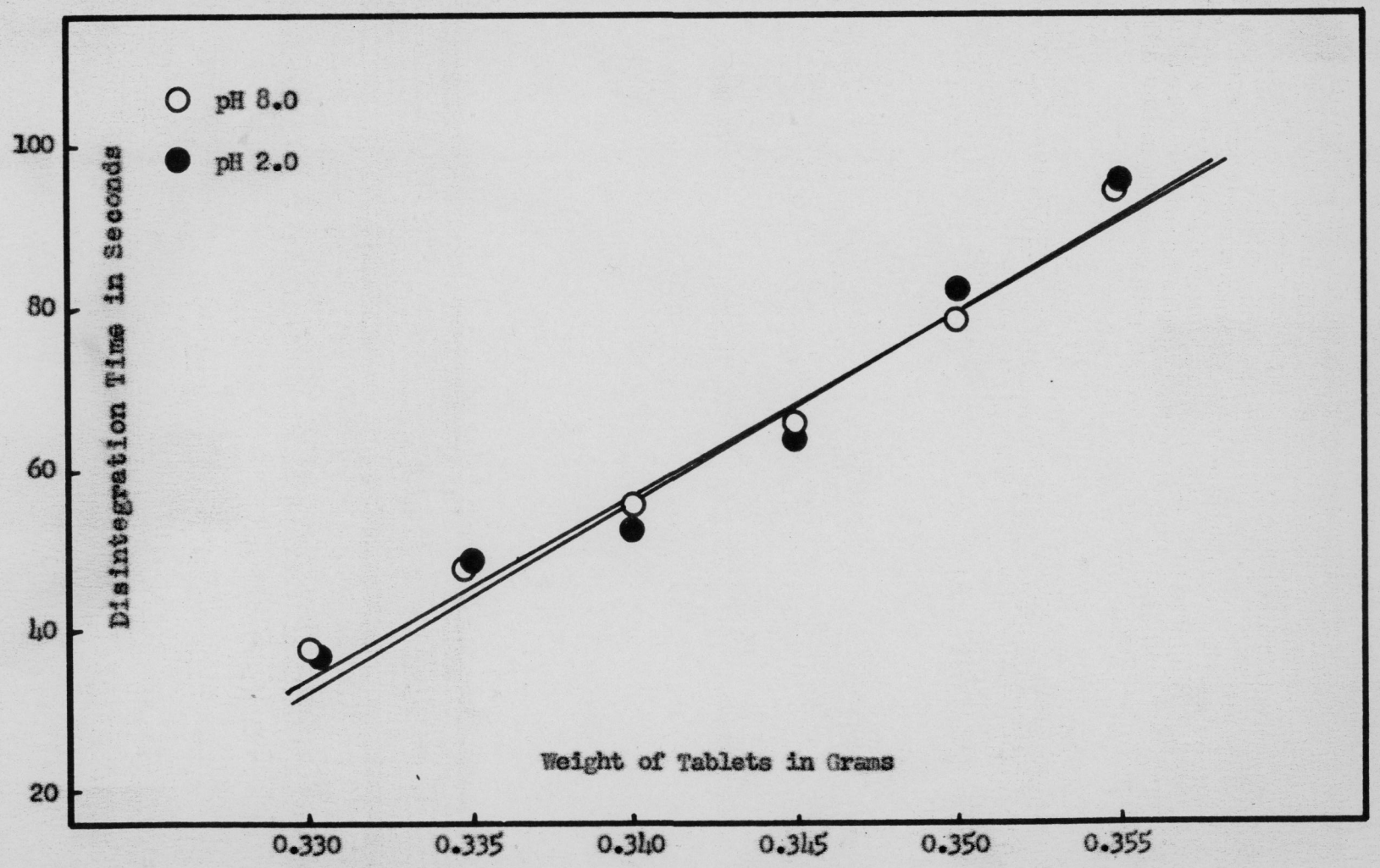

Fig. 4. The Influence of pH on the Disintegration Time of Sodium Bicarbonate and Mint Tablets.

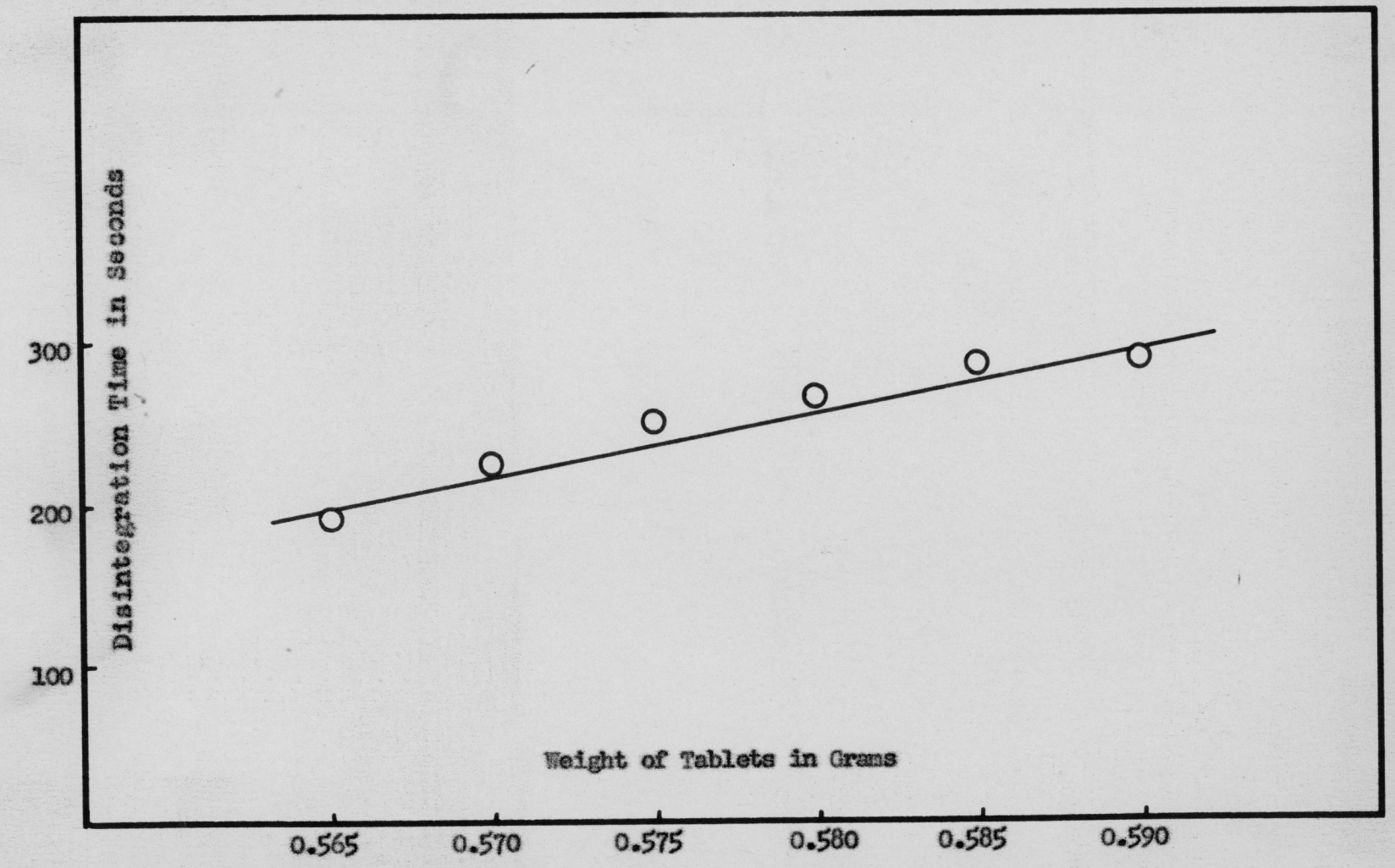

Fig. 5. Disintegration Time vs. the Weight of Sulfathiazole Tablets.

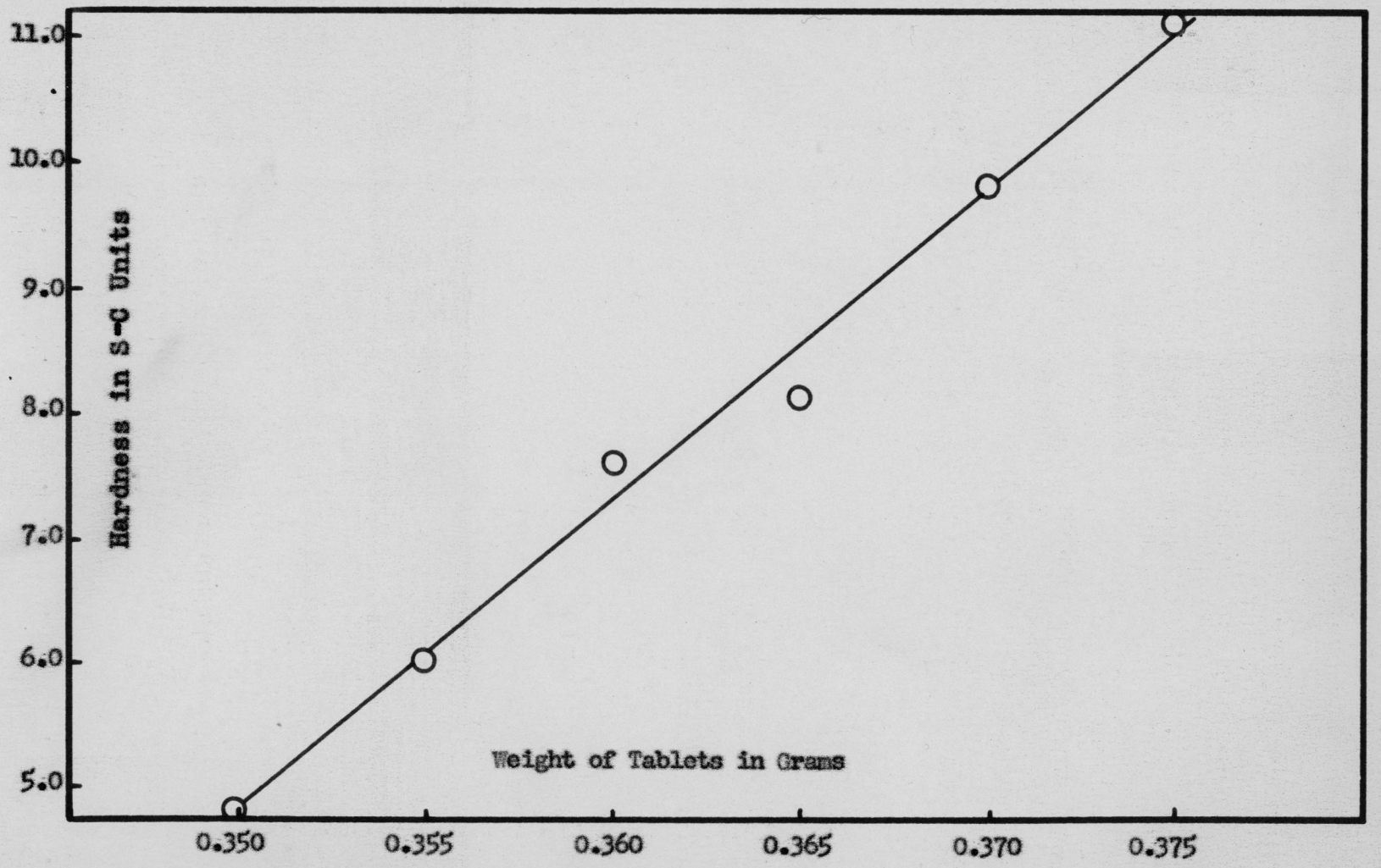

Fig. 6. Hardness vs. the Weight of Aspirin Tablets.

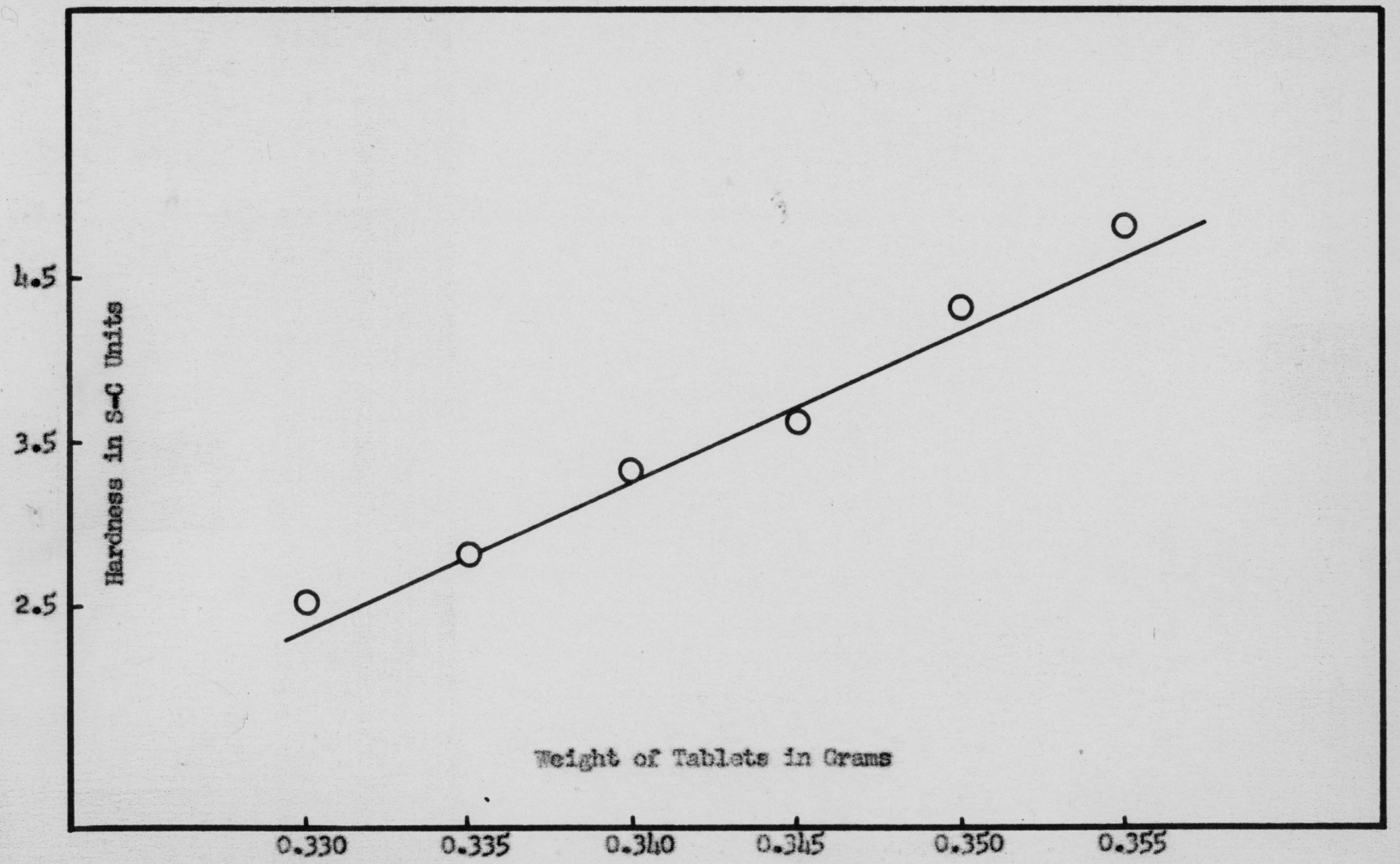

Fig. 7. Hardness vs. the Weight of Sodium Bicarbonate Tablets.

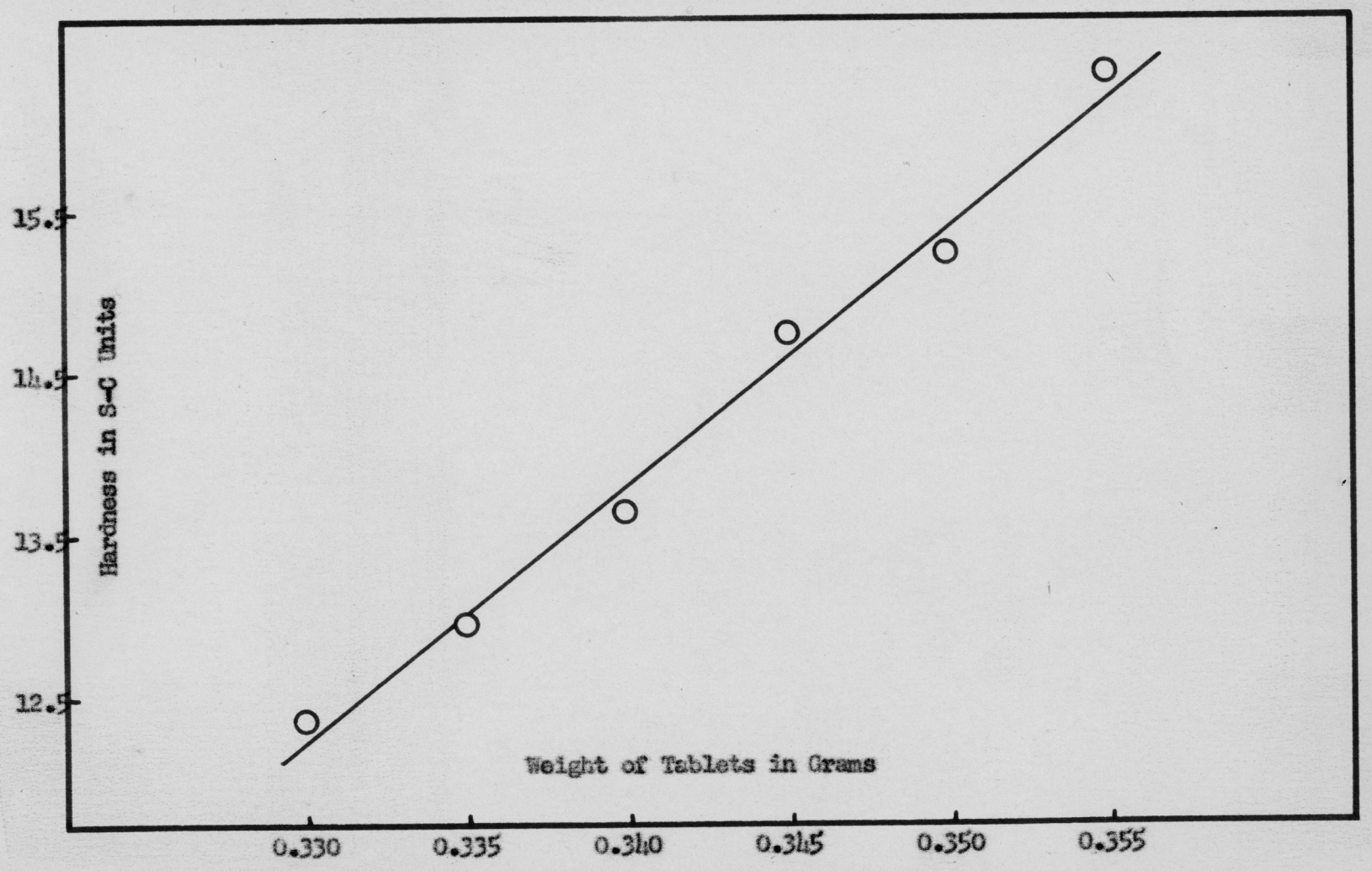

Fig. 8. Hardness vs. the Weight of Sodium Bicarbonate and Mint Tablets.

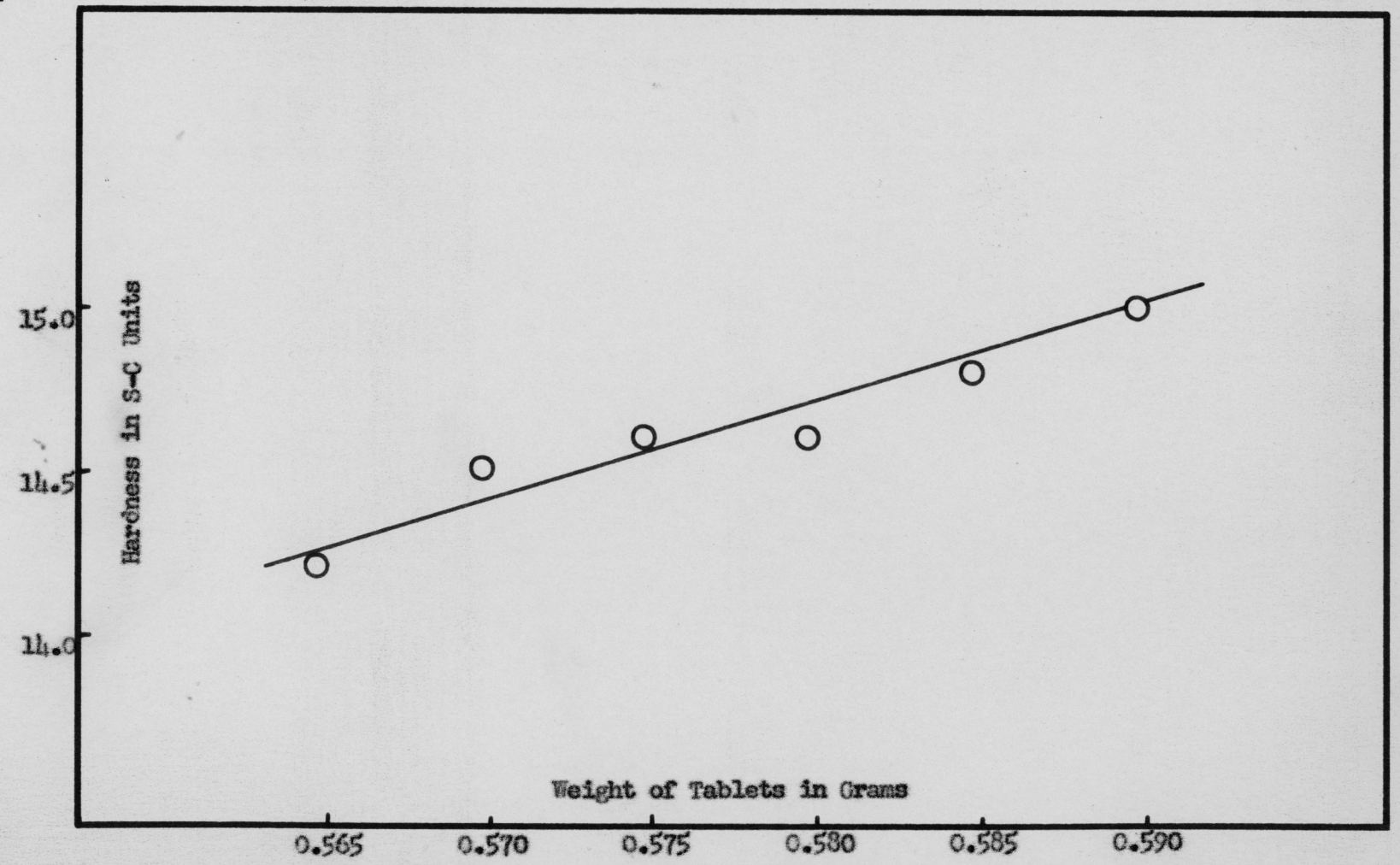

Fig. 9. Hardness vs. the Weight of Sulfathiazole Tablets.

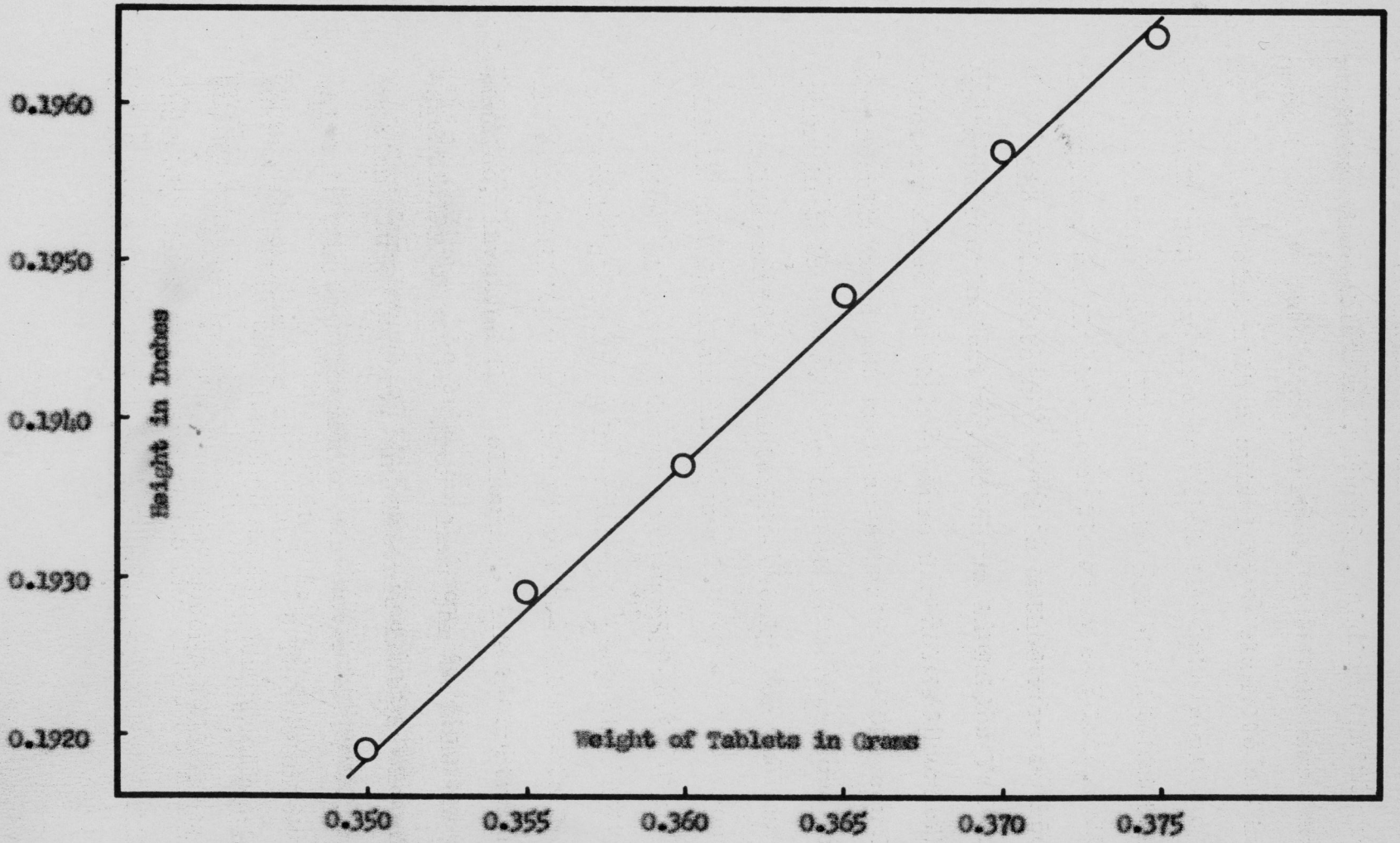

Fig. 10. Height vs. Weight of Aspirin Tablets.

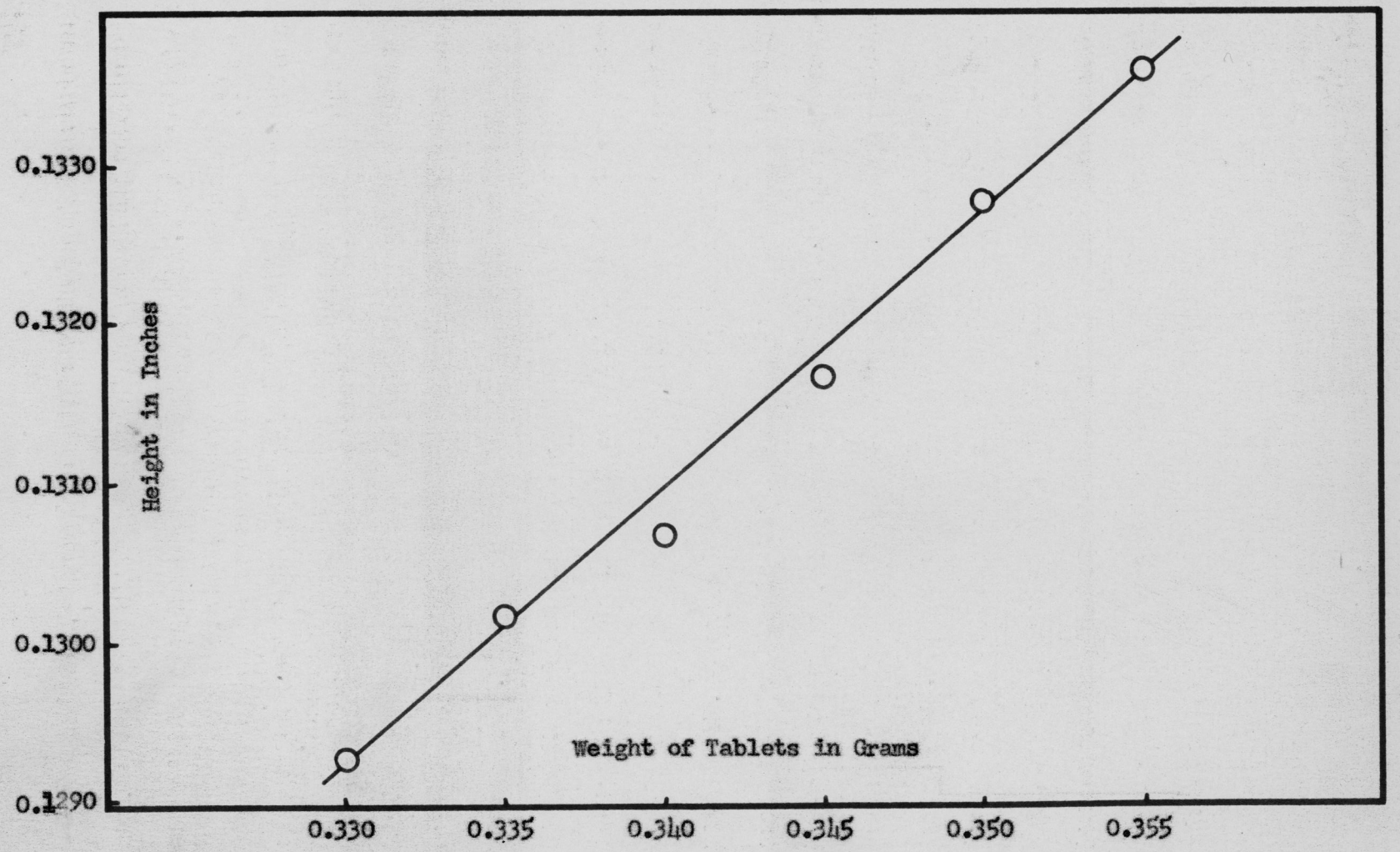

Fig. 11. Height vs. Weight of Sodium Bicarbonate and Mint Tablets.

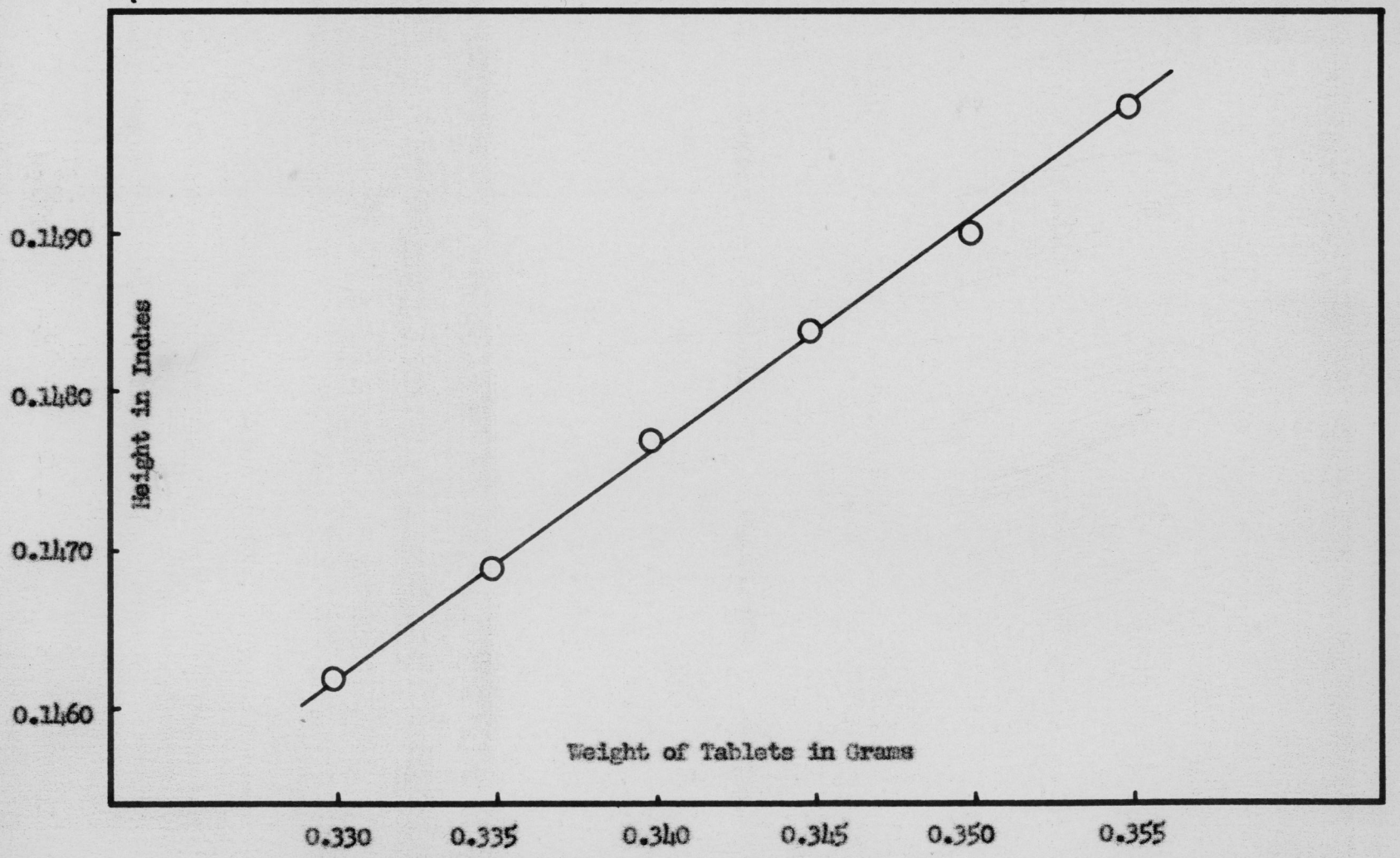

Fig. 12. Height vs. Weight of Sodium Bicarbonate Tablets.

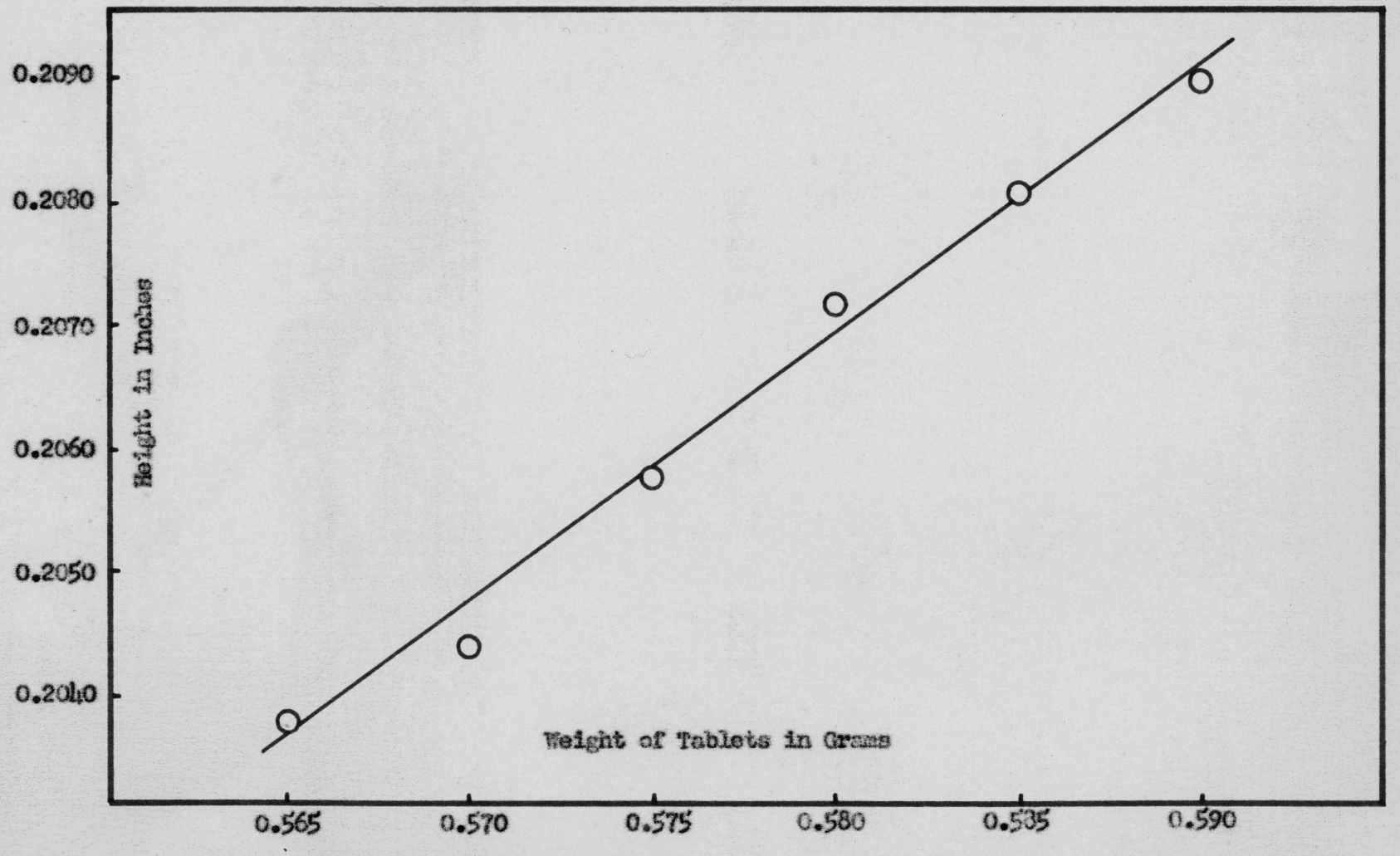

Fig. 13. Height vs. Weight of Sulfathiazole Tablets.

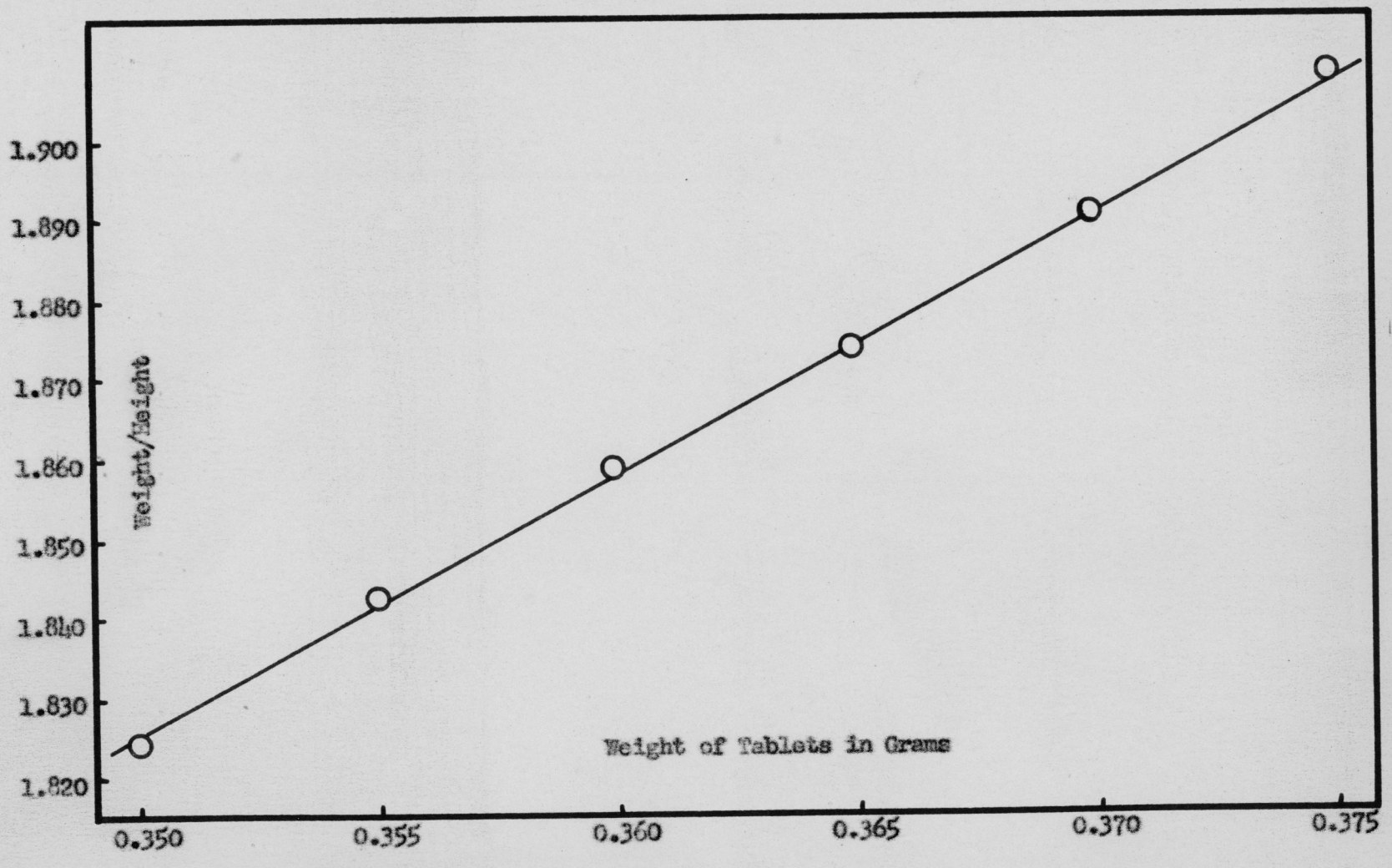

Fig. 14. Weight over Height vs. Weight of Aspirin Tablets

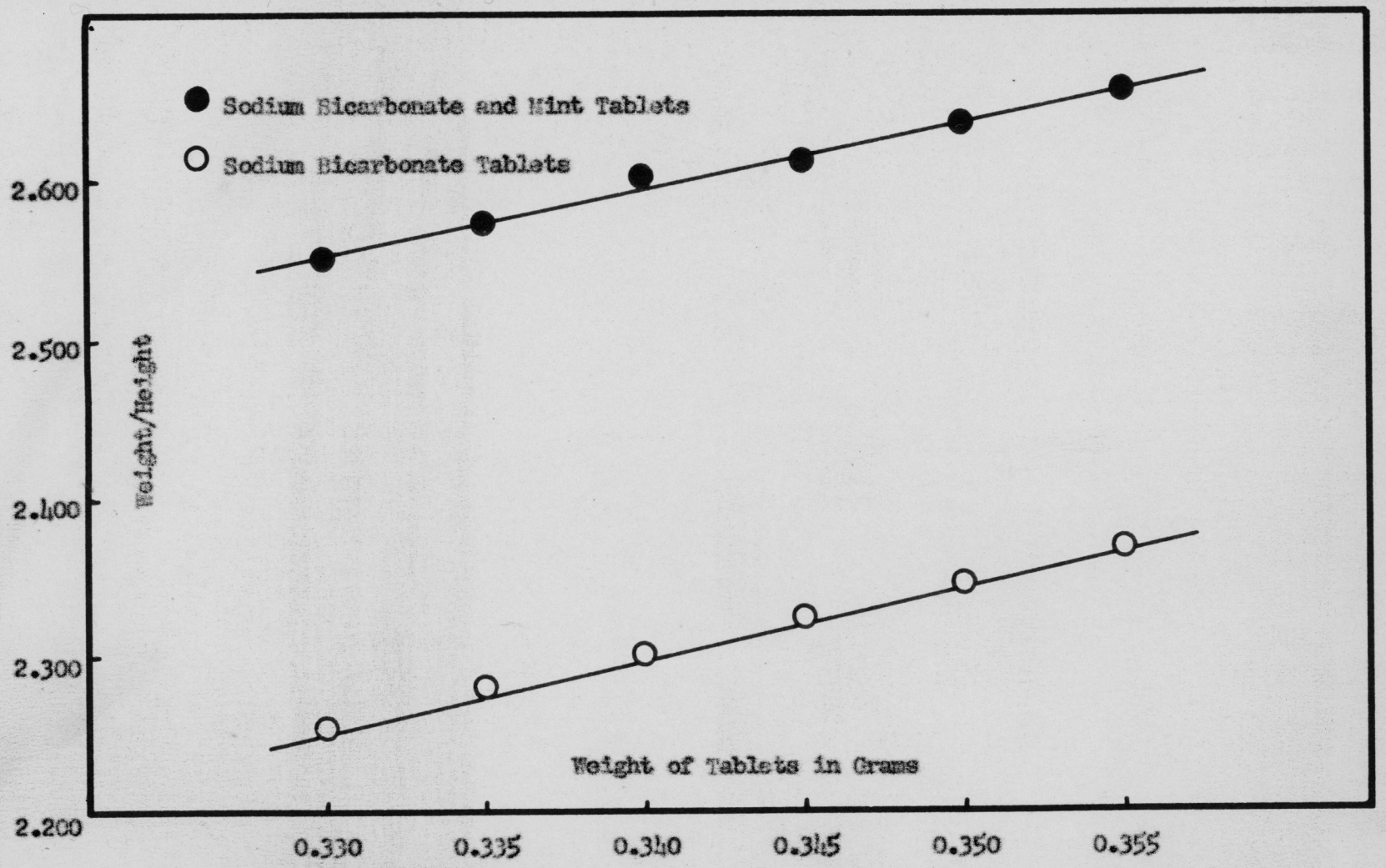

Fig. 15. Weight over Height vs. Weight.

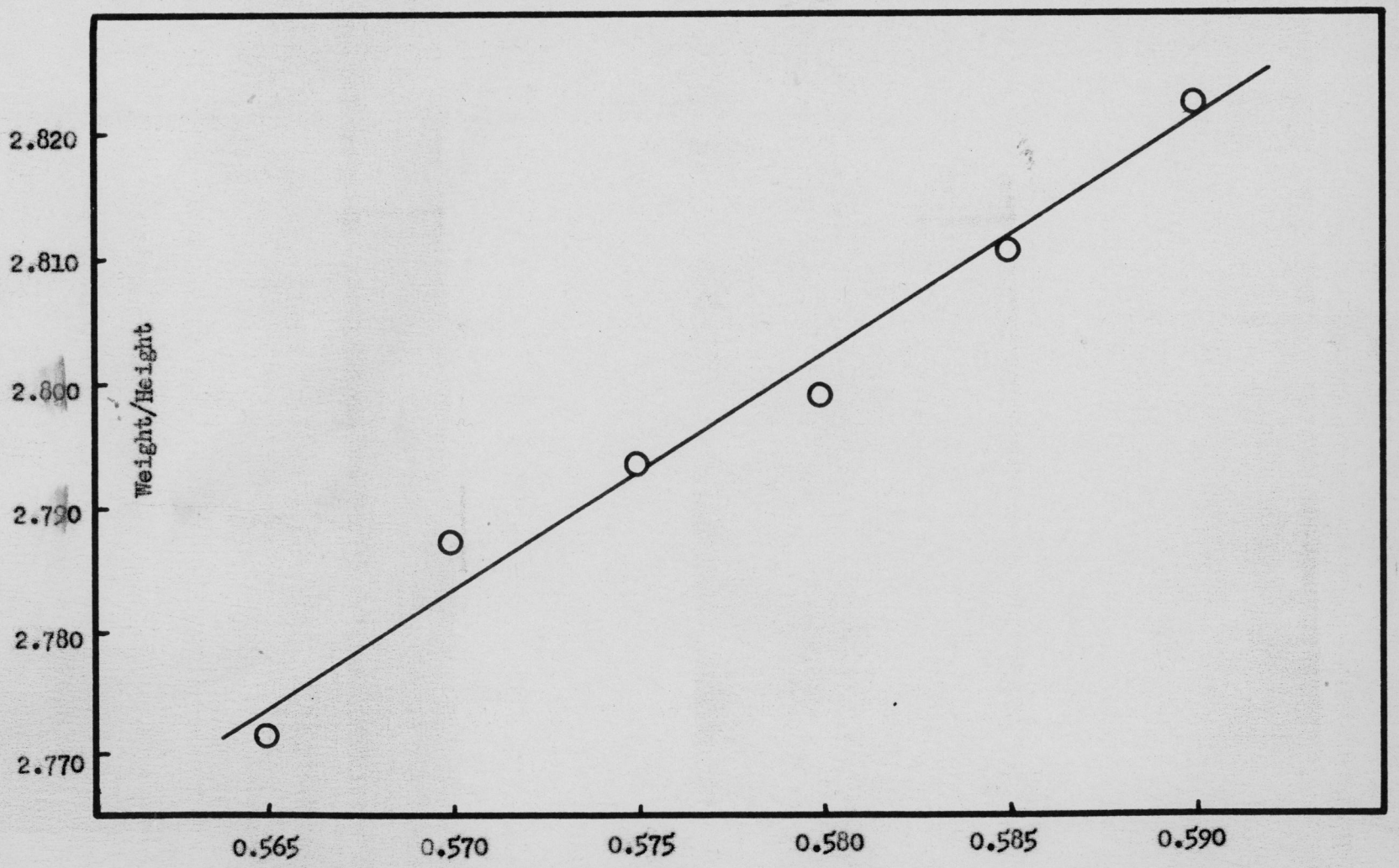

Fig. 16. Weight over Height vs. Weight of Sulfathiazole Tablets.

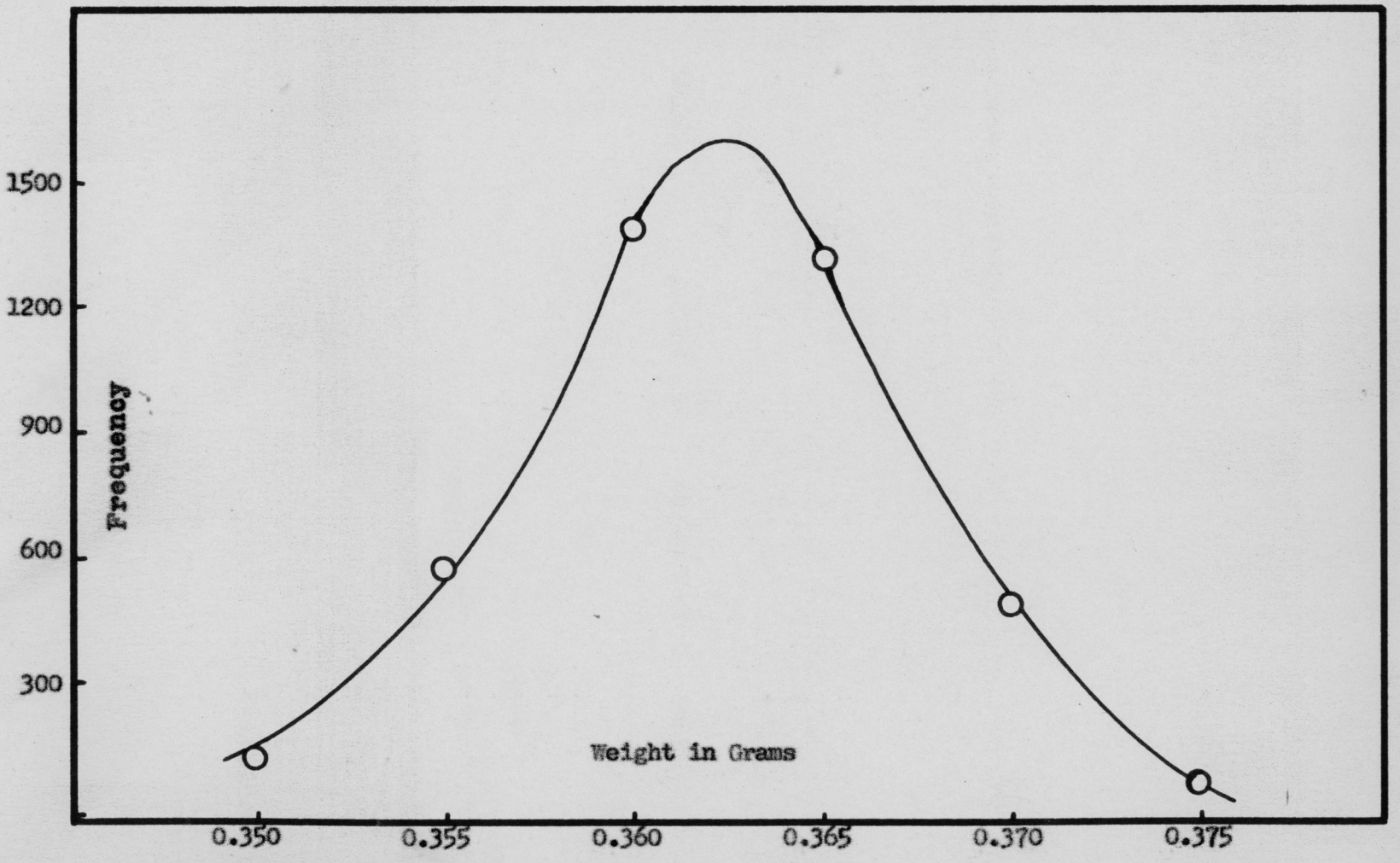

Fig. 17. Weight Distribution Curve for Aspirin Tablets.

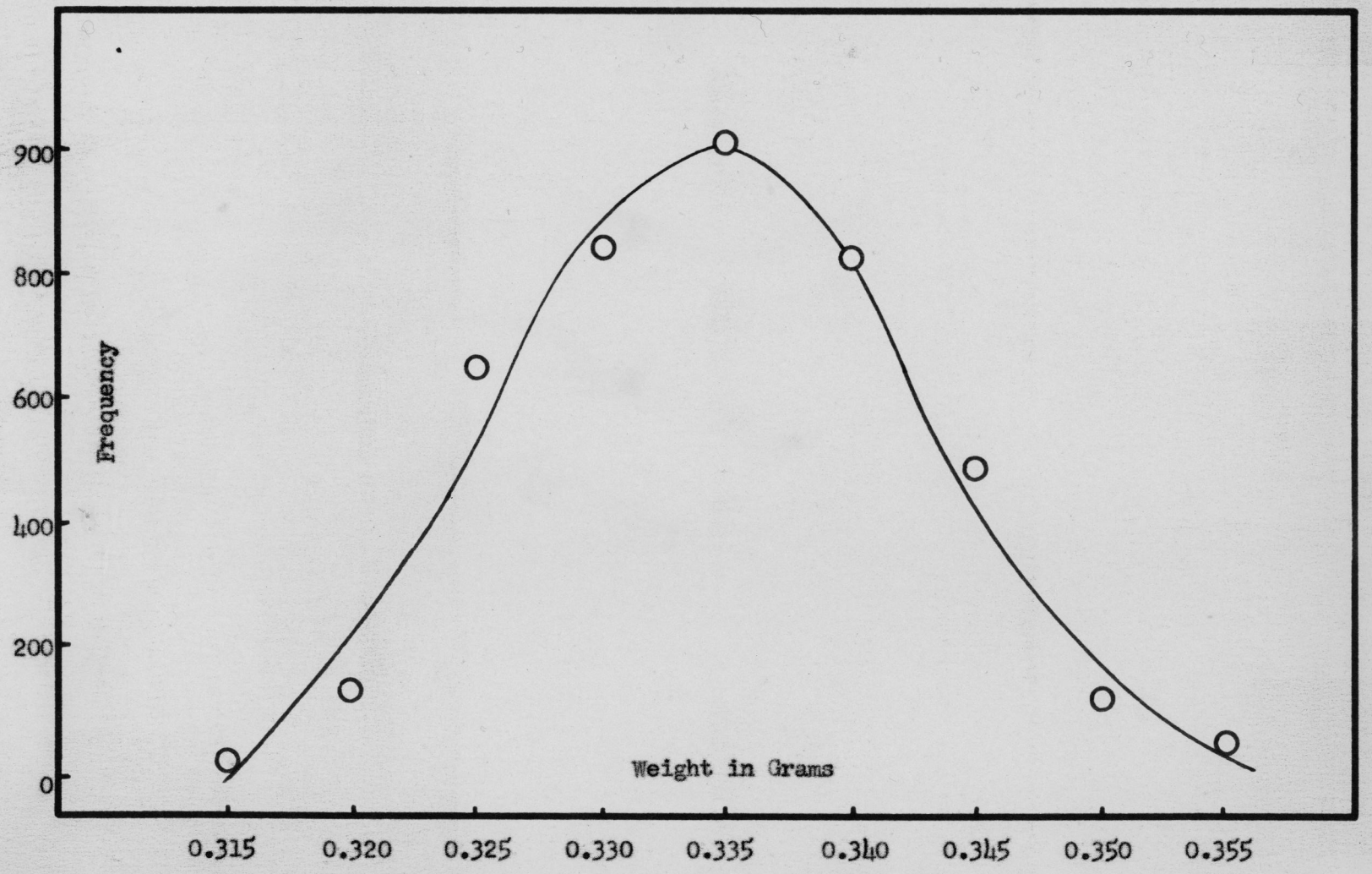

Fig. 18. Weight Distribution Curve for Sodium Bicarbonate Tablets.

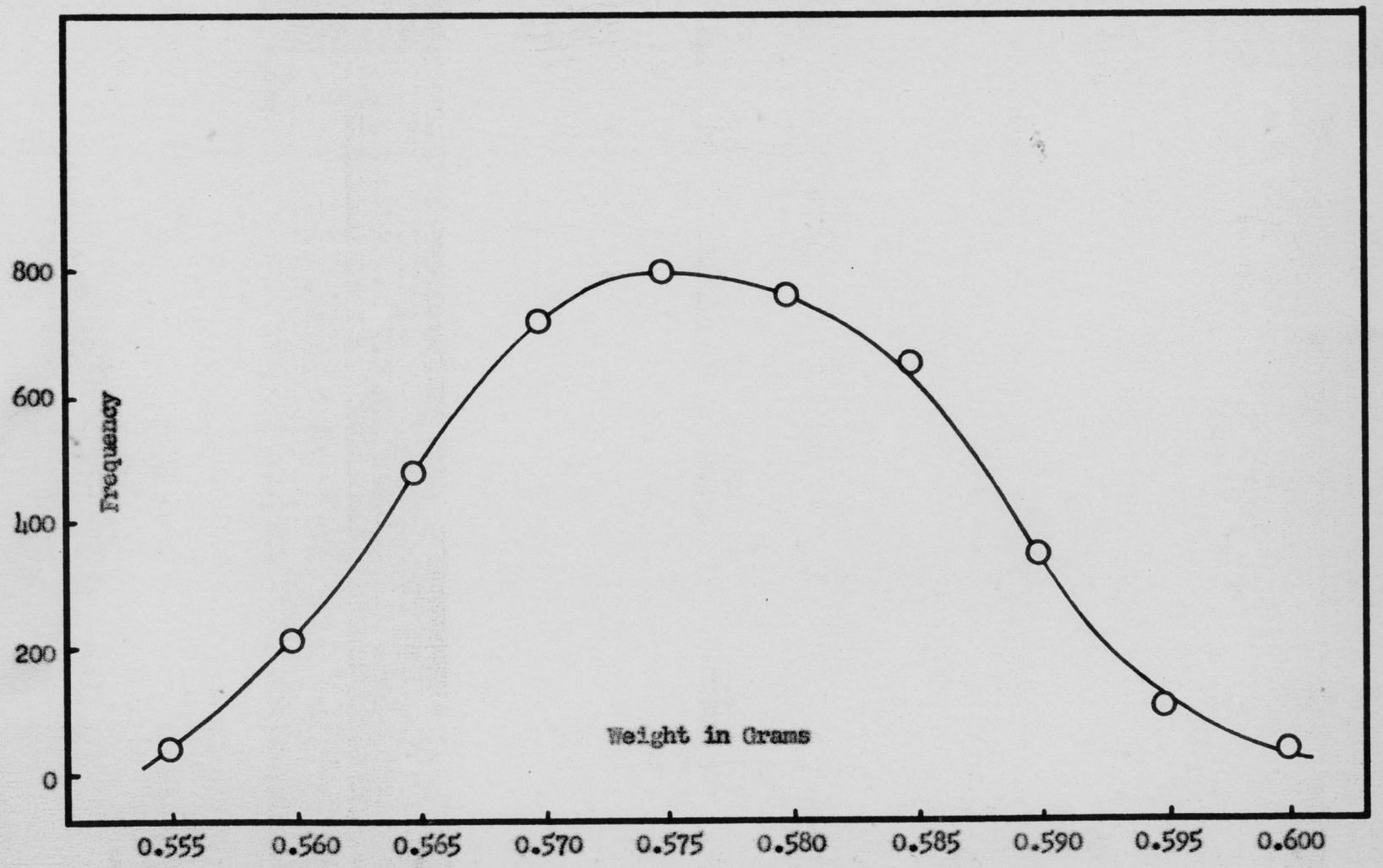

Fig. 19. Weight Distribution Curve for Sulfathiazole Tablets.

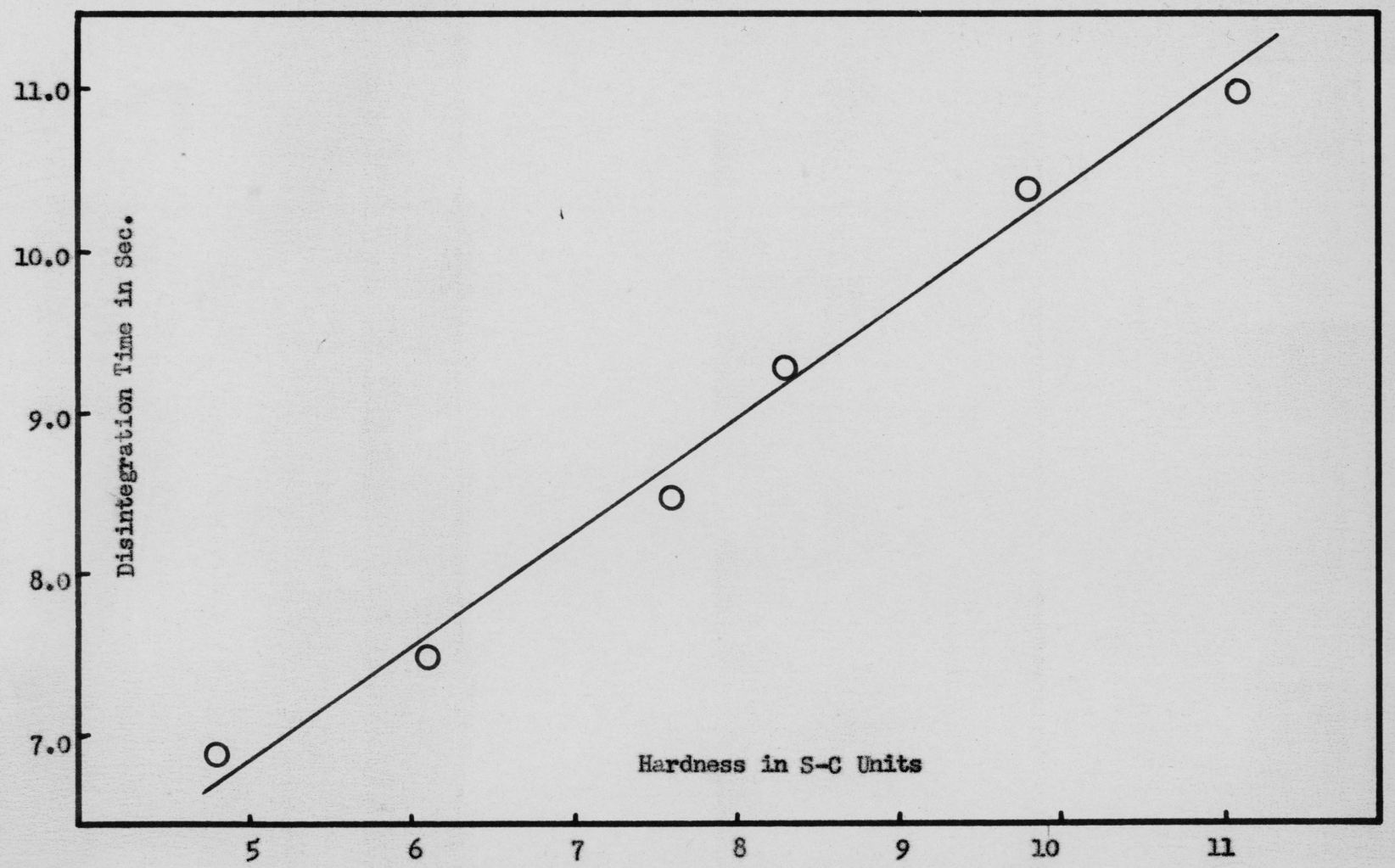

Fig. 20. The Effect of Hardness on the Disintegration Time of Aspirin Tablets.

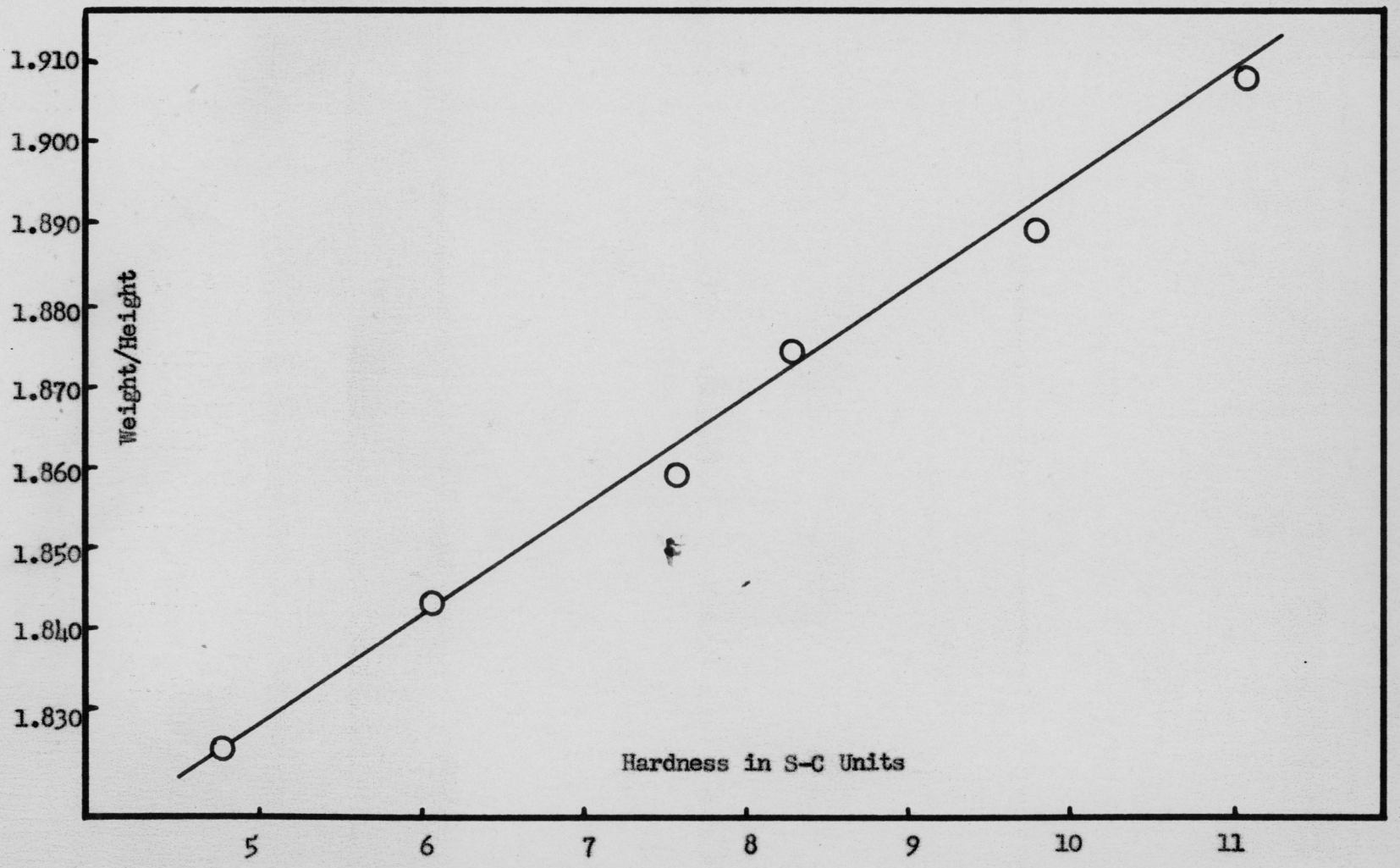

Fig. 21. Weight over Height vs. Hardness of Aspirin Tablets.

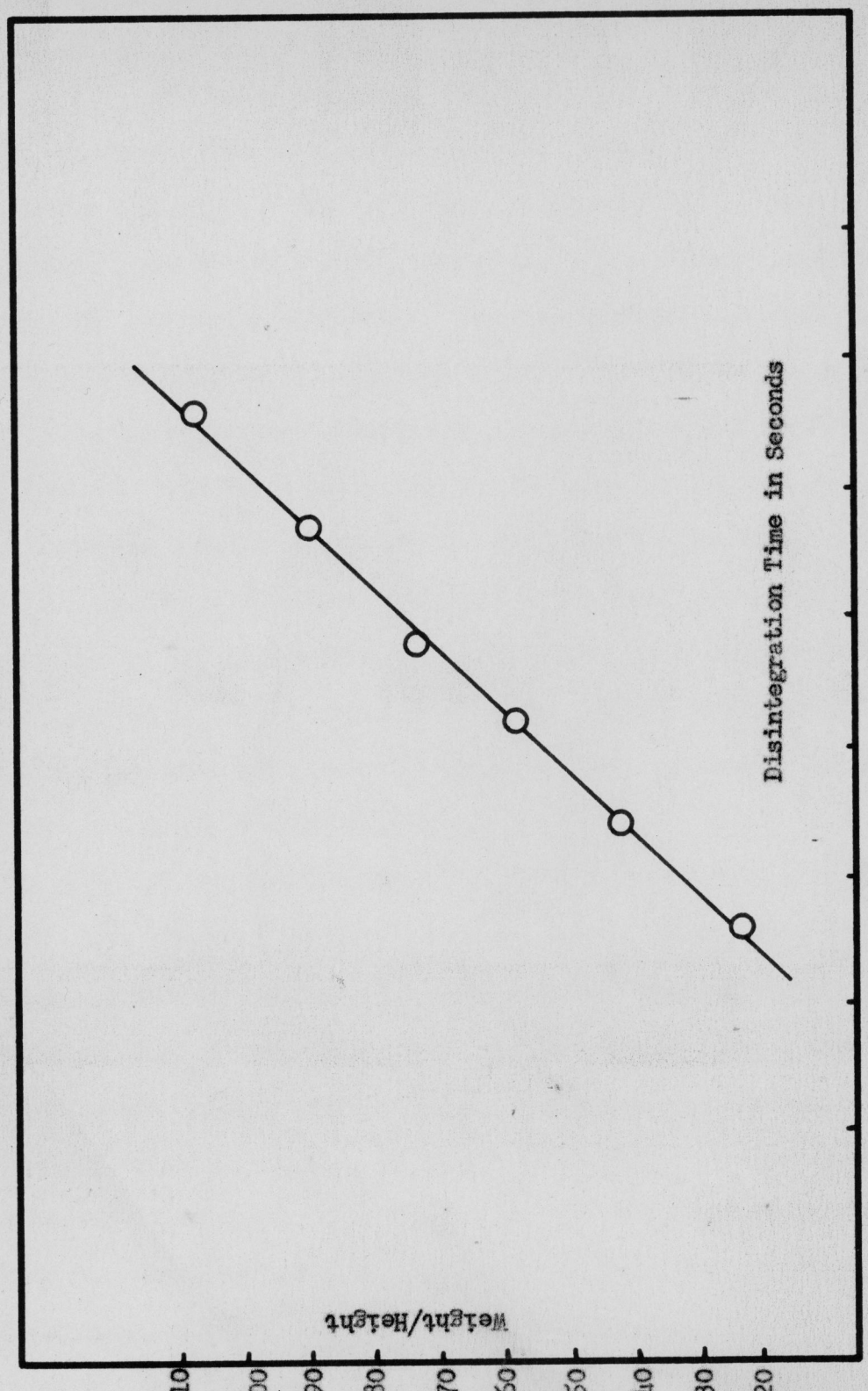

Fig. 22. The Effect of Weight over Height on the Disintegration Time of Aspirin Tablets.

DISCUSSION OF RESULTS

The interpretation of the analyses of the physical data on variables of the tablets is based on the premises that the length of the compressional stroke is very nearly constant and the variable, compressional force, changes with the variable, weight of the granulation in the die. That the degree of force, exerted during compression of the tablets, is dependent upon the relative weight of granulation in the die can be readily comprehended, if one visualizes the extreme situation where nothing is in the die. In the latter instance there would be no force or pressure since there is no opposing force distributed over the surfaces of the punches and the die. That the machine feeds varyingly is clearly evident from the data on the frequency distribution of the weights of the tablets.

Linear relationships with positive slopes are indicated where the various physical properties of the tablets are plotted against weight and each other. The increase of compressional force with each successive weight increment causes concomitant increases in hardness, disintegration time and density of the tablets. The form of the curves indicates that these variables are linear functions of each other at the levels of force used with an industrial type tablet machine.

The correlations found between compressional force,

hardness, density and, disintegration time agree qualitatively with the results obtained by Higuchi et al, holding compressional force constant.

Discussion of Weight Variation

The range and the standard deviation are used as measures of weight variation. In a normal distribution one standard deviation on each side of the arithmetic mean includes about two-thirds of the number of observations in an entire distribution; two standard deviations similarly measured off on each side includes about 95% of the observations.

When the frequency of weight distribution curves are characterized by arithmetic means and standard deviations, fairly close conformity to the normal frequency or probability curve is noted with an overall discrepancy of only about 4%. Since there is no marked asymmetry or skewness of the curves, it appears likely that variables, other than weight, are also normally distributed. The results are tabulated in Tables V and XII and illustrated graphically in Figures 17, 18 and 19.

In Table XII the variations in the weights of the tablets are tabulated as follows: deviation ranges of 10, 20, 30, 40 and 50 mg. are listed with the percentage of the total number of tablets that falls within each range. The percentage of deviation for each range and the weighted percentage deviation for each total is also listed.

Reproducibility

See Tables X and XI for data and calculations. The degree of uniformity or reproducibility is considered to be inversely proportional to the magnitude of the standard deviation.

CONCLUSIONS

The results for all the tablets studied are qualitatively similar and the following conclusions are drawn accordingly.

Although the length of the compressional stroke may be held relatively constant with production type tablet machines, the varying feed causes variance in compressional force which, in turn, influences such physical properties of compressed tablets as, hardness, density and rate of disintegration.

At the levels of force involved in the compression of these tablets, the variables of hardness, density, rate of disintegration, weight and size are positively sloped, linear functions of each other.

From the differences in hardness obtained for tablets varying in weight, it would seem justified to conclude that there was an appreciable variation of compressional force in the process of manufacturing these tablets.

The close conformity of the frequency of weight distribution curves to the normal frequency or probability curve, indicates the likelihood of variables, other than weight, being normally distributed, also.

No correlation appears to exist between the disintegration properties of sodium bicarbonate tablets and the three different pH levels employed.

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