# ANALYSIS OF THE PHYSICAL CHARACTERISTICS OF COMPRESSED TABLETS

BY

LOUIS NASIR ELOWE

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of
DOCTOR OF PHILOSOPHY
at the
UNIVERSITY OF WISCONSIN

1954

## ACKNOWLEDGEMENT

The author wishes to express his sincere thanks and appreciation to Dr. L.W. Busse for suggesting this study and for his guidance in directing it to completion.

Gratitude is also extended to Dr. T. Higuchi for valuable suggestions and assistance rendered throughout the duration of this work.

The author is also grateful to the Wisconsin Alumni Research Foundation for grants which helped to make this investigation possible.

TABLE OF CONTENTS

# INTRODUCTION

It is true that compressed tablets are one of the most commonly used dosage forms of medication today. While the many advantages they hold over other dosage forms of medication have enabled compressed tablets to occupy such an important place, it must not be forgotten that these advantages have been very much enhanced through continued and sustained research for over a hundred years. As a result of extensive work by numerous investigators on the formulation and production equipment of compressed tablets, the pharmaceutical manufacturer today has better insight into the problems of tablet formulation and certainly possesses faster and superior methods of production than his predecessors could claim. To realize the tremendous progress made in the field of compressed tablets, one has only to consider the vast number of tablet formulations available today in conjunction with machines having a production capacity of nearly 100,000 tablets per hour. The developement in this field has been great since Brockedon patented his invention under the title of "Shaping Pills and Lozenges and Black Lead by Pressure in Dies" in 1843.

The literature reveals that most of the work done in the field of tablets has been in the form of empirical approaches to numerous problems. Different

workers have studied many physical properties of tablets using a variety of methods, but no serious effort has been exerted to correlate the findings into an integrated picture. Such a correlation of the factors which influence the manufacture of tablets and their subsequent effectiveness is of paramount importance for any desired standardisation in the manufacturing processes.

Recently, however, a trend in this direction is noted in the form of a more systematic approach to the study of tablet properties and the correlation of the factors which influence them. Considerations of compressed tablets have been divided by Higuchi et al (1) into two categories, static and dynamic, with a view toward better elucidation of the factors involved during compression. Work has been in progress since 1950, studying tablet compressional behavior from these two points of view.

Regarding static considerations, a vertical study on a single sulfathiazole formulation has been undertaken, and semi-empirical results and relationships were drawn from the investigation (2,3). In the way of dynamic studies of the compressional behavior of tablets, a fully instrumented tablet machine has been constructed and is currently in use (4).

It is clear that before any conclusions could be made, horizontal extension of the investigation over a number of similar and dissimilar systems had to be under-

taken. It is the purpose of this study to analyze and interpret the findings in relation to the static considerations of compressed tablets and to present new quantitative data obtained through such a horizontal extension of the investigation over several new formulations. An attempt is made to draw up some general conclusions pertaining to the compressional behavior of the tablets made from these various formulations.

## PAST WORK ON PROPERTIES OF COMPRESSED TABLETS

### I. Review of the Literature with respect to Hardness and Disintegration time .

The two physical properties of tablets, hardness and disintegration time, have received the attention of many workers in the tablet field. The literature abounds with discussion of these two all important properties and extensive treatment is accorded them in many places (5-33). Whereas a general agreement exists that compressed tablets must possess an optimum balance between hardness and disintegration properties, it is unfortunate to find that it is altogether impossible to integrate the work of the investigators in this field. This is because of the fact that these two terms have been used to designate a variety of characteristics, confusion thus arising as to their exact meanings.

Because of the vastness of the literature dealing with hardness and disintegration time, a review of all the work done in this respect would be outside the scope of this report. However, a brief treatment of these two properties will be made here, pointing to review articles wherever possible.

No specific and precise definition has been generally accepted for the term hardness in the tablet field. It has been used in the literature to designate a large

number of resistances offered by tablets to several types of treatment. Spengler and Kaelin in 1945 (19) enumerated resistance by tablets to (a) wear and tear, (b) rolling, (c) shaking, (d) shock, (e) abrasion, (f) pressure, (g) bending and (h) penetration. Each of these individually has been termed hardness. Filleborn in 1948 (22) defined hardness as being the resistance to piercing offered by tablets, thus using the term much in the same way as it is employed in European countries and in Spengler and Kaelin's own work (19). In the United States, the term is primarily taken to mean either the resistance to wear and tear ( including rolling, shaking, shock and abrasion ) or the resistance to mechanical breaking of the tablets. In this connection, Rao (2) in 1952 states:

> "Thus in general it can be stated that the term hardness as used today may mean any one of the following resistances exhibited by tablets : (a) resistance to surface penetration, (b) resistance to wear and tear and (c) resistance to mechanical breaking."

In his own work, he uses the term hardness to designate the resistance of tablets to mechanical breaking.

In the absence of a general agreement on the definition of the term, it follows that workers have used a variety of devices in the measurement of what they call hardness of tablets.

Smith in 1949 (25) mentions the Shore Scleroscope and the Sclerographe in the measurement of the resistance

of tablets to surface penetration. The former determines the rebound of a hammer striking a tablet and the depth of the indentation made; in the latter the distance of the fall of the hammer can be varied at will until no measureable rebound is left. Earlier, Filleborn in 1948 (22) reports the use of a special apparatus of French origin by which he measured the resistance of tablets to piercing. These instruments are normally used to test the hardness of metals.

The resistance to wear and tear of tablets have been tested by various empirical manual methods, as well as by controlled simple mechanical devices. Observing the effect of shaking about ten tablets in the cupped hand, and the effect when a tablet is allowed to fall several feet on to a hard surface, have been described by Smith (25) as simple manual tests in the direction of noting wear at the edges of the tablets. Many manufacturers still employ such empirical tests despite the availability of simple controllable mechanical means. Some of the latter devices have been described by Spengler and Kaelin in 1945 (19) and Smith in 1949 (25) and in 1950 (26). They measure the percentage of powder produced when a weighed number of tablets are mechanically agitated for a fixed period of time, in this way determining the resistance of the tablets to wear and tear.

'Feel judgement' has been the common test employed

to determine the resistance of tablets to mechanical breaking. The amount of pressure required to break the tablet between the thumb and fingers is taken in this method to evaluate the degree of firmness of the tablets. Obviously, such results can never be of any real scientific value. In 1938, Miller and Shalkova (11) described a small crushing press and the derivation of a formula for estimating the strength or hardness of tablets. This was followed in 1939 by a method introduced by Brown (12) for the quantitative determination of the resistance of tablets to mechanical breaking. With the aid of a balanced beam he could determine the weight necessary to break a tablet while dry and the weight necessary to break it while the whole assembly was immersed in water or any other disintegration medium. Correlation of the two breaking weights will be discussed later.

The Monsanto Pressure Tester, which was introduced in the U.S.A. in 1933, has been mentioned by Bandelin in 1945 (20) and Smith in 1949 (25) to have been used by various workers to assess the breaking point of compressed tablets. It consists of a spring equipped with a screw to tighten down a hammer against the tablet held in a stirrup. An indicator on the spring moves along a scale which is calibrated in kilograms. This shows the stress required to break the tablet.

Hosler in 1950 (30) compares the Monsanto Pressure

Tester with a Tablet Hardness Tester introduced by Strong Cobb and Company. He prefers the latter because of the precision piston operated by air pressure and the standard maximum register gauge that have gone into its construction. Unlike a spring type register, this instrument, he claims, cannot register further pressure once the tablet breaks.

The term 'disintegration time' has also been used ambiguously by different workers. Some points of controversy in this respect are:

(a) the merits of water or artificial gastric juice as a disintegrating medium,

(b) the type of agitation to be used during the disintegration process and

(c) the degree to which the tablet should disintegrate.

Diverse thinking among workers exists regarding these points and it would be clear that the term 'disintegrating time' by itself has no significance unless the test and the conditions used are described in detail.

Evanson and DeKay (28) estimated that by 1950 joint and individual research had produced twenty seven disintegration methods. Comprehensive review articles regarding the disintegration of tablets and the advantages and the disadvantages of the different tests used have been published earlier by Hoehn in 1945 (17), Filleborn in 1948 (22) and Sperandio et al in 1948 (23).

A method for measuring the disintegration time of tablets, reported used by the Laboratories of the United States Army Medical Department since 1940 and mentioned in 1946 by Gershberg and Stoll (34), was adopted in November 1950 by the United States Pharmacopoeia Committee. The British Pharmacopoeia, in turn, has accepted a method reported by Berry and Smith in 1944 (16).

## II. Quantitative Determination and Correlation of the Physical Properties of Compressed Tablets.

One of the main deterrents to the quantitative study of the physical properties of compressed tablets and their correlation has been the large number of variables encountered in this field. As early as 1902, Hance (5) pointed to this fact stating that the individuality of each separate formula would make it impossible to apply one general rule to the manufacture of all tablets. It is, however, generally agreed that such quantitative research is imperative if sound scientific methods are to replace the empirical approaches that have characterized tablet making for over a century.

In spite of this agreement upon the necessity of such organized studies, a review of the literature reveals very little work in this direction; this fact is well reflected in the absence of standardized requirements for compressed tablets. The need for such standards, however, has continually been emphasized by different investigators. To illustrate,

Berry and Smith in 1944 (16) stated that a good appearance was not the main consideration in tablet manufacture and that, although there had been considerable progress in the standard and quality of tablets, there was still room for further improvement. A year later, in 1945, Bandelin (20), discussing the physical control and standardization of compressed and coated tablets, observed that little had been published in the pharmaceutical literature in that respect. Firth (35), in 1948, emphasized the need for considerable research into fundamental factors before any coordination of the numerous variations arising in tablet manufacture could be made. Still more emphasis on the need for further research in this connection was made as late as 1950 by Burlinson (29) who mentioned that there was much to be learned about such problems as the nature and function of lubricants, the hardness and friability of tablets and their measurements, and the determination of the influence of pressure on the structure of the tablets.

There is no doubt that the formulation, the age of the tablets and the degree of compression are variables that influence the physical properties of tablets considerably. These will be discussed very briefly in what follows.

1. <u>The Formulation</u> .

The effect of the formulation is noticeable on the properties of the tablets made. The influence of the type and proportion of such materials as disintegrating, binding,

and lubricating agents are well known to those acquainted with tablet manufacture. Such matters as variation in the composition of the formulation with the view of alterring the final physical properties of the tablets occupy a very prominent place in the pharmaceutical literature.

2. The Age of the Tablets .

While the influence of the formulation on the properties of the tablets is of universal agreement, the same cannot be said about the age of the tablets. Some investigators assert that age has an effect on hardness and disintegration; others hold the opposite view.

E'we in 1934 (9) reports that 9.5 per cent out of 137 types of compressed tablets he studied have hardened after one year from the time they were made. In his study, E'we used the term hardened or softened according to whether the time required for disintegration at the end of the ageing period was respectively longer or shorter than the initial disintegration time. Hoehn in 1945 (17) alludes to an agreement among several workers that aging does change the disintegration properties of certain tablets. This view is held by Burlinson and Pickering who, in 1950, (29), report that tablets may be said to have hardened a little after storage for four years.

Kelly and Green (18), in 1945, Burlinson and Pickering in 1950 (29) and Evanson and DeKay in 1950 (28) hold the common view that the age of the tablets contributes little

to the disintegration time or to the character of the disintegrated materials.

There is nothing conclusive, then, to be found as to whether or not age is a contributing factor in the disintegration time of tablets. Leonard (36) commented in 1933 regarding the importance and practicability of aging tablets for long times by saying :

> "Deteriorations other than those of hardening, deteriorations of chemical nature which interfere with the pharmacodynamic action of some products, may be expected to occur in 5 years, and are more serious than any hardening. The problem of failure to move out retail stock in half a decade is a problem of economics and medical psychology, and can best be dealt with by a policy of detail attention and return credits in case of overstocking."

3. <u>The Degree of Compression</u> .

In 1939, Brown (12), with the aid of a balanced beam, determined the weight to break a tablet while dry, and the weight necessary to break a tablet of the same batch while the whole assembly was immersed in water or any disintegration medium. Correlating the two, he used a term 'disintegration ratio' which he defined as the ratio of the average dry breaking weight to the average wet breaking weight. While studying the effect of compressional force on these breaking weights, he obtained results which showed a linear relationship between the compression used and the logarithm of the breaking weight, in both the dry and the wet procedures. Brown's work was an attempt in the direction of correlation of some of the physical properties of tablets, as a result

of which he states that the higher the disintegration ratio, the better the tablet. In evaluating his work, one has to keep in mind the fact that the degree of compression which Brown used was reached by the number of turns he applied to the compression screw on the tabletting machine. This certainly would not give very accurate results; the exactness and reproducibility of these results are therefore in question.

Berry and Ridout (33) in 1950 studied disintegration time of phenacetin tablets as a function of 'compression ratio' which they defined as the ratio of the weight of the tablets in gms. to the thickness of the tablets in cms. This 'compression ratio' is related to the density of the tablets by a constant factor and hence is a measure of the compressional force. Using 5 gr. phenacetin tablets containing 15 per cent dried potato starch, they observed an initial decrease in the average disintegration time with increasing compressional ratio until a critical compression was reached after which further increases in the latter caused slower rates of disintegration.

Berry and Ridout explained the above phenomenon by correlating the swelling of the starch grains with the volume of the void spaces in the tablet. They mentioned that, under a very light compression, the starch grains can swell but that, owing to large intergranular spaces, they can do so to a considerable extent before they begin to exert

pressure on the surrounding granules. At the critical pressure, they added, as soon as the grains swell they exert pressure on the surrounding granules and the tablet disintegrates rapidly. With a heavy compression, time is required for the water to seep through the outer layers of the tablets before the starch grains can start to swell and commence to disintegrate the tablet.

Referring to the above phenomenon, Rao in 1952 (2) mentions that Berry and Ridout's report was the only place in the literature where this initial decrease in the disintegration time by increasing the degree of compression was described. In the present work, several such instances were found. These will be described later.

E'we in 1934 (9), Filleborn in 1948 (22), Smith and Stephenson in 1950 (27) and Evanson and DeKay also in 1950 (28) attempted to correlate hardness with disintegration time. While E'we states that the degree of hardness of a tablet is not a criterion of its disintegration time, the other workers above mentioned have reported the existence of a correlation, although their results are in no case quantitatively expressed.

In 1951, Tucker (37) measured the apparent densities of several types of tablets by mercury displacement, and Arnold (38) studied the compressional behavior of several sugars by measuring the displacement of the upper punch as a function of compressional force. He used a mechanical

lever machine capable of delivering the exact degree of compression required, and measured the displacement by means of a dial micrometer.

Higuchi et al (1), in a preliminary report on the physics of tablet compression in 1952, state that much empirical information is available on the relative efficacies of different lubricants, binders, fillers and disintegrating agents in various combinations but that no serious attempt had been made to correlate such physical properties as porosity, density, hardness, crystalline structure, compressibility, etc., of both the tablets and the tablet ingredients. Labelling their work as an attempt in that direction, they divided considerations of tablets formed by compression into two types: (a) static ones relating to the pore size, porosity, tensile strength, the cohesive forces involved, the modulus, etc., of the tablets, and (b) the dynamic energetic considerations of pressures of formation, rates of compression, energies involved, etc. Considering the structure of tablets from a static point of view they said:

> "The elucidation of the structure of tablets will necessarily be based in part on the following factors (a) bulk density of the granulation and the density of the tablet, (b) pore size, and (c) the cohesive strength and hardness."

They then went on to describe a specially designed mercury displacement tablet pycnometer which was used by Tucker (37) in his evaluation of the densities of tablets, and a

high precision helium densitometer for thedetermination of the true density of the granulations. They also showed how porosity could be calculated from a knowledge of the true and apparent densities. Regarding cohesive strength and hardness, they referred to the Strong Cobb and Company's Tablet Hardness Tester which was then under design and had since been used to measure the resistance of tablets to mechanical breaking. Reference was also made to the instrumentation of a tabletting machine for dynamic measurements. Such a machine has also been constructed and is at present in operation.

In 1953, Kennon (39) reported on the effect of compressional force on the hardness and disintegration time of tablets. He compared the effect of carboxymethylcellulose and dried corn starch, in various proportions, on the two physical properties of sulfathiazole tablets made under different degrees of compression.

Also in 1953, Rehberg (40) studied weight variation of tablets obtained on a rotary type tabletting machine and correlated weight with disintegration time and hardness of the tablets. His results are essentially the dependence of these latter physical properties on compressional force. On the premise that the length of the compressional stroke is constant, varying weights of granulation in the die will mean varying compressional force under which the tablets having different weights are made.

Arambulo et al (41) in 1953 correlated particle size with average weight of tablets. Using a single punch tablet press, they found that as the particle size decreased, the average tablet weight increased, passed through a maximum at 150-350 microns, and decreased. They also observed that as particle size decreased, the percentage of physically perfect tablets increased, the tablets became more glossy and, in general more satisfactory. This trend also passed through a maximum followed by production of tablets of decreasing quality.

Arambulo et al (42) also determined weight variation of tablets made from lactose-starch granulation and from sodium chloride granulation with respect to particle size. Their results indicated that as the particle size decreased, the tablet weight variation decreased, passed through a minimum, and then increased. The particle size range leading to minimum weight variation was found in their study to be 400-800 microns for lactose-starch and 200-250 microns for sodium chloride. In their studies, particle size always referred to the particles before compression.

A comparison of different disintegrating agents was made by Firouzabadian and Lee Huck (43) in 1954. They compared the effect of corn starch, alginic acid, methylcellulose and starch-agar mixture with respect to their

disintegration properties in tablets. Such comparative work on different disintegrating agents has also been carried out lately by Swintosky and Kennon (44).

In 1953, Higuchi et al (3) reported on the effect of the maximal force employed during the compressional process on several tablet properties including (a) apparent density and porosity, (b) particle size, (c) hardness and (d) disintegration time. They found that the two physical properties of the tablets, hardness and apparent density, increased linearly with the logarithm of the compressional force with a deviation occuring at very high degrees of compression. Porosity showed a decrease as the compressional force was increased. It also varied linearly with the logarithm of the force used in compression of the tablets, except at very high levels where a deviation occurred. The surface area of the tablets increased with compressional force; a maximum was, however, reached, at 2500 lb. force, after which further increases in compressional force resulted in lower surface area measurements.

In their study of the disintegration time of the tablets as a function of the degree of compression used, the above workers found a linear relationship between the logarithm of the disintegration time of the tablets and the compressional force used. They found also that the size of the original granules compressed did not

alter the disintegration properties of the final tablets only, but affected the surface area of the tablets to some degree also. Variation of the original granule size, however, had a very slight effect on the hardness of the tablets.

Correlating some of the physical properties of the tablets they studied, Higuchi et al (3) noticed a straight line relationship between density and hardness of the tablets, and also between hardness and porosity.

All the relationships obtained by the above authors in their study were limited in nature to a single formulation of sulfathiazole. Consequently, no general conclusions could be made until the same tests were applied to more formulations. They commented on this point by saying:

> "The present study is of a vertical type in that an intensive investigation has been made of a single formulation in an attempt to gather as much experimental information as possible for this one situation. Such a situation permits more extensive correlation of the variables involved but leaves in doubt the general application of the conclusions. Horizontal extension of the present investigation over a large number of systems is necessary before the empirical relationships discussed can be of practical value."

The present work is such a horizontal extension of the investigation over several other similar and dissimilar tablet formulations and has the purpose of testing whether or not the relationships observed by Higuchi

et al in the case of the sulfathiazole granulation are of general application to all tablet formulations.

# THEORY OF TABLET COMPRESSION

Tablet compression has been compared by Rao (2) to the initial steps of compression used in the powder metallurgic production process. The various theories which have been propounded to explain these latter processes seem to be operative in the case of tablet compression also. While metals are used in the one case and granulations in the other, the operations for compression are essentially the same. There exist, in both, the identical stages of (a) filling the material to be compressed into thedie, (b) the exertion of the necessary pressure to effect compression, and (c) ejection of the compact mass from the die.

During the application of compressional force, certain successive effects are manifested in the form of a modification in the interparticle spaces followed by possible changes in the shapes of the particles themselves. These effects have been classified by Seeling and Wulff (45) into three phases in their discussion of compacting metallic powders. These are:

1. Packing of the particles
2. Elastic and plastic deformation of the particles
3. Cold-working with or without fragmentation of the particles.

Rao expressed the view that these same concepts might apply to the somewhat analogous process involved in the compression of pharmaceutical powders.

Before initial compression is started, the particles are packed at random. This type of packing results in considerable 'bridge formation' (46) which is manifested in a fairly large percentage of void space. As force is applied to the particles, void space decreases in magnitude due to the closer packing of the particles.

As compressional force increases, its effect begins to show on the particles themselves. The strain on these particles will lead to their deformation which may be either plastic or elastic according to whether it is respectively of a permanent or a reversible nature. Upon release of the stress causing it, an elastic deformation disappears completely in the absence of overcoming forces whereas a plastic one is retained.

It is reasonable to assume that a plastic deformation of the particles will result in better compressibility. An elastic type of deformation can give rise to defective tablets when the stress is removed, unless of course such elasticity is counterbalanced by sufficient binding forces among the deformed particles. In consequence, it is believed that higher proportions of binding agents have to be used in case of elastic deformation of particles to obtain tablets free from physical defects.

Fragmentation of the particles may occur as the compressional force is taken to still higher levels unless the particles are very resistant to crushing. If fragmentation occurs, higher surface area values will be obtained. In this connection, Axelson and Piret (47) studied the changes in surface area due to crushing of a single crystal and then of multiple particles of quartz. Their results indicated proportionately higher surface area values in the crushing of single crystals. Multiple particles, they believe, interfere with each other and the overall effect of force will be less than what it is in the case of a single crystal. In tablet making, the crushing of multiple particles is the problem.

With or without fragmentation of the particles, as still higher forces are reached, cold-bonding may occur. In tablets, the proportion of binding agent used and its type play an important role at this stage.

As a result of these successive, though not necessarily separable phases in compression, it would be expected that density and hardness of the tablets increase, approaching a limit, with ascending values of stress. This is what actually happens during the compression of tablets; the density of the tablets approach the bulk density of the granules, and hardness increases with density in a linear relationship, as higher compressional forces are reached.

## BIBLIOGRAPHY


1. Higuchi, T., Arnold, R.D., Tucker, S.J., and Busse, L.W., J. Am. Pharm. Assoc., 41, 93 (1952).

2. Rao, A.N., Doctor of Philosophy Thesis, University of Wisconsin, 1952.

3. Higuchi, T., Rao, A.N., Busse, L.W., and Swintosky, J.V., J. Am. Pharm. Assoc., 42, 194,(1953).

4. Nelson, E., Naqvi, S., Busse, L.W., and Higuchi, T., J. Am. Pharm. Assoc., in press.

5. Hance, A.M., Am. J. Pharm., 74, 80 (1902).

6. Dunnet, Chem. and Drugg., 77, 206 (1911).

7. E'we, G., Proc. Am. Pharm. Mfrer's Assoc., No. 75, (1930).

8. Trunkel, Pharm. Ztg., 76, 567 (1931).

9. E'we, G.E., J. Am. Pharm. Assoc., 23, 1205 (1934).

10. Davis and Gillette, Pharm. J., 79, 475, 503 (1934).

11. Miller, M., and Shalkova, A., Farm. Zhur., 11, 25 (1938).

12. Brown, C.L.M., Quart. J. Pharm. & Pharmacol., 12, 489 (1939)

13. Berry, H., Quart. J. & Year Book of Pharmacy, 12, 501 (1939).

14. Calamari, J.A., and Roth, P.B., Proc. Am. Pharm. M'frer's Assoc., 27 (1942).

15. Malpass, G.N., Am. J. Pharm., 114, 167 (1942).

16. Berry, H., and Smith, A.N., Quart. J. Pharm. & Pharmacol., 17, 248 (1944).

17. Hoehn, W.M., Bull. Natl. Formulary Comm., 13, 162 (1945)

18. Kelly, K.L., and Green, M.W., Bull. Natl. Formulary Comm., 13, 48(1945).

19. Spengler, O.H., and Kaelin, H.A., Pharm. Acta Helvet., 20, 227 (1945).

20. Bandelin, F.J., Am. J. Pharm., 117, 124 (1945).

21. France, H.P., Stephenson, D., and Taylor, A., Quart. J. Pharm., 19, 286 (1946).

22. Filleborn, V.M., Am. J. Pharm., 120, 233 (1948).

23. Sperandio, G.J., Evanson, R.V., and DeKay, H.G., J. Am. Pharm. Assoc., 37, 71 (1948).

24. Granberg, C.B., and Benton, B.E., J. Am. Pharm. Assoc., 38, 648 (1949).

25. Smith, A.N., Pharm. J., 163, 194, 227, 477 (1949).

26. Smith, A.N., Pharm. J., 164, 73, 132 (1950).

27. Smith, D.S., and Stephenson, D., Pharm. J., 164, 439 (1950)

28. Evanson, R.V., and DeKay, H.G., Bull. Natl. Formulary Comm., 18, 45 (1950).

29. Burlinson, H., and Pickering, G., J. Pharm. Pharmacol, 2, 630 (1950).

30. Hosler, W.H., Bull. Natl. Formulary Comm., 18, 1(1950)

31. Gross, H.M., and Becker, C.H., J. Am. Pharm. Assoc., 41, 157 (1952).

32. Burlinson, H., Pharm. J., 164, 437 (1950).

33. Berry, H., and Ridout, C.W., J. Pharm. & Pharmacol., 2, 619 (1950).

34. Gershberg, S., and Stoll, F.D., J. Am. Pharm. Assoc., 35, 284 (1946).

35. Firth, A., Pharm. J., 161, 283 (1948).

36. Leonard, C.S., Proc. Am. Pharm. M'frer's Assoc.,(1933).

37. Tucker, S.J., Master of Science Thesis, University of Wisconsin, 1951.

38. Arnold, R.D., Master of Science Thesis , University of Wisconsin, 1951.

39. Kennon, L., Master of Science Thesis, University of Wisconsin, 1953.

40. Rehberg, W.F., Master of Science Thesis, University of Wisconsin, 1953.

41. Arambulo, A.S., and Deardoff, D.L., J. Am. Pharm. Assoc., 42, 690 (1953).

42. Arambulo, A.S., Fu, H.S., and Deardoff, D.L., J. Am. Pharm. Assoc., 42, 692 (1953).

43. Firouzabadian, A., and Huck, C.L., J. Am. Pharm. Assoc., 43, 248 (1954).

44. Swintosky, J.V., and Kennon, L., J. Am. Pharm. Assoc., in press.

45. Seeling, R.P., and Wulff, J., Trans. Am. Inst. Mining Met. Engrs., Metals Division, Tech. Pub., 166, 204 (1946).

46. Schwarzkopf, P., "Powder Metallurgy", The Macmillan Co., New York, 1947.

47. Axelson, J.W., and Piret, E.L., Ind. Eng. Chem., 42, 665 (1950).

## PLAN OF STUDY

Several physical properties of compressed tablets were measured as a function of maximal compressional force. The work covered true and apparent densities, porosity, hardness, disintegration time and specific surface area of tablets compressed from various formulations within the range of 500-8000 lb. force levels per tablet.

To test whether or not the relationships observed were of general application to all tablet formulations, compounds similar and dissimilar in chemical and physical properties were selected for investigation. The compounds studied were : sulfadiazine, aspirin, lactose, lactose-aspirin, methacetin and phenacetin with various binding agents.

The preparation of tablets and experimental determination of their physical properties are next considered, along with a discussion and correlation of the results obtained. Some general conclusions are then presented.

## PRESENTATION OF DATA AND RESULTS

Experimental methods used in the preparation of the tablets and the devices employed for the measurement of their physical properties are discussed briefly in Part I. Data obtained in the present study are also included in Part I in the form of tables following the experimental methods.

Since discussion of some of the results is covered in two papers prepared for publication, these papers are reproduced in that form in Parts II and III of this thesis.

Part IV deals with data and results not discussed in the two papers.

# PART I

## EXPERIMENTAL

## PHYSICAL PROPERTIES STUDIED & METHODS OF THEIR DETERMINATION

## DATA

## EXPERIMENTAL

A. Preparation of Formulations

1) Lactose, Sulfadiazine and Methacetin: These formulations were prepared by adding starch paste ( 10 per cent ) to the different powders. After granulating the masses obtained and drying them at 110° F. for four hours, the percentage of partially hydrolyzed starch in each was as follows : lactose granulation, 4 per cent; sulfadiazine granules, 5 per cent; methacetin granules, 5.2 per cent.

2) Aspirin : Two series of aspirin tablets were made, a) from commercial granules obtained from the Dow Chemical Company, Midland, Michigan, prepared by slugging and containing 10 per cent dried corn starch, and b) from the starch and aspirin crystals incorporated into Dow's granules ( 90 per cent aspirin and 10 per cent dried corn starch ).

3) Lactose-aspirin : This formulation was prepared by mixing 45 per cent each of aspirin and lactose crystals with 10 per cent dried corn starch.

4) Phenacetin : Five different formulations of phenacetin were compressed into tablets. These were prepared as follows : a) by adding 10 per cent starch paste to phenacetin, b) by adding 20 per cent starch paste to phenacetin, c) spray-drying a suspension of phenacetin in

mucilage of acacia, d) spray-drying a suspension of phenacetin in methyl cellulose solution and d) spray-drying a suspension of phenacetin in cellulose acetate hydrogen phthalate solution. Formulations "a" and "b" contained respectively 4.7 per cent and 20 per cent partially hydrolyzed starch after granulating and drying at 110° F. for four hours. Formulations "c", "d" and "e" were obtained from the Smith, Kline and French Co., Philadelphia, Pennsylvania. Assay of these formulations showed that "c" and "d" each contained 80 per cent phenacetin and "e" 92 per cent phenacetin.

B. Size of Granules used for Compression

All formulations prepared from crystals without the aid of binding agents, were compressed in that form. On the other hand, granules prepared with the aid of starch paste were ground, and then those granules passing through a No. 20 but not a No. 60 sieve were selected for compression.

C. Compression into Tablets

A mechanical lever machine capable of delivering the desired levels of force was used for the preparation of the tablets. In conjunction with this, a set of 3/8" die and flat punches was employed (1,2). Exactly the same weights of each particular granulation were fed into the die for compression. Further, to keep the true volume of all tablets constant throughout this study, the true densities of the various

formulations were determined by helium densitometry (1). From these, and starting with an arbitrary weight of 0.3950 Gm. of sulfadiazine granules, the corresponding weights of all other formulations yielding the same true volume could be calculated. The true densities, and the weights compressed into tablets, of these different formulae are listed in Table I.

Table I

True Densities and Weights Compressed into Tablets of various Formulations

| Formulation | True Density in Gm/cc | Wt. Compressed in Gm. |
|---|---|---|
| Sulfadiazine granules | 1.554 | 0.3950 |
| Aspirin granules " Dow's " | 1.404 | 0.3570 |
| Aspirin crystals and 10 per cent dried corn starch | 1.383 | 0.3515 |
| Lactose granules | 1.552 | 0.3945 |
| Lactose-aspirin | 1.485 | 0.3775 |
| Phenacetin with 4.7 per cent partially hydrolyzed starch | 1.297 | 0.3300 |
| Phenacetin with 20 per cent partially hydrolyzed starch | 1.331 | 0.3380 |
| Phenacetin with acacia | 1.306 | 0.3320 |
| Phenacetin with methyl cellulose | 1.284 | 0.3265 |
| Phenacetin with cellulose acetate hydrogen phthalate | 1.295 | 0.3290 |
| Methacetin granules | 1.281 | 0.3255 |

## PHYSICAL PROPERTIES STUDIED AND METHODS OF THEIR DETERMINATION

### A. True and Apparent Densities

True density is the density of the solid particles measured by displacement in fluids such as helium gas which penetrate into the smallest pores, whereas apparent density is the density measured by some fluids such as mercury which cannot enter into the pores of the particles.

In the present study, true density was obtained on a helium densitometer, designed and constructed by Higuchi (1). To get the true density of a substance, two determinations have to be made for the deadspace in the critical section of the apparatus. One is made with the sample tube empty and the other with the sample tube filled with the substance. From these two values, the true density can be calculated. The methods employed in the determination of the deadspace have already been completely described by Strickland (3) and Rao (4). The calculations are illustrated below:

| | |
|---|---|
| Total deadspace with empty sample tube | x |
| Wt. of Sample in sample tube | w |
| Total deadspace with sample filling sample tube | y |
| True volume of sample | x-y |
| True density of sample | $\frac{w}{x-y}$ |

The apparent density of the tablets was obtained by means of a specially designed mercury displacement tablet pycnometer. This device and the procedure used in the deter-

mination of apparent densities of tablets have already been described (1, 4,5). The pycnometer is weighed twice, first filled with mercury alone and then filled with mercury after the introduction of weighed tablets. From this and knowing the density of mercury at the temperature these measurements are made, the apparent density of the tablets can be obtained. These calculations are illustrated below:

| | | |
|---|---|---|
| Wt. of Pycnometer and mercury | | x |
| Wt. of tablets | | w |
| Wt. of pycnometer and mercury and tablets | | y |
| Wt. of mercury displaced by tablets | | x + w - y |
| Density of mercury at the temperature of measurements | | d |
| Volume of mercury displaced by tablets | $v =$ | $\frac{x + w - y}{d}$ |
| Apparent density of tablets | | w/v |

Also, geometric apparent densities were calculated in some instances as a check on the pycnometric apparent densities. Since the tablets in this study were all cylindrical of 3/8" diameter, their apparent density was readily calculated geometrically after measurement of their heights by a starret micrometer caliper.

B. Porosity

Porosity is the ratio of the void volume to the tablet's total apparent volume. The voids in this case include all space not occupied by the true solid material, i.e. the internal pores and the interstices between the particles.

Mathematically, porosity of the tablets can be calculated from a knowledge of the true and apparent densities, as follows:

| | |
|---|---|
| Wt. of tablets | $w$ |
| Apparent tablet density | $d$ |
| Apparent tablet volume | $w/d$ |
| True density | $d_o$ |
| True volume of tablet | $w/d_o$ |
| Per cent porosity | $\frac{w/d - w/d_o}{w/d} \times 100$ |

C. Specific Surface Area

A low temperature nitrogen adsorption apparatus (B.E.T.) was used for the purpose of specific surface area measurements of the tablets. The apparatus has already been described by Swintosky (6) and has been used for the determination of particle size of pharmaceutical powders (7 -11). With the introduction of a few modifications, the same apparatus was used by Rao (4,12), and in the present study, to measure the specific surface area of tablets.

It must be emphasized that the specific surface area of the tablets measured by the B.E.T. procedure is only relative. Since it is necessary that the gas to be adsorbed must penetrate into the pores of the tablets to reach all particles, it is clear that the smaller the size of the gas molecules, the more surface area will be measured.

D. Hardness

All hardness measurements in the present study refer

to the resistance offered by tablets to breaking. A Strong-Cobb Tablet Hardness Tester based on Hosler's design (13) was used to measure this property of the tablets. Results are expressed in Strong-Cobb units corresponding to the scale divisions on the instrument.

E. Disintegration Time

In this study, two different methods were used for the measurement of disintegration rates of tablets. One is based on the U.S.P. XIV method (14) with the exception of replacing the No. 10 screen by a No. 8 screen. The second method is essentially that of the B.P. 1953 (15) with some modifications. A larger tube was used ( 18" x 5/8" effective measurements ), allowing 1" space for bubble-forming when filled with water at 37°C and stoppered. Since it has been found that the temperature co-efficient of tablet disintegration is small, and owing to the slight fall in temperature during the disintegration of the tablets (16), no constant temperature water bath was used in this case.

## DATA

Tables II - XIV contain the measurements obtained for the physical properties of the various tablets studied, as a function of compressional force. Discussion of these results follows in Parts II and III of this thesis.

Table XI

Physical Properties of Sulfadiazine Tablets* made at varying Compressional Forces

| Force in lb. | Surface Area in sq.m/gm | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units |
|---|---|---|---|---|
| 0 granules | 0.22 | ----- | ----- | ----- |
| 500 | 0.49 | 1.106 | 29.33 | 4.8 |
| 1000 | 0.58 | 1.239 | 20.79 | 11.0 |
| 1500 | 0.68 | 1.318 | 16.13 | 14.9 |
| 2000 | 0.90 | 1.364 | 12.74 | 18.2 |
| 2500 | 1.00 | 1.400 | 10.43 | 19.8 |
| 4000 | 0.68 | 1.431 | 8.23 | 24.0 |
| 6000 | 0.58 | 1.463 | 6.30 | 26.6 |
| 8000 | 0.29 | 1.474 | 5.47 | 27.6 |

True Density of Granulation : 1.554 gm/cc

*Tablets made from granulation containing 90 per cent sulfadiazine with 5 per cent corn starch as binding agent and 5 per cent dried corn starch.

## Table III

Physical Properties of Aspirin Tablets* made at varying Compressional Forces

| Force in lb. | Surface Area in sq.m/gm | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units | Disintegration time in seconds |
|---|---|---|---|---|---|
| 0 granules | 0.48 | ----- | ----- | ----- | ----- |
| 500 | 0.54 | 1.211 | 13.69 | 2.5 | 6.0 |
| 1000 | 0.62 | 1.271 | 9.68 | 8.7 | 6.6 |
| 1500 | 0.55 | 1.309 | 6.63 | 11.7 | 8.5 |
| 2000 | 0.49 | 1.334 | 5.49 | 15.2 | 11.4 |
| 2500 | 0.48 | 1.346 | 4.21 | 15.4 | 17.5 |
| 4000 | 0.37 | 1.365 | 3.08 | 17.2 | 27.5 |
| 6000 | 0.24 | 1.377 | 2.30 | 18.7 | 40.9 |
| 8000 | 0.18 | 1.386 | 2.00 | 14.7 | 50.4 |

True density of the granules : 1.404 gm/cc

* Tablets made from Dow's aspirin granulation containing 90 per cent aspirin and 10 per cent dried corn starch.

Table IV

Physical Properties of Aspirin Tablets* made at varying Compressional Forces

| Force in lb. | Surface Area in sq.m/gm | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units | Disintegration time in seconds |
|---|---|---|---|---|---|
| 0 crystals | 0.10 | ----- | ----- | ---- | ----- |
| 500 | 0.40 | 1.198 | 13.37 | 2.0 | 5.8 |
| 1000 | 0.41 | 1.246 | 9.90 | 7.0 | 6.4 |
| 1500 | 0.46 | 1.286 | 7.01 | 11.0 | 8.1 |
| 2000 | 0.35 | 1.311 | 5.21 | 13.5 | 12.1 |
| 2500 | 0.35 | 1.323 | 4.33 | 14.0 | 15.6 |
| 4000 | 0.32 | 1.347 | 2.58 | 16.5 | 26.3 |
| 6000 | 0.25 | 1.356 | 1.93 | 17.5 | 34.3 |
| 8000 | 0.17 | 1.365 | 1.27 | 11.0 | 46.6 |

TRUE DENSITY OF CRYSTALS : 1.383 gm/cc

* Tablets prepared from 90 per cent aspirin crystals and 10 per cent dried corn starch.

## Table V

**Physical Properties of Lactose Tablets* made at varying Compressional Forces**

| Force in lb. | Surface Area in sq.m/gm | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units | Disintegration time in seconds |
|---|---|---|---|---|---|
| 0 granules | 0.16 | ----- | ----- | ----- | ----- |
| 500 | 0.21 | 1.109 | 28.68 | 5.0 | 20.5 |
| 1000 | 0.35 | 1.178 | 24.24 | 9.2 | 30.0 |
| 1500 | 0.41 | 1.245 | 19.85 | 12.7 | 38.5 |
| 2000 | 0.49 | 1.301 | 16.24 | 17.0 | 60.0 |
| 2500 | 0.61 | 1.343 | 13.52 | 19.0 | 85 |
| 4000 | 0.77 | 1.407 | 9.41 | 22.5 | 255 |
| 6000 | 0.48 | 1.459 | 6.01 | 25.5 | 1040 |
| 8000 | 0.27 | 1.488 | 4.20 | 27.0 | 5100 |

True Density of Granules : 1.552 gm/cc

*Tablets made from Lactose granulation containing 86 per cent lactose, 4 per cent corn starch for binding purposes and 10 per cent dried corn starch as disintegrant.

## Table VI

Physical Properties of Lactose-Aspirin Tablets* made at varying Compressional Forces

| Force in lb. | Surface Area in sq.m/gm | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units | Disintegration time in seconds |
|---|---|---|---|---|---|
| 0 crystals | 0.18 | ----- | ----- | ----- | ----- |
| 500 | 0.39 | 1.191 | 19.81 | 4.2 | 26.8 |
| 1000 | 0.46 | 1.267 | 14.70 | 10.5 | 20.5 |
| 1500 | 0.52 | 1.302 | 12.33 | 13.2 | 17.9 |
| 2000 | 0.60 | 1.327 | 10.66 | 15.8 | 17.2 |
| 2500 | 0.63 | 1.353 | 8.89 | 17.2 | 19.8 |
| 4000 | 0.56 | 1.385 | 6.73 | 20.0 | 21.9 |
| 6000 | 0.53 | 1.406 | 5.33 | 21.2 | 23.2 |
| 8000 | 0.47 | 1.413 | 4.84 | 22.0 | 28.5 |

True Density of Formulation : 1.485 gm/cc

*Tablets made from a mixture containing 45 per cent of each of lactose and aspirin crystals and 10 per cent dried corn starch.

## Table VII

Physical Properties of Phenacetin-Starch Tablets* made at Varying Compressional Forces

| Force in lb. | Surface Area in sq.m/gm | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units |
|---|---|---|---|---|
| 0 granules | 0.21 | ----- | ------ | ----- |
| 500 | 0.22 | 1.012 | 22.65 | 4.0 |
| 1000 | 0.40 | 1.07¼ | 18.10 | 7.0 |
| 1500 | 0.5¼ | 1.12¼ | 12.10 | 10.0 |
| 2000 | ---- | 1.156 | 11.48 | 11.5 |
| 2500 | 0.64 | 1.17¼ | 10.08 | 12.5 |
| 4000 | 0.39 | 1.185 | 9.10 | 14.0 |
| 6000 | 0.27 | 1.188 | 8.71 | 5.0 |
| 8000 | 0.32 | 1.191 | 8.31 | 5.0 |

True Density of Granules: 1.297 gm/cc

*Tablets made from granulation containing 95.3 per cent phenacetin and 4.7 per cent starch as binding agent.

Table VIII

Physical Properties of Phenacetin-Starch Tablets* made at varying Compressional Forces

| Force in lb. | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units |
|---|---|---|---|
| 500 | 1.011 | 24.03 | 3.5 |
| 1000 | 1.102 | 17.19 | 8.0 |
| 1500 | 1.157 | 13.07 | 10.5 |
| 2000 | 1.195 | 10.20 | 12.2 |
| 2500 | 1.225 | 7.96 | 13.5 |
| 4000 | 1.254 | 5.77 | 15.0 |
| 6000 | 1.265 | 4.97 | 15.5 |
| 8000 | 1.271 | 4.49 | 16.0 |

True Density of Granulation: 1.331 gm/cc

*Tablets made from granulation containing 80 per cent phenacetin and 20 per cent starch as binding agent.

Table IX

Physical Properties of Phenacetin-Acacia Tablets* made at varying Compressional Forces

| Force in lb. | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units |
|---|---|---|---|
| 500 | 0.922 | 29.41 | 3.5 |
| 1000 | 1.077 | 17.55 | 8.0 |
| 1500 | 1.127 | 13.71 | 11.5 |
| 2000 | 1.180 | 9.64 | 14.0 |
| 2500 | 1.229 | 5.90 | 15.0 |
| 4000 | 1.260 | 3.53 | 16.5 |
| 6000 | 1.278 | 2.13 | 17.5 |
| 8000 | 1.283 | 1.75 | 18.0 |

True Density of Formulation: 1.306 gm/cc

*Tablets made from a formulation containing 80 per cent phenacetin and 20 per cent acacia

Table X

Physical Properties of Phenacetin-Methylcellulose Tablets* made at varying Compressional Forces

| Force in lb. | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units |
|---|---|---|---|
| 500 | 0.971 | 24.37 | 4.0 |
| 1000 | 1.077 | 16.12 | 8.5 |
| 1500 | 1.150 | 9.94 | 12.0 |
| 2000 | 1.160 | 9.63 | 12.5 |
| 2500 | 1.184 | 7.77 | 13.5 |
| 4000 | 1.229 | 4.26 | 15.5 |
| 6000 | 1.235 | 3.79 | 16.0 |
| 8000 | 1.239 | 3.47 | 16.5 |

True Density of Formulation : 1.284 gm/cc

*Tablets made from a formulation containing 80 per cent phenacetin and 20 per cent methylcellulose .

Table XI

Physical Properties of Phenacetin-Cellulose acetate hydrogen phthalate Tablets* made at varying Compressional Forces

| Force in lb. | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units |
|---|---|---|---|
| 500 | 0.925 | 28.58 | 3.5 |
| 1000 | 1.034 | 20.17 | 7.5 |
| 1500 | 1.128 | 12.93 | 11.0 |
| 2000 | 1.151 | 11.13 | 12.0 |
| 2500 | 1.171 | 9.60 | 12.7 |
| 4000 | 1.220 | 5.82 | 14.5 |
| 6000 | 1.244 | 3.98 | 15.5 |
| 8000 | 1.255 | 3.10 | 16.0 |

True Density of Formulation: 1.295 gm/cc

*Tablets made from a formulation containing 92 per cent phenacetin and 8 per cent cellulose acetate hydrogen phthalate

Table XII

Physical Properties of Methacetin Tablets made at varying Compressional Forces

| Force in lb. | Apparent density in gm/cc | Porosity in per cent | Hardness in S-C units |
|---|---|---|---|
| 500 | 0.923 | 27.96 | 3.0 |
| 1000 | 1.023 | 20.14 | 11.0 |
| 1500 | 1.079 | 15.76 | 15.0 |
| 2000 | 1.119 | 12.65 | 18.5 |
| 2500 | 1.139 | 11.09 | 19.5 |
| 4000 | 1.180 | 7.90 | 23.0 |
| 6000 | 1.216 | 5.08 | 25.5 |
| 8000 | 1.227 | 4.23 | 26.0 |

True Density of the Granules : 1.281 gm/cc

## Table XIII

**Disintegration Time of Sulfadiazine Tablets** made at varying Compressional Forces**

| Force in lb. | DISINTEGRATION TIME IN SECONDS of Tablets Containing | | | |
|---|---|---|---|---|
| | 1% Dried | 5% Corn | 10% Starch | 15% |
| 500 | 185 | 47.6 | 30.6 | 14.2 |
| 1000 | 430 | 62.7 | 29.2 | 12.3 |
| 1500 | 595 | 110 | 40.1 | 13.0 |
| 2000 | 1470 | 172 | 51.0 | 20.2 |
| 2500 | 3800 | 235 | 70.3 | 22.9 |
| 3000 | 4900 | 395 | 81.4 | 27.6 |
| 4000 | 20650 | 940 | 165 | 48.0 |
| 6000 | ----- | 4030 | 420 | 95.0 |
| 8000 | ----- | 17100 | 920 | 210 |

*U.S.P. XIV procedure, using No. 8 screen in place of a No. 10 screen

**Tablets contain 5 per cent starch as a binding agent.

Table XIV

Disintegration Time* of Sulfadiazine Tablets** made at Varying Compressional Forces

| Force in lb. | DISINTEGRATION TIME IN SECONDS OF TABLETS containing 1% Dried Corn starch | 5% Dried Corn starch | 10% Dried Corn starch | 15% Dried Corn starch |
|---|---|---|---|---|
| 500 | 110 | 29.1 | 22.1 | 10.3 |
| 1000 | 340 | 32.3 | 22.0 | 7.9 |
| 1500 | --- | 53.0 | 27.2 | 9.2 |
| 2000 | --- | 71.6 | 36.7 | 11.6 |
| 2500 | --- | 138 | 53.5 | 14.7 |
| 3000 | --- | 275 | 66.0 | 19.2 |
| 4000 | --- | 430 | 108 | 26.4 |

*Modified B.P. procedure
**Tablets contain 5 per cent starch as a binding agent

## BIBLIOGRAPHY


1. Higuchi, T., Arnold, R.D., Tucker, S.J., and Busse, L.W., J. Am. Pharm. Assoc., 41, 93 (1952)

2. Arnold, R.D., Master of Science Thesis, University of Wisconsin, 1951

3. Strickland, W., Master of Science Thesis, University of Wisconsin, 1952

4. Rao, A.N., Doctor of Philosophy Thesis, University of Wisconsin, 1952

5. Tucker, S.J., Master of Science Thesis, University of Wisconsin, 1951

6. Swintosky, J.V., Doctor of Philosophy Thesis, University of Wisconsin, 1948

7. Swintosky, J.V., Riegelman, S., Higuchi, T., and Busse, L.W., J. Am. Pharm. Assoc., 38, 210 (1949)

8. Ibid, 38, 308 (1949)

9. Ibid, 38, 378 (1949)

10. Riegelman, S., Swintosky, J.V., Higuchi, T., and Busse, L.W., J. Am. Pharm. Assoc., 39, 444 (1950)

11. Swintosky, J.V., and Rao, A.N., J. Am. Pharm. Assoc., 41, 441 (1952)

12. Higuchi, T., Rao, A.N., Busse, L.W., and Swintosky, J.V., J. Am. Pharm. Assoc., 42, 194 (1953)

13. Hosler, W.H., Bull. Natl. Formulary Comm., 18, 1 (1950)

14. Pharmacopoeia of the United States, XIV th edition, p. 700

15. British Pharmacopoeia 1953, p. 555

16. Kelly, K.L., and Green, M.W., Bull. Natl. Formulary Comm., 13, 48 (1945)

## PART II

# THE PHYSICS OF TABLET COMPRESSION V. Studies on Aspirin, Lactose, Lactose-aspirin and Sulfadiazine Tablets.

# THE PHYSICS OF TABLET COMPRESSION V. Studies on Aspirin, Lactose, Lactose- aspirin and Sulfadiazine Tablets.


## ABSTRACT

A study has been made of the effect of compressional force on various physical properties of compressed tablets made from several different formulations. Comparison of the results with those obtained earlier from a similar investigation of sulfathiazole tablets revealed a general qualitative relationship applicable to all formulations with regard to the influence of the maximal force used in compression and the physical properties of the tablets.


## INTRODUCTION

The influence of maximal force used in compression on the physical properties of tablets prepared from a single sulfathiazole granulation was discussed in an ealier publication (1). Since substances commonly compressed into tablets vary in their physical and chemical properties and range from inorganic salts to complex organic molecules, the relations obtained in the case of the sulfathiazole studies

may not necessarily hold in all tablet formulae. The purpose of the present work was to study the compressional behavior of several other formulations and determine whether or not the relations observed in the earlier investigation were generally valid.

The compounds for the present study were therefore selected to provide a representative sample, insofar as physical and chemical properties are concerned, of substances commonly compressed into tablets. This paper deals specifically with results obtained from compression of sulfadiazine, aspirin, lactose and lactose-aspirin tablets.

As in the earlier study, the following physical characteristics and properties of tablets were determined as functions of the maximal force used during the compressional process:

(1) Specific surface area

(2) Apparent and true densities

(3) Hardness

(4) Disintegration time.

In the study of the disintegration time of sulfathiazole tablets (1), only one per cent dried corn starch was used in all the tablets. In the present study, a more extensive investigation of the disintegration rates of sulfadiazine tablets was undertaken by incorporating various proportions of dried corn starch in different batches of the sulfadiazine granulation.

## RESULTS AND DISCUSSION

In nearly all cases, the results obtained by these studies were in general qualitative agreement with those previously found in the sulfathiazole granulation (1). Such differences as were found could be attributed mainly to the difference in relative hardness and cohesive properties of the granulations employed.

### Specific Surface Area

In considering the influence of compressional force on the specific surface area of the tablets in our study, a qualitative relationship is found similar to that observed in the case of the sulfathiazole granulation. An increase in the maximal compressional force resulted in larger values for the specific surface area of the tablets. This relation continued until a certain force was reached after which further increments of force caused the specific surface area to decrease. The value of the maximum specific surface area, and the force at which it appeared, varied with the structure of the substances compressed. The nature of the relation between specific surface area of the tablets and maximal compressional force is shown in Figs. 1 and 2.

An examination of these figures will show that sulfadiazine tablets resemble to a great extent the sulfathiazole tablets of the earlier study (1), both in the position

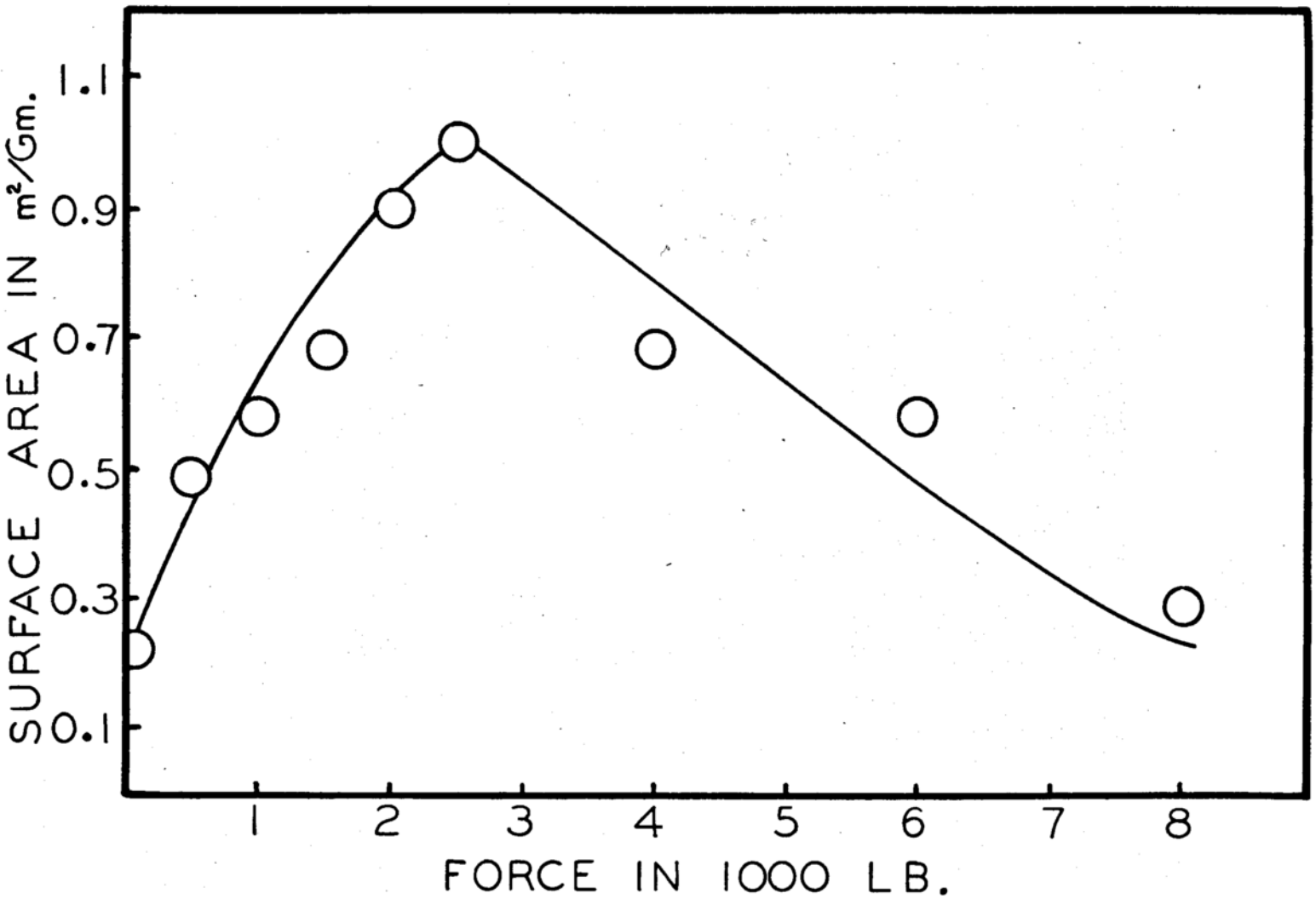


**Fig. 1. The effect of Compressional Force on the Specific Surface Area of Sulfadiazine Tablets.**

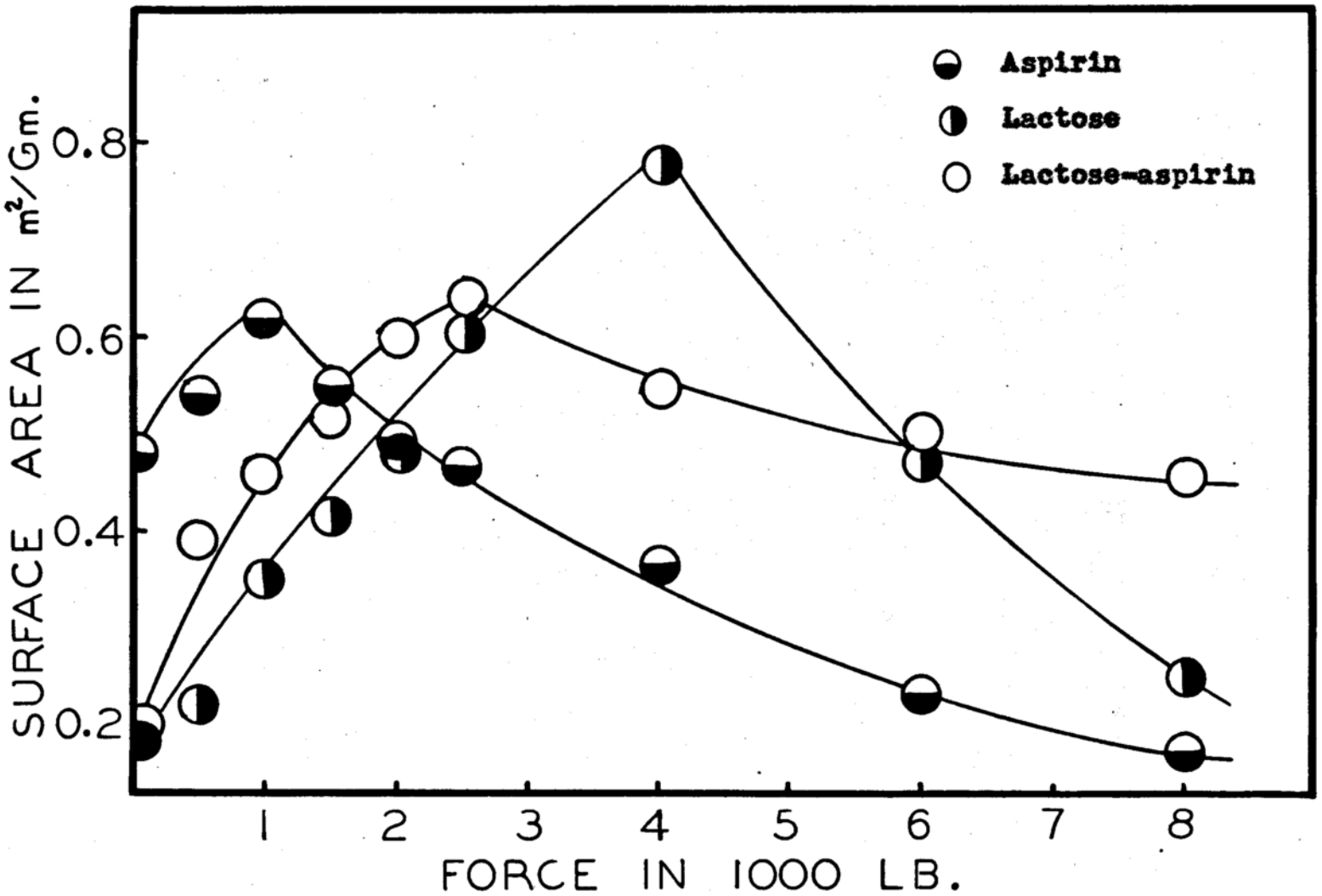


**Fig. 2. The effect of Compressional Force on the Specific Surface Area of various Tablets.**

of the maximum specific surface areas and in their values. This was expected in view of the closely related structures of the two substances.

Aspirin particles appear to be easily crushed as can be inferred from the rapid increase in their specific surface area which reaches a peak at only 1000 lb. force. In the case of lactose, the force required to obtain the maximum specific surface area is 4000 lb., indicating that lactose particles are more resistant to crushing.

Specific surface area values between those of lactose and aspirin tablets were expected for the lactose-aspirin formula. In this latter case, the maximum specific surface area appeared at 2500 lb., as expected, but the surface areas did not show values between those of lactose and aspirin tablets at every force level. A marked deviation in the force range of 6000-8000 lb. occurred in particular. In this range, the specific surface areas of the tablets made from the mixed granulation remained higher than those made from either constituent.

The relationship between the specific surface area of the different tablets and their porosity at various force levels is illustrated in Fig. 3. It can be seen that all the tablets exhibit maximum specific surface area at around ten per cent void space even though the forces at which these maxima occur vary widely with the different formulations studied.

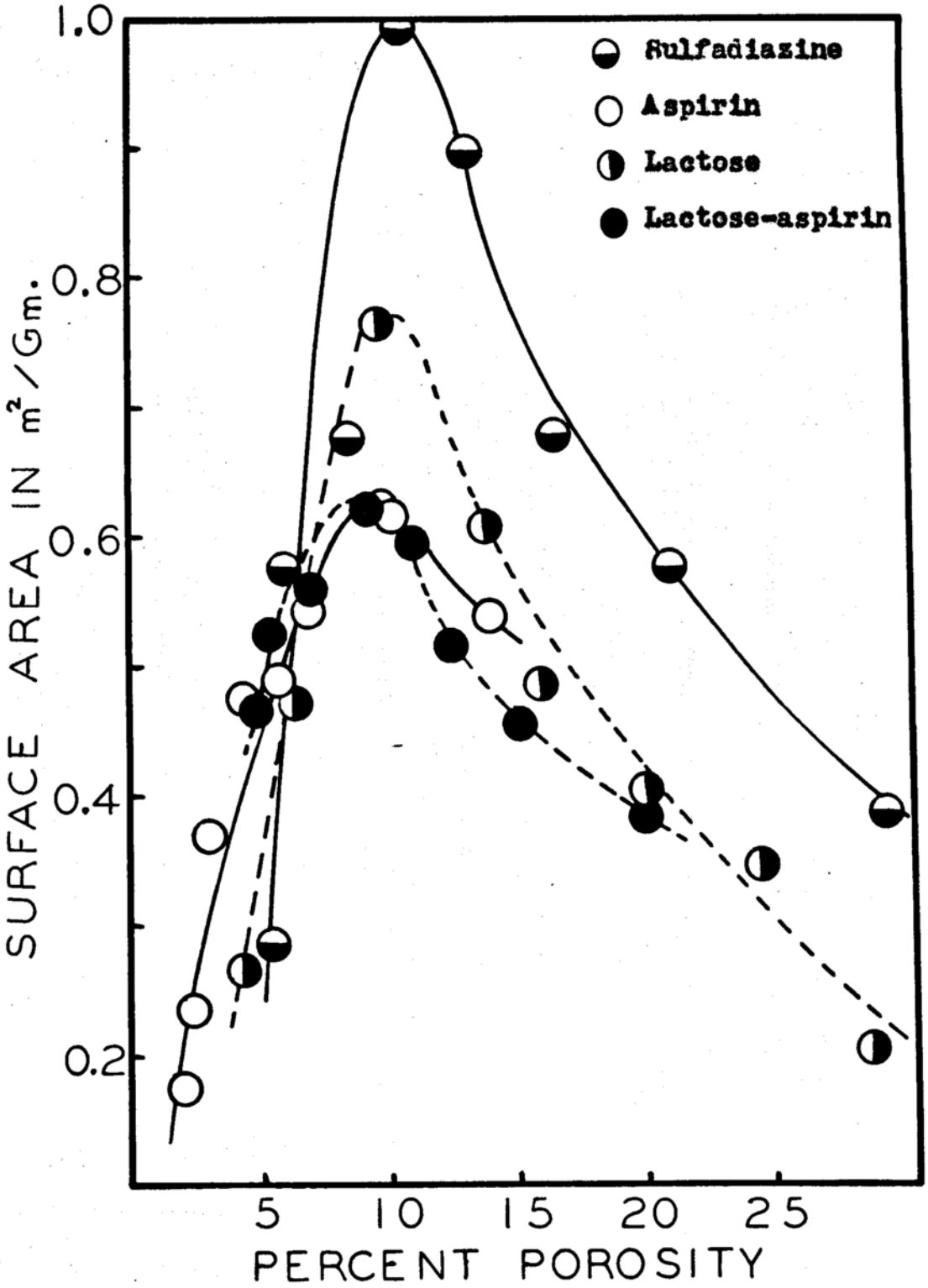


**Fig. 3. Porosity vs Specific Surface Area of various tablets.**

Since it is necessary in the method used for measuring surface areas that nitrogen gas penetrates all capillary spaces within the tablet, it would be expected that with small void spaces penetration of the gas into the tablet might be impaired. At less than ten per cent void space, the diameter of the capillaries, whose total volume constitutes the void space, appears to have become too small to allow the free penetration of nitrogen gas into all void spaces. While this by itself could lead to the measurement of reduced surface areas at elevated compressional forces, 'cold bonding' of the particles is an additional factor that contributes to these reduced measurements.

An essentially similar relationship between specific surface area and compressional force was obtained in the case of the aspirin tablets made from Dow's precompressed granulation and the tablets prepared from the original crystals used in the manufacture of Dow's granulation. The maximum specific surface areas occurred for both formulations at 1000 lb. and, at corresponding compressional force levels, the surface areas were of the same order of magnitude. The specific surface area of the crystals was about one fourth that of the precompressed granulation. This indicates that there is an appreciable decrease in the particle size of the materials during the slugging process.

Porosity and Apparent Density

Here again, the qualitative relationships of porosity and apparent density with maximal compressional force follow the same pattern as that observed in the case of sulfathiazole tablets (1). There appears to be a good correlation between porosity and molecular structure in the comparison of sulfadiazine with the sulfathiazole tablets. Fig. 4 shows that sulfadiazine tablets have a porosity of 29.3 per cent when compressed at a maximal force of 500 lb.; this decreases to 5.5 per cent at 8000 lb. The corresponding values for sulfathiazole tablets were 29.9 and 4.2 per cent.

Fig. 5 illustrates that aspirin tablets have porosities of 13.7 and 2 per cent at 500 and 8000 lb. force, respectively. The porosity of lactose tablets at these two forces are respectively 28.7 and 4.2 per cent. Except for a small deviation in the force range of 6000-8000 lb., the porosity of lactose-aspirin tablets is of a magnitude between that of the individual lactose and aspirin tablets at corresponding force levels.

Porosity is related to the hardness of tablets in a linear form. Its importance in connection with the disintegration time of tablets will be pointed out later.

Since the apparent densities of tablets were determined for the purpose of the calculation of porosities, it

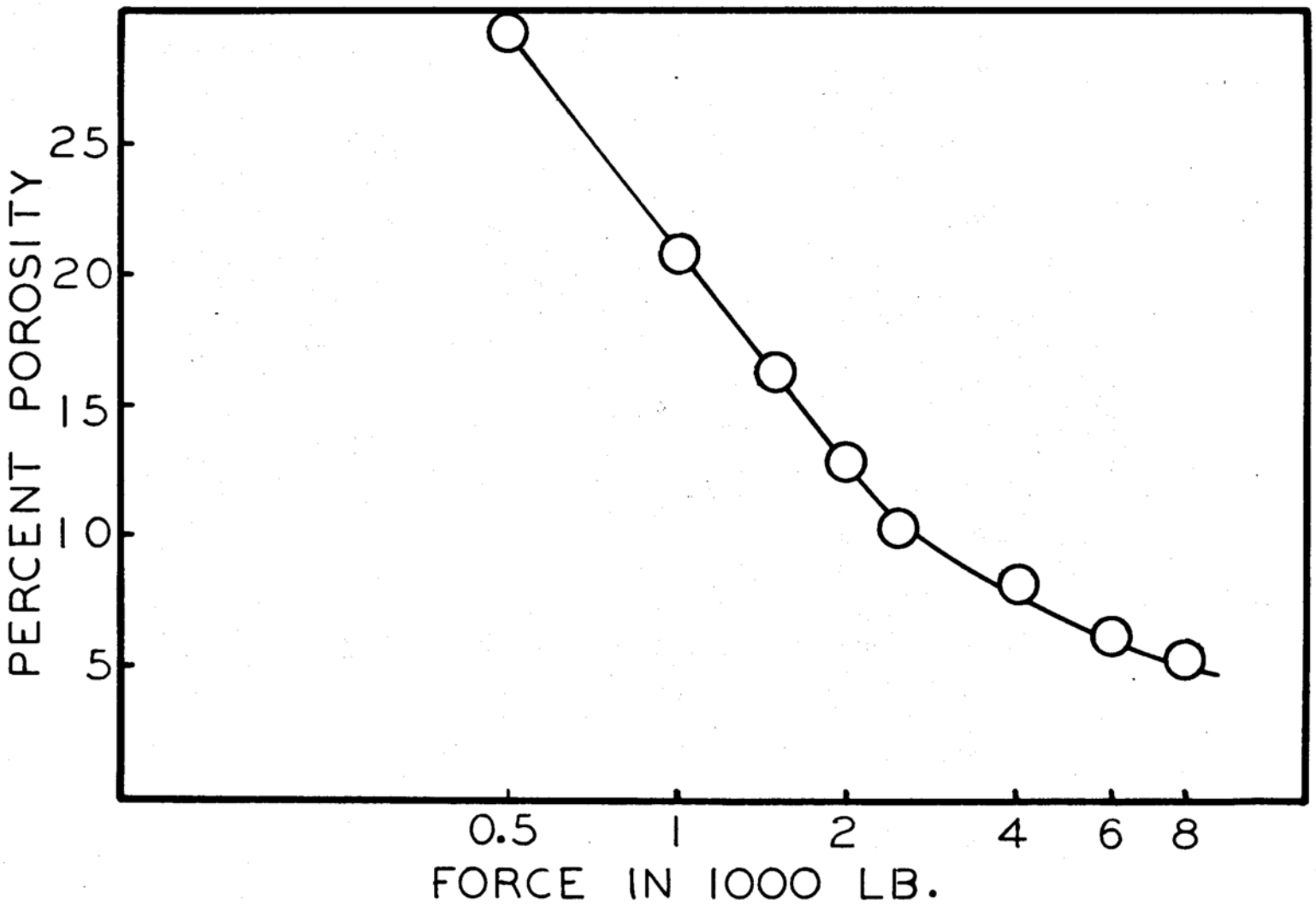


**Fig. 4. The effect of Compressional Force on the Porosity of Sulfadiazine Tablets.**

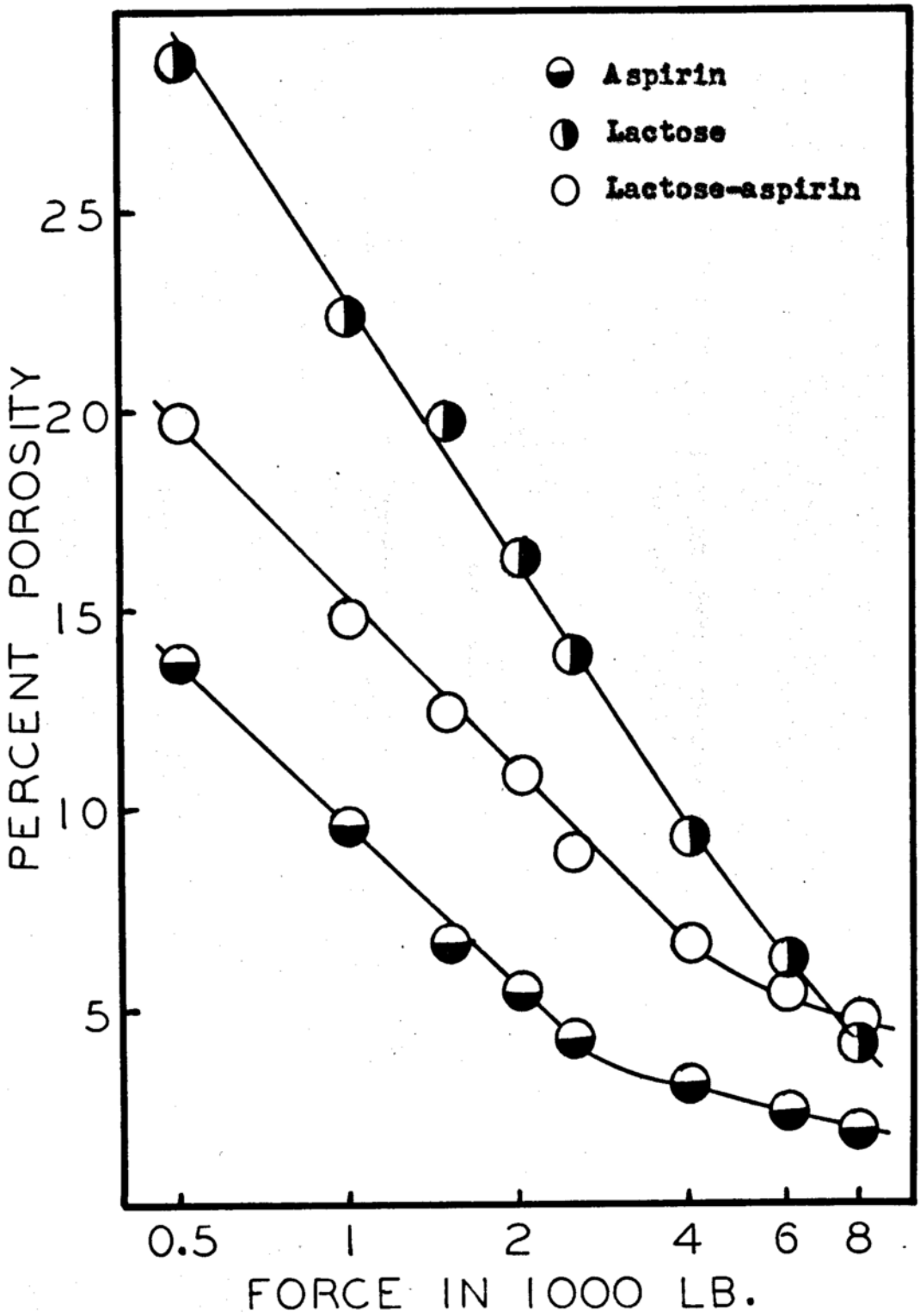


**Fig. 5. The effect of Compressional Force on the Porosity of various table ts.**

was of interest to examine their relationship with the maximal compressional force. A direct linear relationship was found between apparent densities and the logarithm of the maximal force of compression, except at high force levels where a deviation from this relation was obtained. This can be expected in view of the fact that with increased compressional force the apparent density of the tablets tends to approach the true density of the granulation as a limit.

Hardness

A direct linear dependency of hardness of tablets on the logarithm of the maximal compressional force, like that in the study of the sulfathiazole granulation, was found for all present systems. A deviation occurred at high force levels as in the case of apparent density of the tablets. This is illustrated in Figs. 6 and 7 which also show that lactose-aspirin tablets have hardness values between those of aspirin and lactose tablets separately.

Since tablet hardness was determined with a Strong-Cobb Hardness Tester which measures resistance to breaking, the relations found are only valid for this property of the tablets. Further, as in the case of disintegration times, the figures plotted for the hardness of tablets represent the mean of five values obtained at each compressional force level.

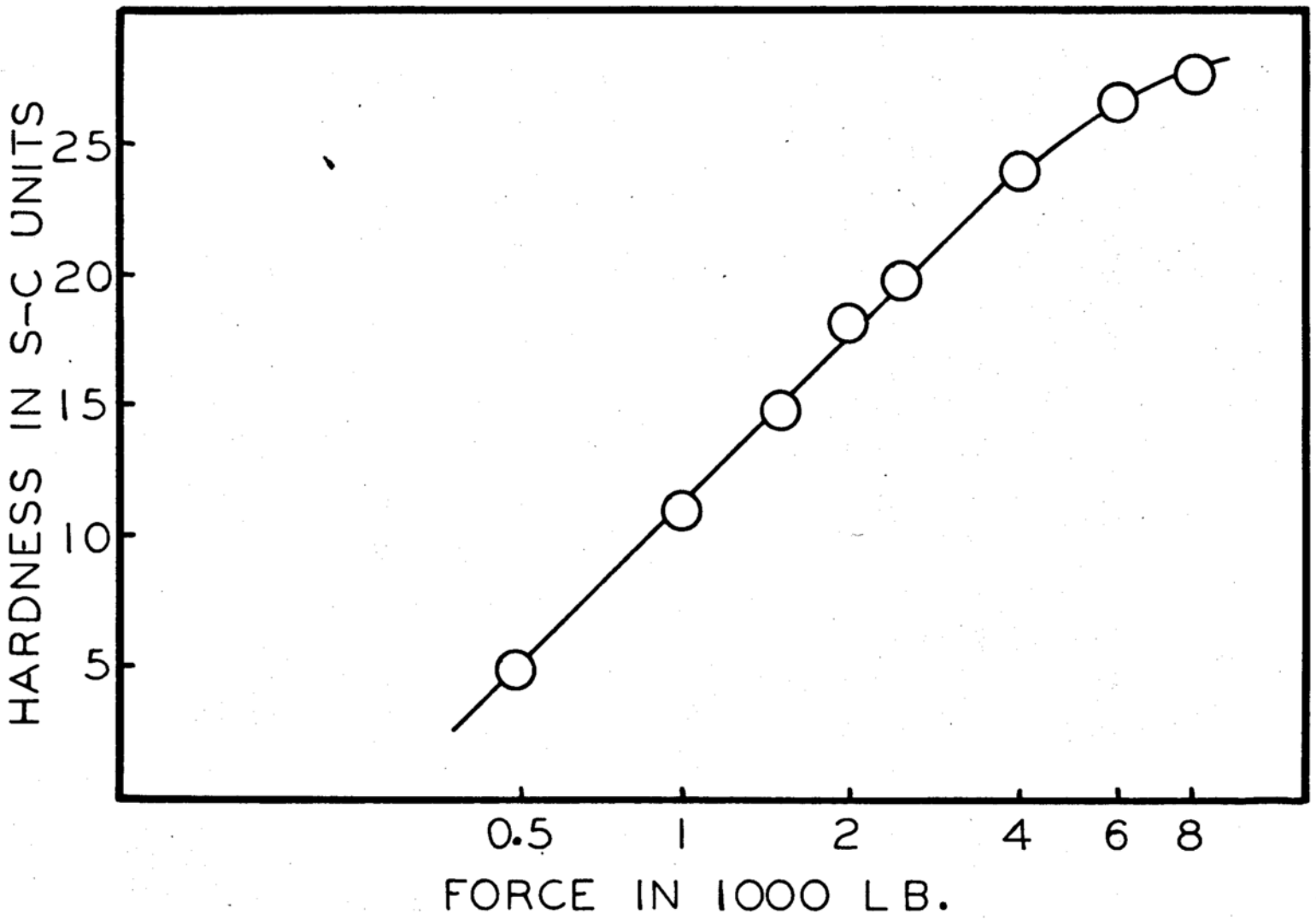


**Fig. 6. The effect of Compressional Force on the Hardness of Sulfadiazine Tablets.**

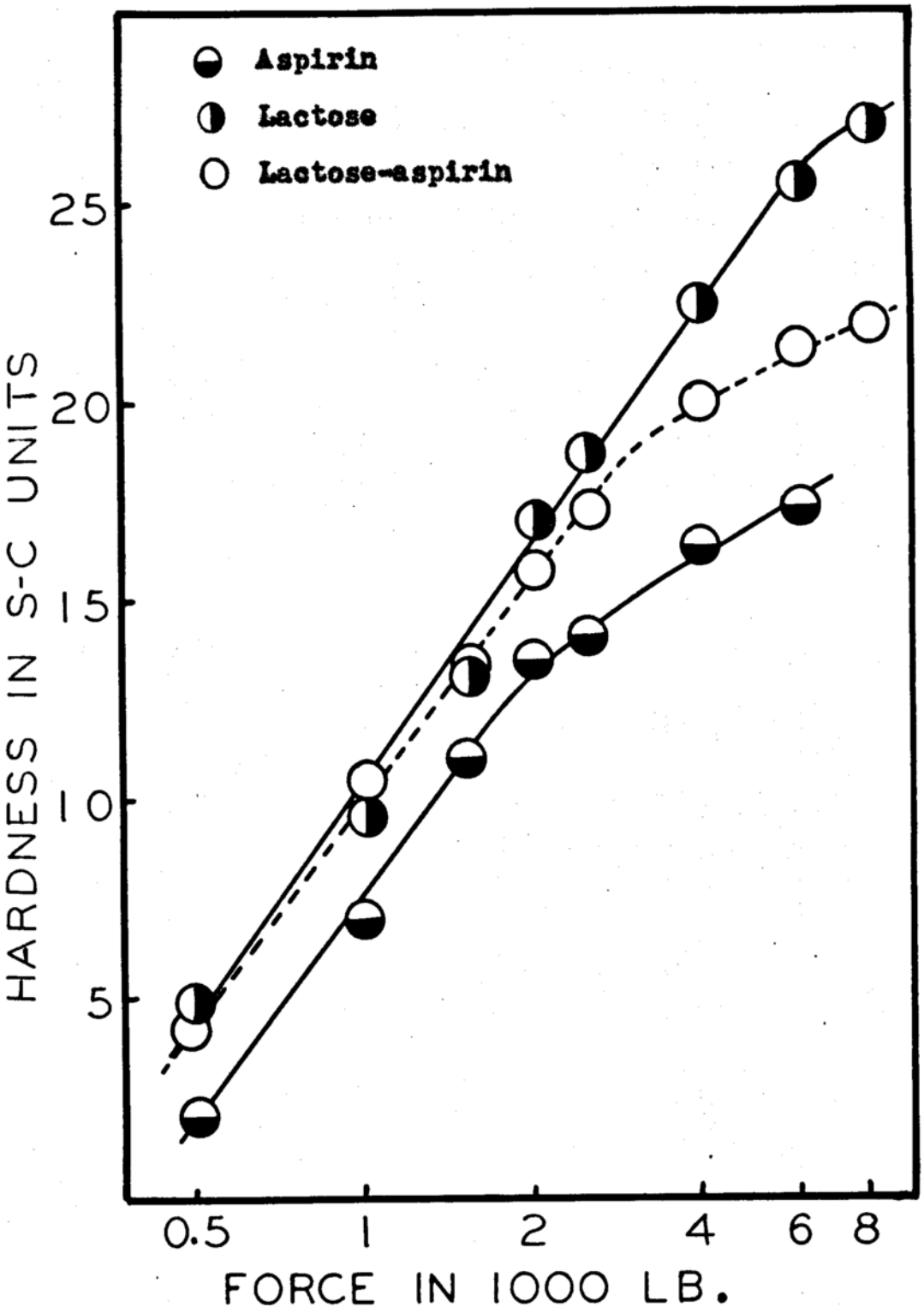


**Fig. 7. The effect of Compressional Force on the Hardness of various tablets.**

Disintegration Time

The disintegration times of lactose, aspirin and lactose-aspirin tablets as a function of compressional force are presented in Fig. 8. All these tablets contained ten per cent dried corn starch as a disintegrating agent. An examination of the figure will show that lactose-aspirin tablets have the most rapid rate of disintegration at the optimum force of 2000 lb. Also, at higher force levels, the disintegration rate of the lactose-aspirin tablets is relatively fast when compared to that of the separate lactose and aspirin tablets. Further, the pronounced minimum which occurs in the curve for the lactose-aspirin tablets is absent in the other two cases.

The comparatively rapid rate of disintegration of lactose-aspirin tablets at high compressional force levels can perhaps be explained by the larger porosities retained allowing more rapid penetration of water, and further by the greater specific surface area of these tablets.

A more extensive investigation was carried out on the disintegration rate of sulfadiazine tablets. In this case, starch was added as disintegrant in four different proportions ( 15, 10, 5 and 1 per cent ) for comparative studies. The results are given in Fig. 9 which shows a minimum in the curve of the time-force relation for sulfadiazine tablets containing 15 per cent dried corn starch. This minimum is less pronounced in the case of the tablets

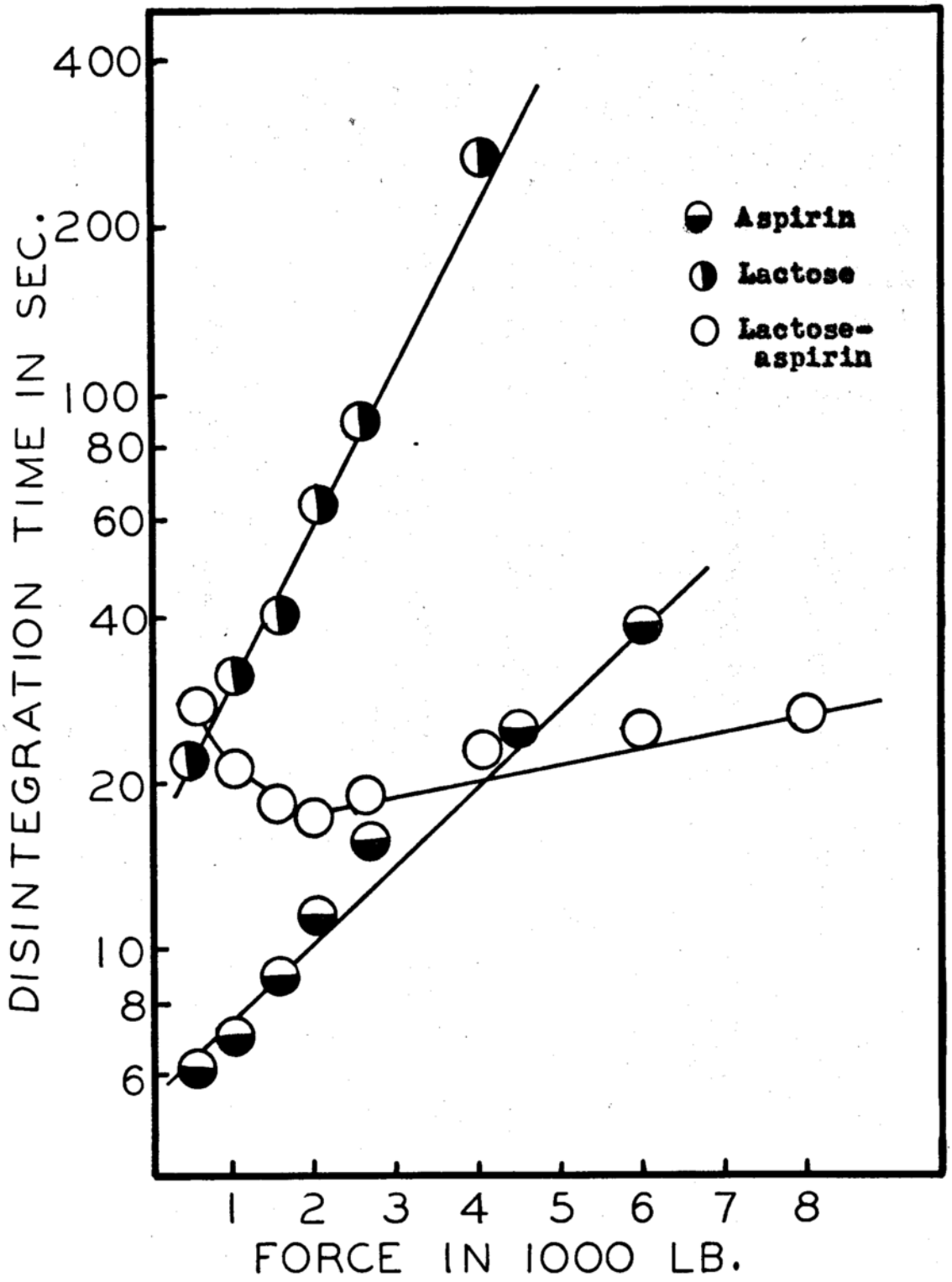


**Fig. 8. The effect of Compressional Force on the Disinte-gration time of various tablets.**

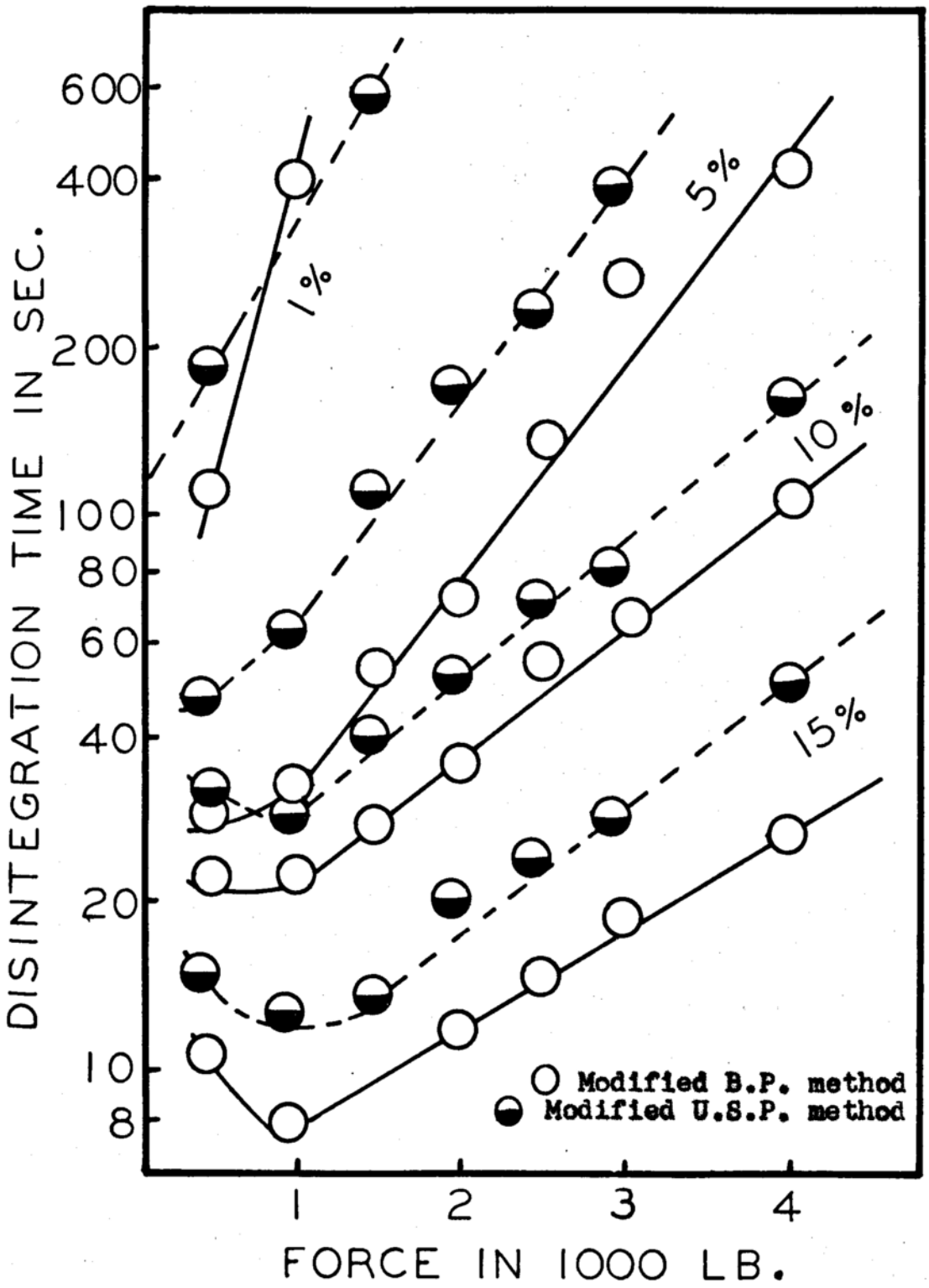


**Fig. 9. The effect of Compressional Force on the Disintegration time of Sulfadiazine tablets with various percentages of dried corn starch.**

with 10 and 5 per cent dried corn starch and is completely absent with those containing only 1 per cent of the same disintegrant. It is also seen from Fig. 9 that the slope of the disintegration time-force curves increases with decreasing percentage of disintegrant.

The above results are in general agreement with those observed by Berry and Ridout (2) who studied phenacetin tablets with 15 per cent potato starch and phenacetin tablets with various proportions of alginic acid as disintegrating agents. These authors determined the disintegration times of the different tablets as a function of the ratio of the weight to height of the tablets which they called 'compression ratio'. It is obvious that this 'compression ratio' is a measure of the maximal force applied during the compression of the tablets. They found that, up to an optimum point, the disintegration time decreased with increased 'compression ratio'. After this point, however, increased 'compression ratio' resulted in lower rates of disintegration. When various proportions of alginic acid were used, they found that the curves representing the 'compression ratio' against disintegration time of the tablets had steeper slopes with decrease in the percentage of alginic acid added.

Our explanation for the occurrence of the minima in the curves representing disintegration time against maximal

compressional force of certain tablets is in agreement with that offered by Berry and Ridout (2) for a similar minimum observed in their study of phenacetin tablets containing 15 per cent potato starch. This explanation takes into account the swelling of starch grains and the porosity of the tablets. Under a very light compression, the grains can swell, but owing to large void spaces there is a certain lag period before they begin to exert pressure on the surrounding granules. At the critical compression, as soon as the grains swell they exert such pressure on the surrounding granules and the tablets disintegrate rapidly. More time is required for the disintegration fluid to seep through the outer layers of tablets made under heavy compression and, as a result, slower disintegration rates are obtained for such tablets.

In the studies with sulfadiazine tablets made here, the disintegration times were determined both by the modified U.S.P. and B.P. methods mentioned in the experimental section of this paper. It was observed that the times obtained with the modified U.S.P. method were uniformly higher than those obtained for the corresponding tablets by the modified B.P. tube method. This is attributed to the thrust exerted on the tablet by the ascending bubble in the tube.

## EXPERIMENTAL

Granulations for sulfadiazine and lactose tablets were prepared by adding 10 per cent starch paste to the compounds until the masses were suitable for granulation. After granulating, drying was effected for four hours at 110°F and then the dried granules were ground. The granules used for compression into tablets were those passing through a No. 20 but not through a No. 60 sieve.

Two series of aspirin tablets were studied. These were made from (a) Dow's commercial aspirin granules which are prepared by slugging and which contain 10 per cent corn starch and (b) a mixture of aspirin crystals and 10 per cent dried corn starch.

Equal weights of lactose and aspirin crystals, incorporating 10 per cent dried corn starch, was the basis of the formulation for the lactose-aspirin tablets.

An arbitrary weight of 0.3950 Gm. of sulfadiazine granulation was taken for compression into tablets. Weights of the other formulations corresponding to the same true volume occupied by the sulfadiazine tablets were calculated. This was made possible by obtaining the true densities of all the formulations on a helium densitometer described earlier (3,4). Table I shows the true densities and the weights compressed of each formula.

TABLE I

True Densities and Weights Compressed into Tablets of Different Formulations

| Formulation | True Density in Gm/cc | Wt. Compressed in Gm. |
|---|---|---|
| Sulfadiazine granules | 1.554 | 0.3950 |
| Lactose granules | 1.552 | 0.3945 |
| Lactose-aspirin crystals | 1.485 | 0.3775 |
| Aspirin (Dow's granules) | 1.404 | 0.3570 |
| Aspirin (from crystals) | 1.383 | 0.3515 |

The tablets were compressed at eight varying force levels, ranging from 500-8000 lb. per tablet, by means of a mechanical lever machine and a set of 3/8" die and punches which have already been described (3).

Specific surface areas, apparent densities and hardness of the compressed tablets were determined by means of the B.E.T. low temperature nitrogen adsorption apparatus, a specially designed mercury displacement tablet pycnometer and a Strong-Cobb Tablet Hardness Tester (1,3,4), respectively.

For disintegration time measurements, the method of the U.S.P. (5) was used with the substitution of a No. 8 for a No. 10 screen. A second disintegration method based on the B.P. procedure (6) was also used, employing a tube of 18" x 5/8" effective measurements. When filled with water

at 37°C an empty space of 1" was left for bubble forming. The use of a constant temperature water bath was not found necessary in this method owing to the small temperature coefficient of tablet disintegration and to the very small fall in the temperature of the water during disintegration time measurements of normal tablets (7).

Porosity was calculated from the following expressions:

$$\text{Porosity} = \left(1 - \frac{\text{apparent density}}{\text{true density}}\right) \times 100 .$$

For true density of the tablets, the true density of the granulation was used in the above expression.

## CONCLUSIONS

The results obtained in this work from the study of the compressional behavior of several tablet formulations show similar qualitative relationships between the maximal compressional force and the corresponding physical properties of the tablets in all instances. These relationships are also similar to those obtained earlier in the study of sulfathiazole tablets (1) and to those found in the case of phenacetin and methacetin formulations( 8 ).

Because essentially the same type of relationships has been obtained for similar and dissimilar formulations, it is reasonable to conclude that these relationships are of general validity in all tablet formulations.

The above relationships can be summarized as follows:

1. The specific surface area of the tablets increases with increased maximal compressional force to a maximum, and then decreases.
2. Apparent density varies directly, and porosity inversely, with the logarithm of the compressional force, up to a force level well above that used in ordinary compression of tablets.
3. Hardness varies directly with the logarithm of compressional force, levelling off at high forces. It also varies directly as the apparent density of tablets.
4. The logarithm of the disintegration time of tablets varies directly with compressional force. Higher rates of disintegration are produced by increasing the proportions of dried corn starch added.
5. In some instances where a high percentage of disintegrating agent is present, faster rates of disintegration of the tablets are obtained as the maximal compressional force is increased. This continues up to an optimum compression after which the ordinary relationship of disintegration time with compressional force is manifested.

## BIBLIOGRAPHY


1. Higuchi, T., Rao, A.N., Busse, L.W., and Swintosky, J.V., J. Am. Pharm. Assoc., 42, 194 (1953).

2. Berry, H., and Ridout, C.W., J. Pharm. Pharmacol., 2, 619 (1950).

3. Higuchi, T., Arnold, R.D., Tucker, S.J., and Busse, L.W., J. Am. Pharm. Assoc., 41, 93 (1952).

4. Rao, A.N., Doctor of Philosophy Thesis, University of Wisconsin, 1952.

5. Pharmacopoeia of the United States, XIV th. edition, p. 700.

6. British Pharmacopoeia (1953), p. 555.

7. Kelly, K.L, and Green, M.W., Bull. Natl. Formulary Comm., 13, 162 (1945).

8. Elowe, L.N., Higuchi, T., and Busse, L.W., to be published.

## PART III

# THE PHYSICS OF TABLET COMPRESSION VI. Compressional Behavior of Phenacetin and Methacetin Granulations.

# THE PHYSICS OF TABLET COMPRESSION VI. Compressional Behavior of Phenacetin and Methacetin Granulations.


## ABSTRACT

A comparative study was made of the compressional behavior of methacetin and phenacetin granulations. Phenacetin tablets made at high compressional forces from a granulation containing a low proportion of partially hydrolyzed starch were physically defective. Incorporation of a higher percentage of partially hydrolyzed starch for binding purposes, as well as other different binding agents, in phenacetin formulations resulted, on compression, in tablets free from capping or splitting. The compressional behavior of a methacetin granulation was found to be different from that of a phenacetin granulation containing approximately the same proportion of the same binding agent.


## INTRODUCTION

Many pharmaceutical manufacturers encounter considerable difficulties in the making of phenacetin tablets, due to the frequent occurrence of splitting and capping during the process of compression. To overcome these difficulties and obtain phenacetin tablets free from physical defects, formulations involving other binding agents such

as acacia, methyl cellulose, cellulose acetate hydrogen phthalate and partially hydrolyzed starch, in a higher percentage than that commonly used in the manufacture of tablets, were prepared and studied.

Earlier work had shown a general qualitative similarity among several formulations when subjected to different degrees of compression (1,2). In the present study, the effect of maximal compressional force on the physical properties of tablets obtained from the commonly used phenacetin granulation and the other phenacetin formulae has been investigated. The purpose has been an attempt in the direction of comparing the compressional characteristics of these with the ordinary compressional behavior of the systems studied earlier.

A further attempt is made to investigate the possibility of correlating structure with compressional behavior. In this direction, tablets were prepared from methacetin (p-methoxyacetanilide), a compound closely related in structure to phenacetin which is the p-ethoxyacetanilide. The effect of the degree of compression on the physical properties of these tablets was investigated in line with the other formulations.

It was found that the phenacetin tablets made from the granulation containing a low percentage of partially hydrolyzed starch showed noticeable capping and splitting at the higher compressional force levels. This troublesome behavior was, however, completely absent, throughout the

whole range of compressional force, 500-8000 lb. per tablet, in the case of the formulations in which other binding agents were used.

No correlation between compressional characteristics and structure was found in this study. The methacetin formulation, although containing approximately the same percentage of partially hydrolyzed starch as that of phenacetin which gave defective tablets, yielded well formed tablets when subjected to the different degrees of compression up to the 8000 lb. level.

## RESULTS AND DISCUSSION

The surface area of phenacetin tablets containing 4.7 per cent partially hydrolyzed starch showed a similar qualitative relationship with compressional force as obtained in earlier studies of various other formulations (1,2). Fig. 1 shows a maximum surface area for these tablets at 2500 lb. compressional force. At this point the surface area is three times that of the phenacetin granules from which the tablets are made. Higher increases in surface areas were obtained for the formulations of the earlier studies (1,2).

It can be seen from Table I that phenacetin tablets with the lower percentage of partially hydrolyzed starch are more resistant to an increase in their apparent density, as a result of rising compressional force, than the tablets made from the other four phenacetin formulations.

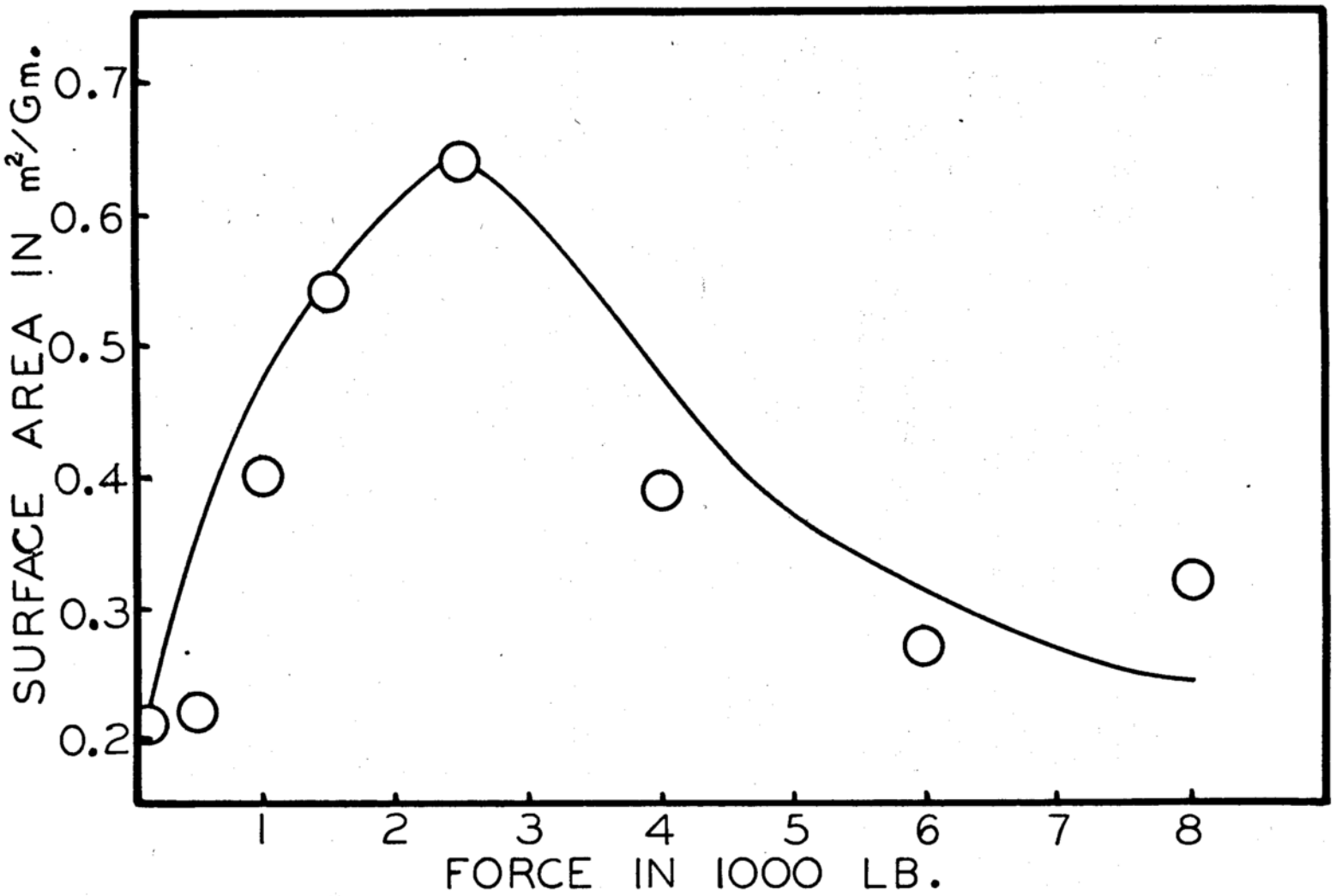


**Fig. 1. The effect of Compressional Force on the Specific Surface Area of Phenacetin Tablets containing 4.7 per cent partially hydrolyzed starch.**

Table I

Apparent Densities* of Phenacetin Tablets

| Force | BINDING AGENTS | | | | |
|---|---|---|---|---|---|
| | 4.7 % partially hydrolyzed | 20 % starch | Acacia | Methyl cellulose | Cellulose acetate H-phthalate |
| 500 | 1.012 | 1.011 | 0.922 | 0.971 | 0.925 |
| 1000 | 1.074 | 1.102 | 1.077 | 1.077 | 1.034 |
| 1500 | 1.124 | 1.157 | 1.127 | 1.150 | 1.128 |
| 2000 | 1.156 | 1.195 | 1.180 | 1.160 | 1.151 |
| 2500 | 1.174 | 1.225 | 1.229 | 1.181 | 1.171 |
| 4000 | 1.185 | 1.254 | 1.260 | 1.229 | 1.220 |
| 6000 | 1.188 | 1.265 | 1.278 | 1.235 | 1.244 |
| 8000 | 1.191 | 1.271 | 1.283 | 1.239 | 1.255 |

* Apparent Densities are given in Gm/cc

This means that the phenacetin tablets containing the higher percentage of partially hydrolyzed starch and the new binding agents are more easily compressed, a fact reflected in their value of porosity as shown in Fig. 2. At 500 lb. compressional force, the porosity of the tablets under comparison shows increasing values in the following order: phenacetin with 4.7 per cent partially hydrolyzed starch, phenacetin with 20 per cent partially hydrolyzed starch, phenacetin with methyl cellulose, phenacetin with cellulose acetate hydrogen phthalate, phenacetin with acacia. In all cases, porosity diminishes with increasing compressional force, declining sharply in the beginning and then levelling off at higher forces. The range of this decrease, however, is a characteristic of the individual formulation and is therefore not necessarily of the same magnitude in all cases. This is clearly seen at 8000 lb. force level where the tablets show values of porosity in an order which is the reverse of that exhibited at the initial compressional force of 500 lb.

The rate of decrease of tablet porosity with increasing compressional force is apparently a measure of the effectiveness of the binding agent used. This, in turn, is a criterion of the ease with which tablets can be compressed and reflects on the physical properties of the tablets after compression. In the case of phenacetin with 4.7 per cent partially hydrolyzed starch, this rate is rather slow, the

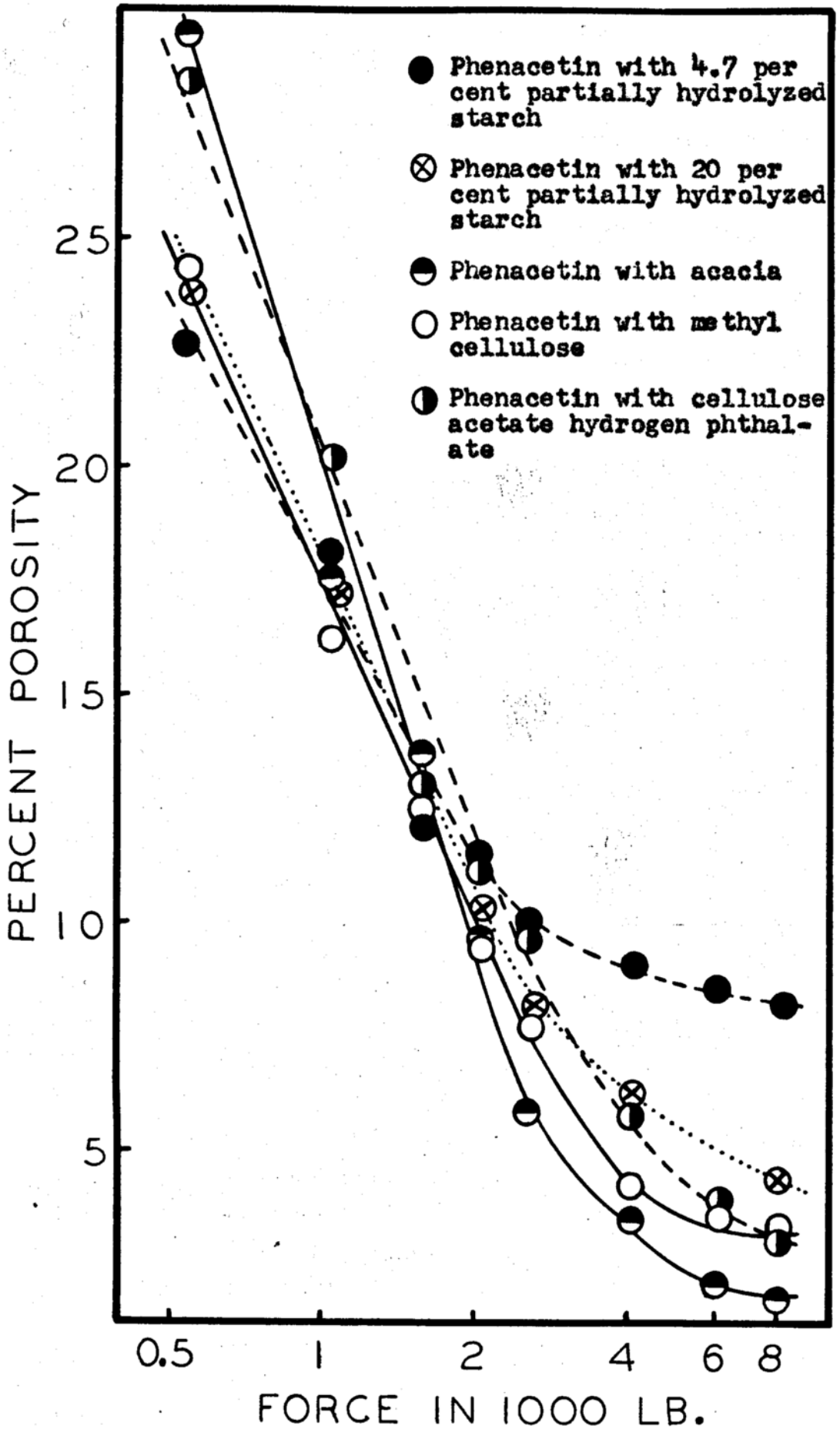


**Fig. 2. The effect of Compressional Force on the Porosity of various tablets.**

tablets still retaining the comparatively high porosity of 8.5 per cent at the 8000 lb. force level. On the other hand, it is faster in the case of the other phenacetin tablets, the phenacetin with acacia showing the most rapid decrease and, consequently, the best compressibility. This is borne out in the values of hardness of these tablets. At corresponding compressional levels, it is seen from Fig. 3 that the phenacetin with acacia tablets are the hardest and the phenacetin tablets with the lower percentage of partially hydrolyzed starch the softest of the five.

Methacetin tablets were expected to show similar characteristics to those of phenacetin in view of the similarity in structure of the compounds. However, in this study, no such correlation between structure and compressional behavior became evident. Absence of capping or splitting in the methacetin tablets was noticeable. This is significant due to the fact that the methacetin granulation contained approximately the same proportion of the binding agent used in the case of the phenacetin granulation that yielded defective tablets. The better compressibility of the methacetin tablets is again reflected in the rate of decrease of their porosity with ascending levels of compressional force. Fig. 4 shows that the decrease is faster in the case of methacetin than it is in the case of phenacetin with the lower percentage of the same binding agent. Also, a smaller porosity is retained by the methacetin tablets at 6000-8000 lb.

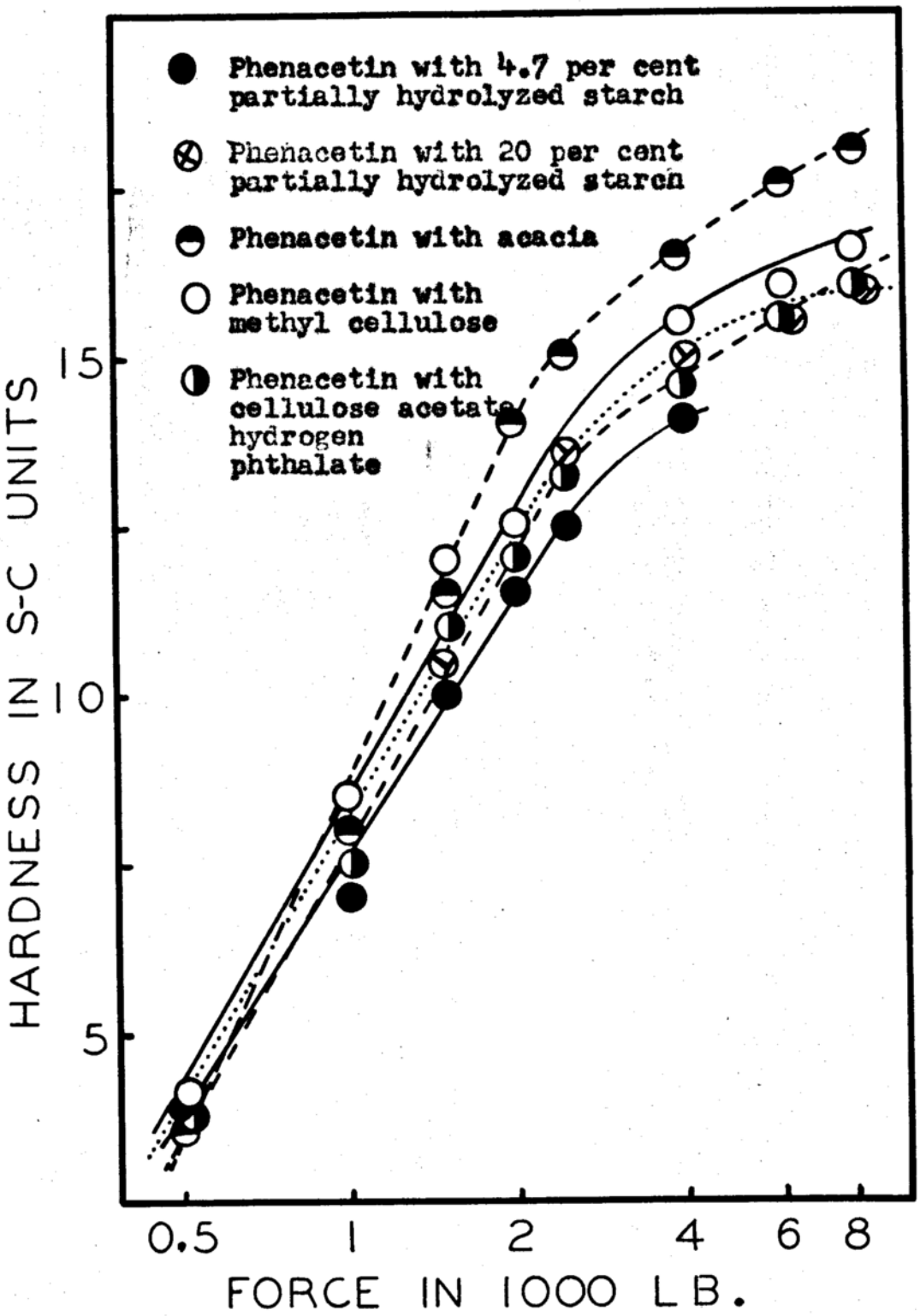


**Fig. 3. The effect of Compressional Force on the Hardness of various tablets.**

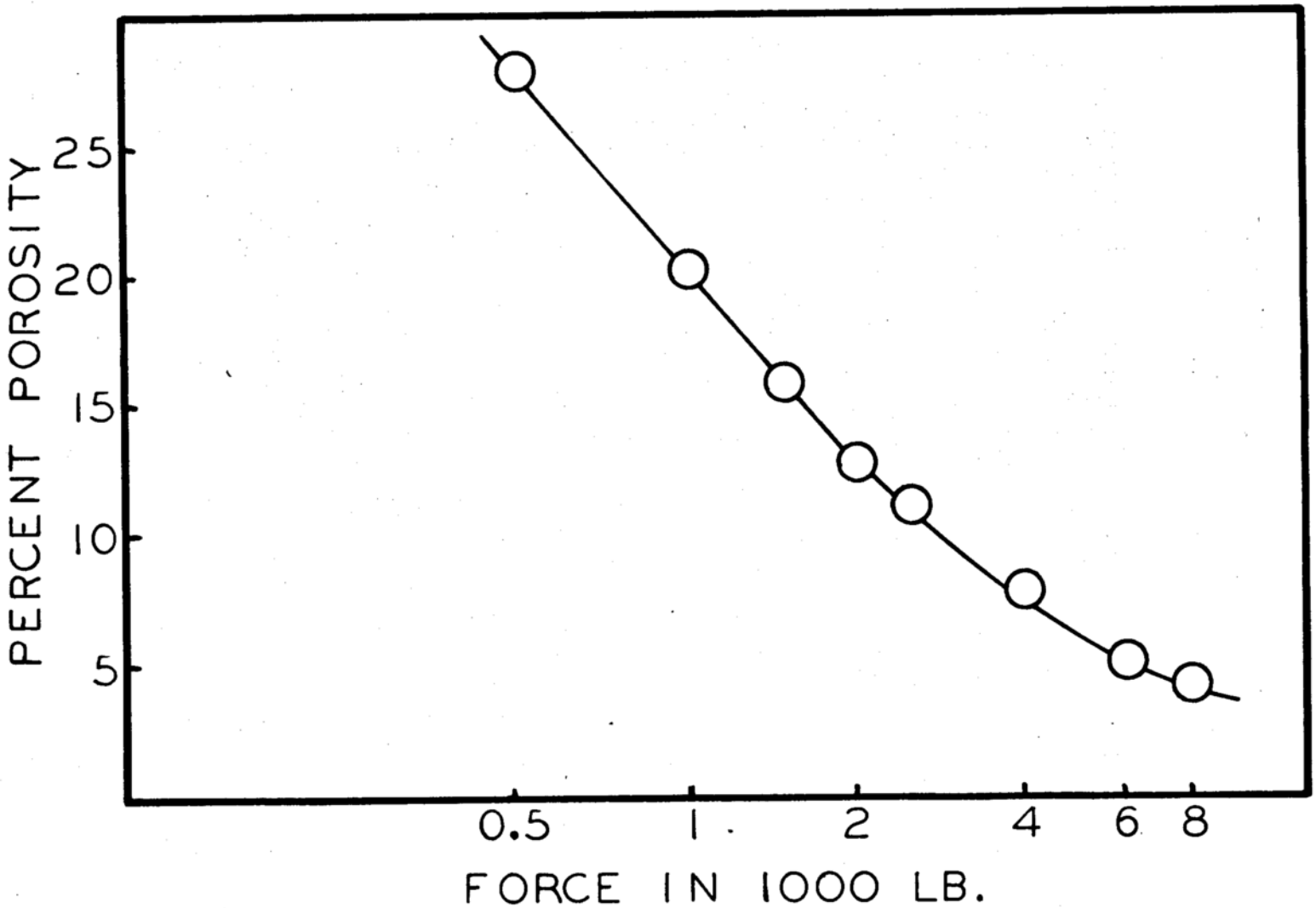


**Fig. 4. The effect of Compressional Force on the Porosity of Methacetin Tablets.**

force levels. The relation of hardness and porosity is once again demonstrated here. At corresponding force levels, the hardness of methacetin tablets can be seen from Fig. 5 to be greater when compared to that of the phenacetin tablets with the 4.7 per cent partially hydrolyzed starch.

The only granulation resulting in defective tablets at high degrees of compression was phenacetin with the lower percentage of partially hydrolyzed starch as binding agent. Tablets made from all other formulations were conspicuously free from such defects. This behavior can perhaps be attributed to two factors: (a) the high resistance to crushing offered by the phenacetin particles and (b) the insufficiency of the binding agent used.

It is apparent that as compressional force increases the particles composing a tablet are brought nearer to each other. This of course results in a smaller percentage of void space. At an optimum degree of compression that is characteristic for each individual granulation, the particles cannot be forced any closer to each other. At this stage, any increase in compressional force will cause one of two things: (a) the fragmentation of the particles and consequently still lower porosity values or (b) the deformation of the particles under pressure if they are resistant to crushing.

The deformation under high pressures of particles that resist crushing can be either permanent or reversible

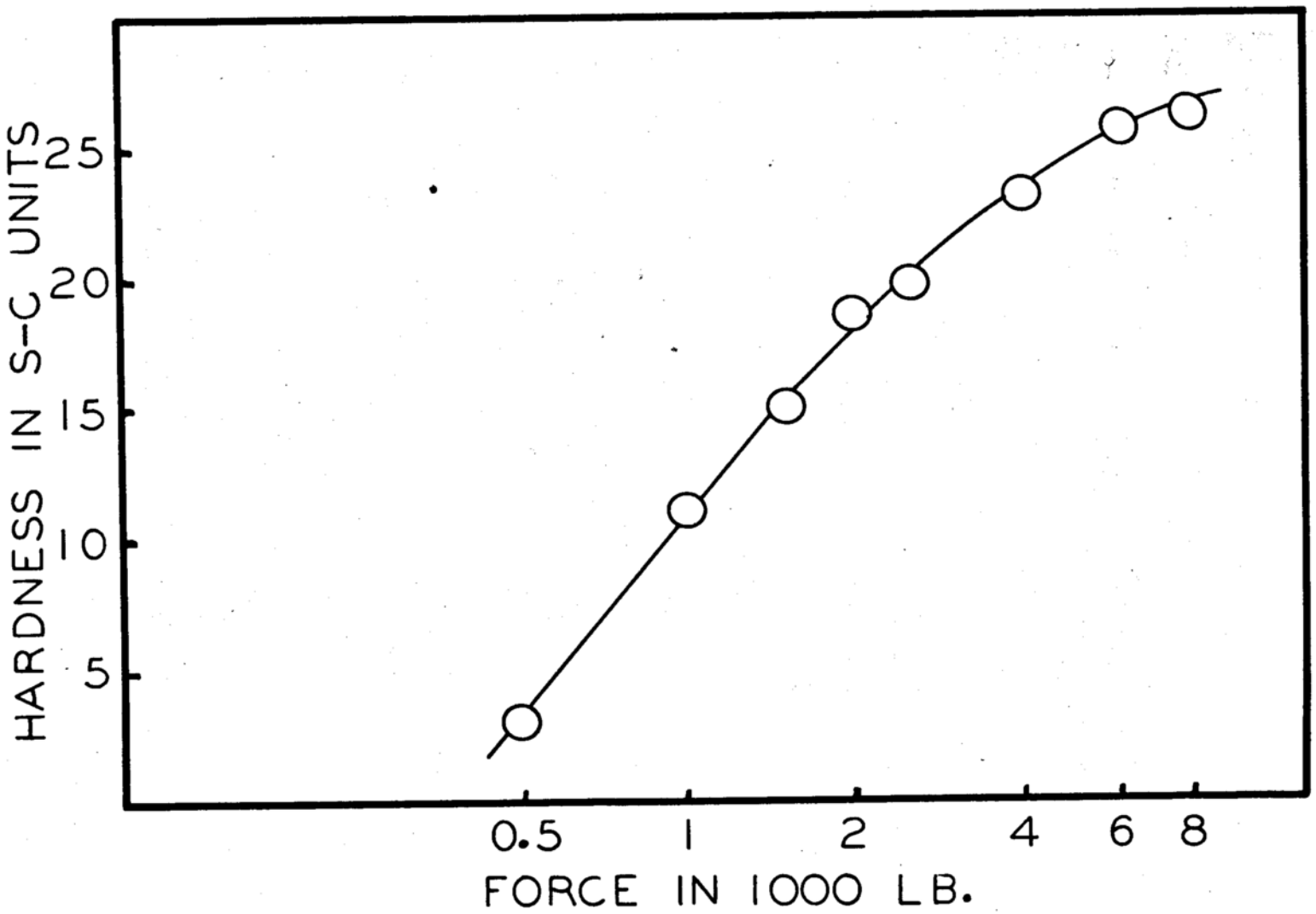


**Fig. 5. The effect of Compressional Force on the Hardness of Methacetin Tablets.**

as demonstrated by various workers in the analogous field of powder metallurgy (3-6). Which of the two will occur depends upon the nature of the particles and the kind and percentage of the binding agent present.

Phenacetin particles appear to be very resistant to crushing, undergoing an elastic deformation at high compressional forces. In the case of the granulation containing 4.7 per cent partially hydrolyzed starch, the binding agent is apparently not sufficient to overcome the tendency by the deformed particles to assume their initial shapes as the force is released. Thus, a sudden removal of the pressure causing this kind of elastic reversible deformation results in a springback of the particles. This finds in relief in a form of capping or splitting. A 20 per cent partially hydrolyzed starch in the phenacetin granulation seems to be of sufficient binding ability to counterbalance the tendency of the deformed particles to regain their original orientation upon release of the pressure. Therefore, this granulation yields tablets free from physical defects. The same explanation can be applied to the phenacetin with acacia, with methyl cellulose and with cellulose acetate hydrogen phthalate, the elasticity of the phenacetin particles being overcome by the different binding agents in the proportions in which they are present.

## EXPERIMENTAL

Preparation of Formulations.- Two different formulations of phenacetin were prepared with starch paste. A 10 per cent starch paste was used in one and a 20 per cent in the other. When dried at 110°F for four hours, the granules contained 4.7 per cent partially hydrolyzed starch in the first and 20 per cent in the second formulation.

Phenacetin with acacia, with methyl cellulose and with cellulose acetate hydrogen phthalate formulations were obtained from Smith, Kline and French Co. They were prepared by spray-drying suspensions of phenacetin solutions of the different binding agents. Assay showed that the phenacetin with acacia and with methyl cellulose each contained 80 per cent phenacetin while the formulation with cellulose acetate hydrogen phthalate had 92 per cent phenacetin.

Methacetin granulation was prepared with 10 per cent starch paste. After drying at 110°F for four hours, it contained 5.2 per cent partially hydrolyzed starch.

Compression into Tablets.- A mechanical lever machine, in conjunction with a set of 3/8" die and punches, was used for the compression of all tablets at various force levels (7).

Measurement of Physical Properties of Tablets.- (a) True densities were measured by means of a helium densitometer (7), (b) apparent densities by means of a specially designed tablet pycnometer (1,7), (c) hardness by the Strong-Cobb Tablet Hardness Tester (1), and (d) surface area on the B.E.T. low temperature nitrogen adsorption apparatus (1).

Weight of Formulations Compressed into Tablets.- The true densities obtained by helium densitometry were utilized for the calculation of the weights of the different formulations that would yield a constant true volume in all tablets. Table II shows the true densities and the weights compressed into tablets in these studies.

Table II

True Densities and Weights Compressed into Tablets of Different Formulations

| Formulation | True Density in Gm/cc | Wt. Compressed in Gm. |
|---|---|---|
| Phenacetin with 4.7 per cent partially hydrolyzed starch | 1.297 | 0.3300 |
| Phenacetin with 20 per cent partially hydrolyzed starch | 1.331 | 0.3380 |
| Phenacetin with acacia | 1.306 | 0.3320 |
| Phenacetin with methyl cellulose | 1.284 | 0.3265 |
| Phenacetin with cellulose acetate hydrogen phthalate | 1.295 | 0.3290 |
| Methacetin with 5.2 per cent partially hydrolyzed starch | 1.281 | 0.3255 |

## SUMMARY

1. The compressional behavior of different formulations made from phenacetin with various binding agents was studied.
2. A comparative study of methacetin granulation was also carried out.
3. All formulations studied gave the same qualitative relationships between maximal compressional force and the different physical properties of the tablets made from them.
4. Apparent density and hardness of tablets were found to vary directly, and porosity inversely, with the logarithm of the maximal compressional force.
5. Phenacetin tablets made from a granulation containing 4.7 per cent partially hydrolyzed starch as binding agent were physically defective when compressed at high force levels. The capping was absent when phenacetin formulations containing a higher percentage of the same binding agent, or other binding agents, were compressed.
6. No correlation between structure and compressional behavior was obtained in the comparative study of phenacetin and methacetin granulations containing approximately the same proportion of the same binding agent.

## BIBLIOGRAPHY


1. Higuchi, T., Rao, A.N., Busse, L.W., and Swintosky, J.V., J. Am. Pharm. Assoc., 42, 194 (1953).

2. Higuchi, T., Elowe, L.N., and Busse, L.W., to be published.

3. Seeling, R.P., and Wulff, J., Trans. Am. Inst. Mining Met. Engrs., Metals Division, 166, 492 (1946).

4. Hausner, H.H., Am. Machinist, 90, No.4, 104 (1946)

5. Skaupy, F., "Principles of Powder Metallurgy", Philosophical Library, New York, 1944.

6. Goetzel, C.G., "Treatise on Powder Metallurgy", Interscience Publishers, Inc., New York, 1950.

7. Higuchi, T., Arnold, R.D., Tucker, S.J., and Busse, L.W., J. Am. Pharm. Assoc., 41, 93 (1952).

# PART IV

## CORRELATION OF HARDNESS, POROSITY AND APPARENT DENSITY

---

### DENSITY GRADIENT IN COMPRESSED TABLETS

## CORRELATION OF HARDNESS, POROSITY AND APPARENT DENSITY

### 1. Apparent Density vs Compressional Force

Since the apparent densities of tablets were determined in the course of obtaining data to make the calculations for porosity values, their relation with maximal compressional force was studied.

Figs. 1-3 show that, in all cases, a linear relationship exists between the apparent density of the tablets and the logarithm of the maximal compressional force, resembling that obtained earlier with sulfathiazole (1). At compressional force levels exceeding 4000-6000 lb. per tablet, a deviation from this linear relationship is manifested. The point of onset of such a deviation in each particular case depends on the nature of the granulation. It is evident that at high compressional force levels, the apparent density of the tablets tends to approach the true density as a limit. It has been shown in powder metallurgy (2) that attainment of complete densities is usually impossible even with high compressional forces because of a certain elastic springback expansion of the compact upon pressure release. This type of springback expansion is more marked, in our studies, in the case of phenacetin tablets containing only 4.7 per cent partially hydrolyzed starch. When made at 8000 lb. compressional force, their apparent density is seen to be still considerably removed from their true density.

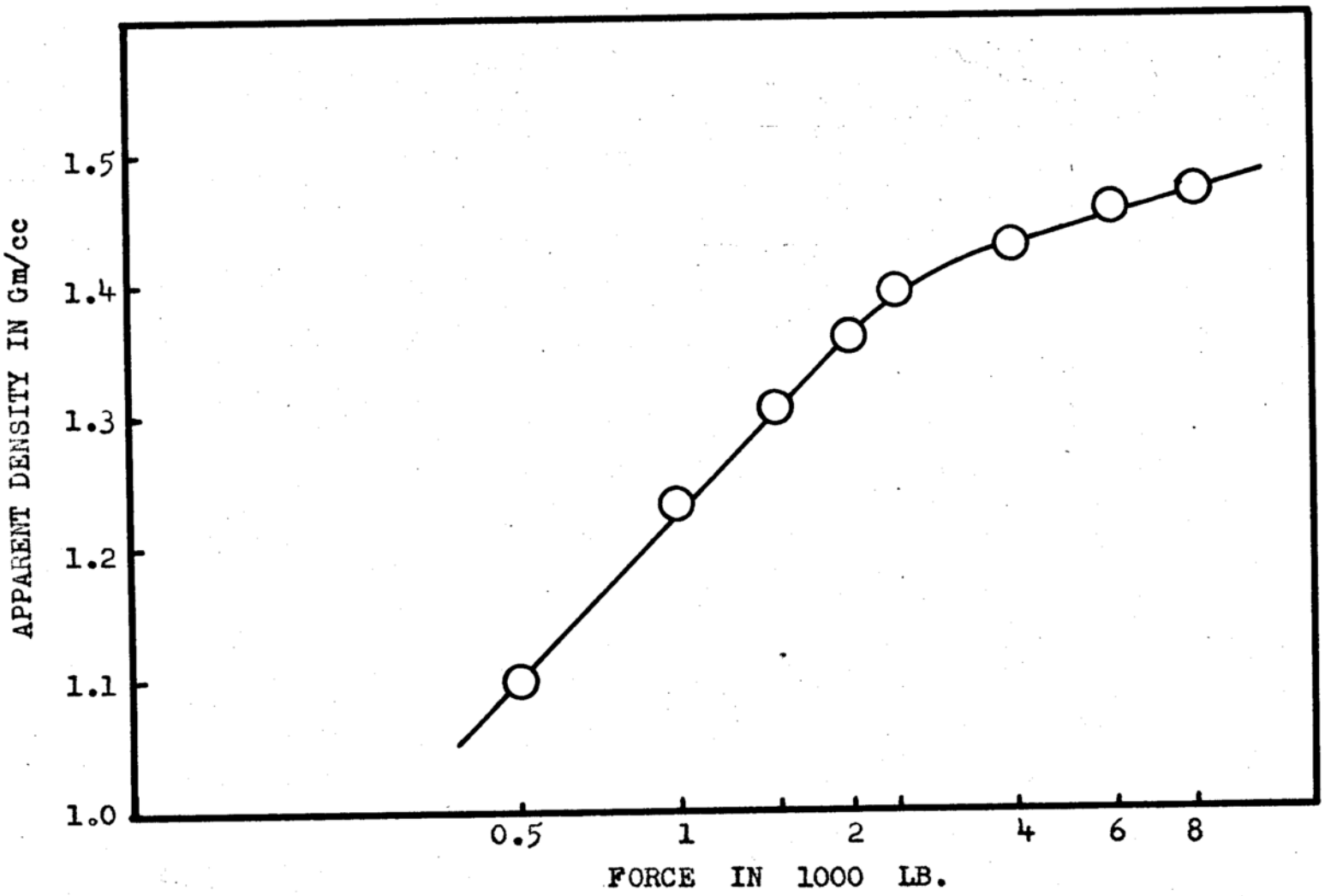


Fig 1 . The effect of Compressional Force on the Apparent Density of Sulfadiazine Tablets.

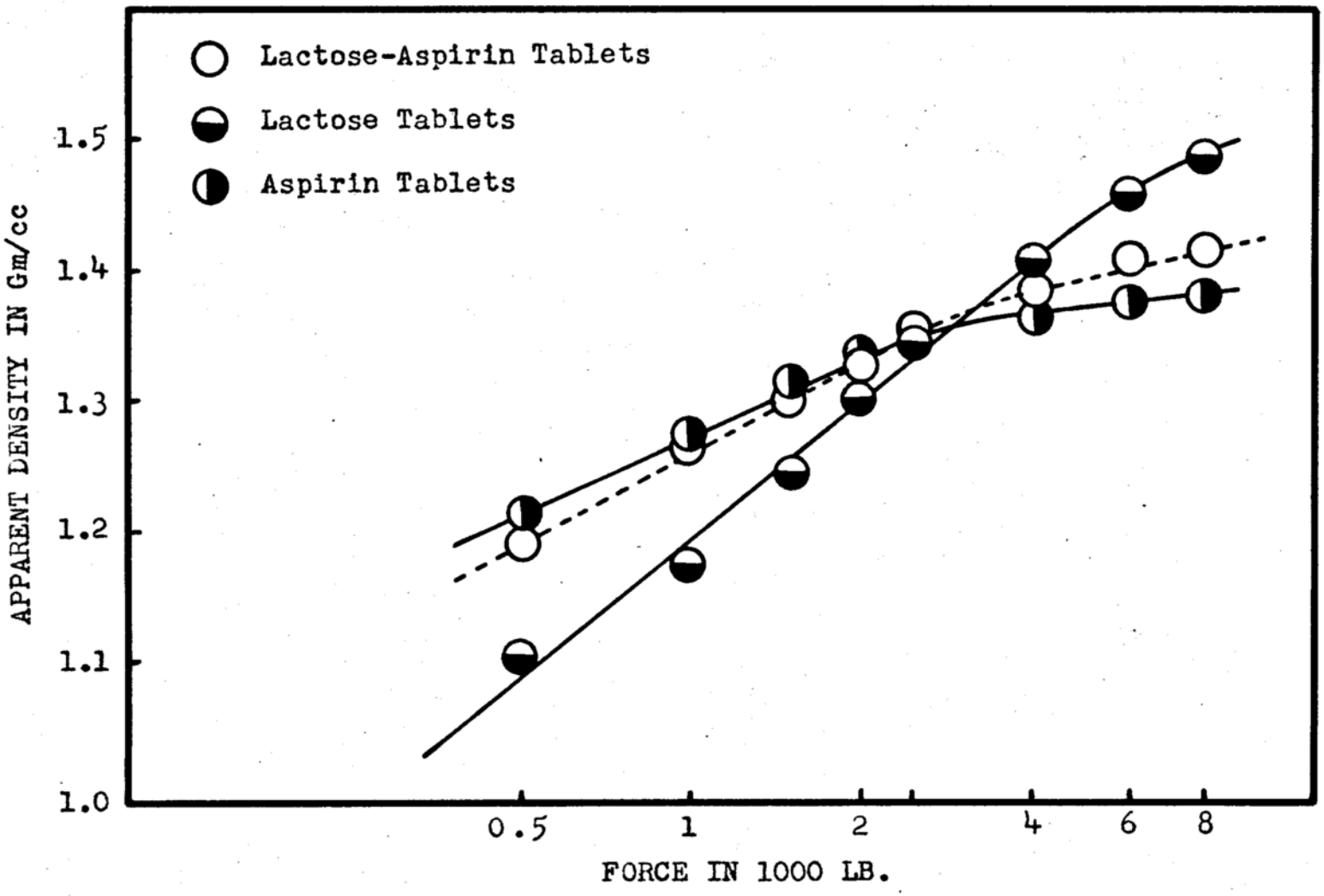


Fig. 2. The effect of Compressional Force on the Apparent Density of various tablets.

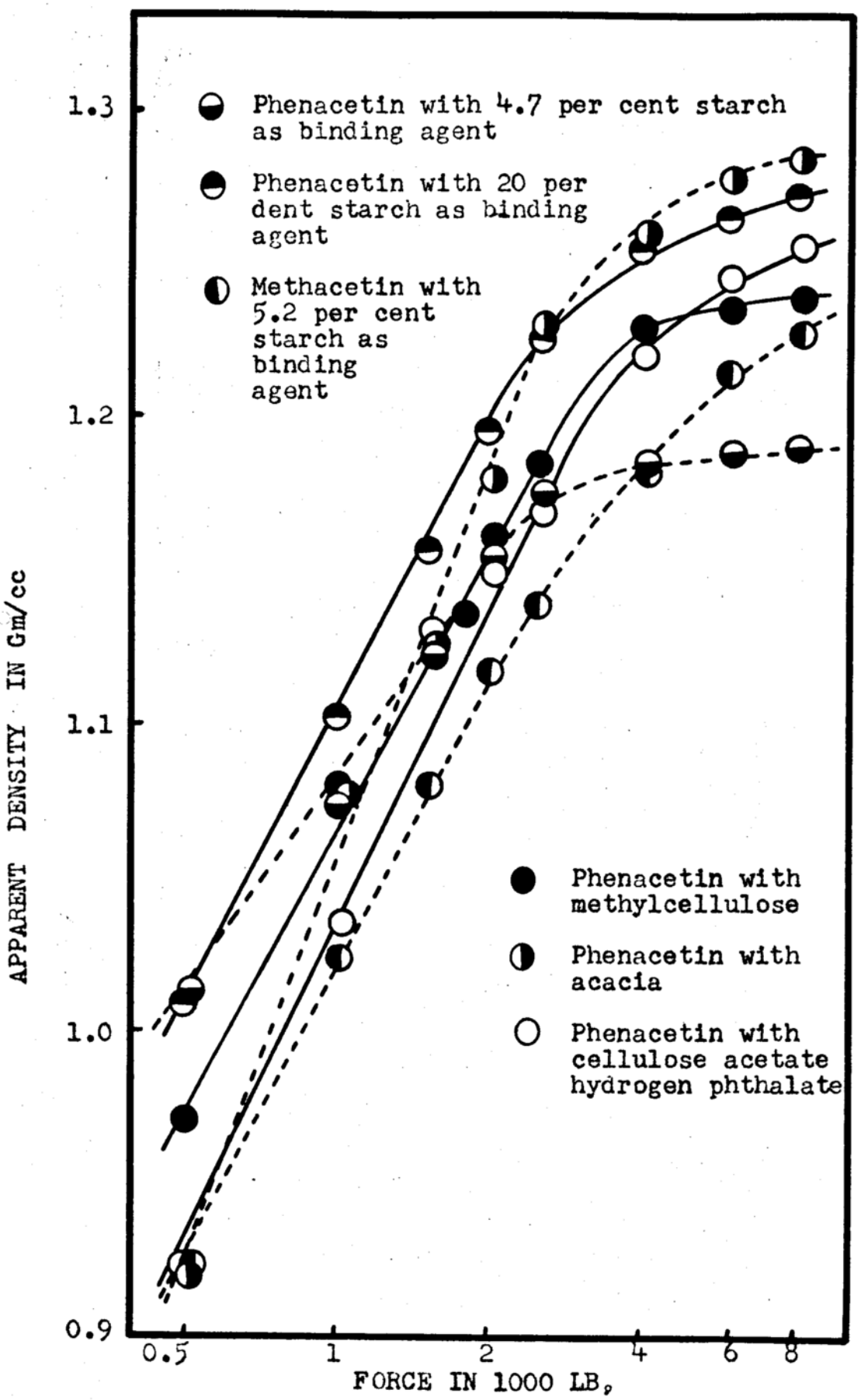


Fig. 3 . The effect of Compressional Force on the Apparent Density of Various Tablets.

2. Hardness vs Apparent Density

Correlation of hardness with the apparent density of tablets results in a direct linear dependency of these two physical properties of the tablets on each other. Such a relationship has also been observed previously in the study of sulfathiazole granulation (1), and is found to be in agreement with the dependency of apparent density on the hardness of compressed metal powders (2).

This relationship is illustrated in Figs. 4-8 for the different formulations studied in the present work.

3. Porosity vs Hardness

Porosity of the tablets is calculated at each compressional force level by utilizing the apparent density of the tablets made at that force and a constant true density of the granulation from which the tablets are made. Because of this, and since the apparent density of the tablets is linearly related to their hardness, it would be expected that such a relationship should also exist between porosity and hardness of the tablets. This was found to be the case earlier in the investigation of sulfathiazole tablets (1) and in the present studies. This type of dependency is illustrated in Figs. 9-12 for all the various formulations in the present work.

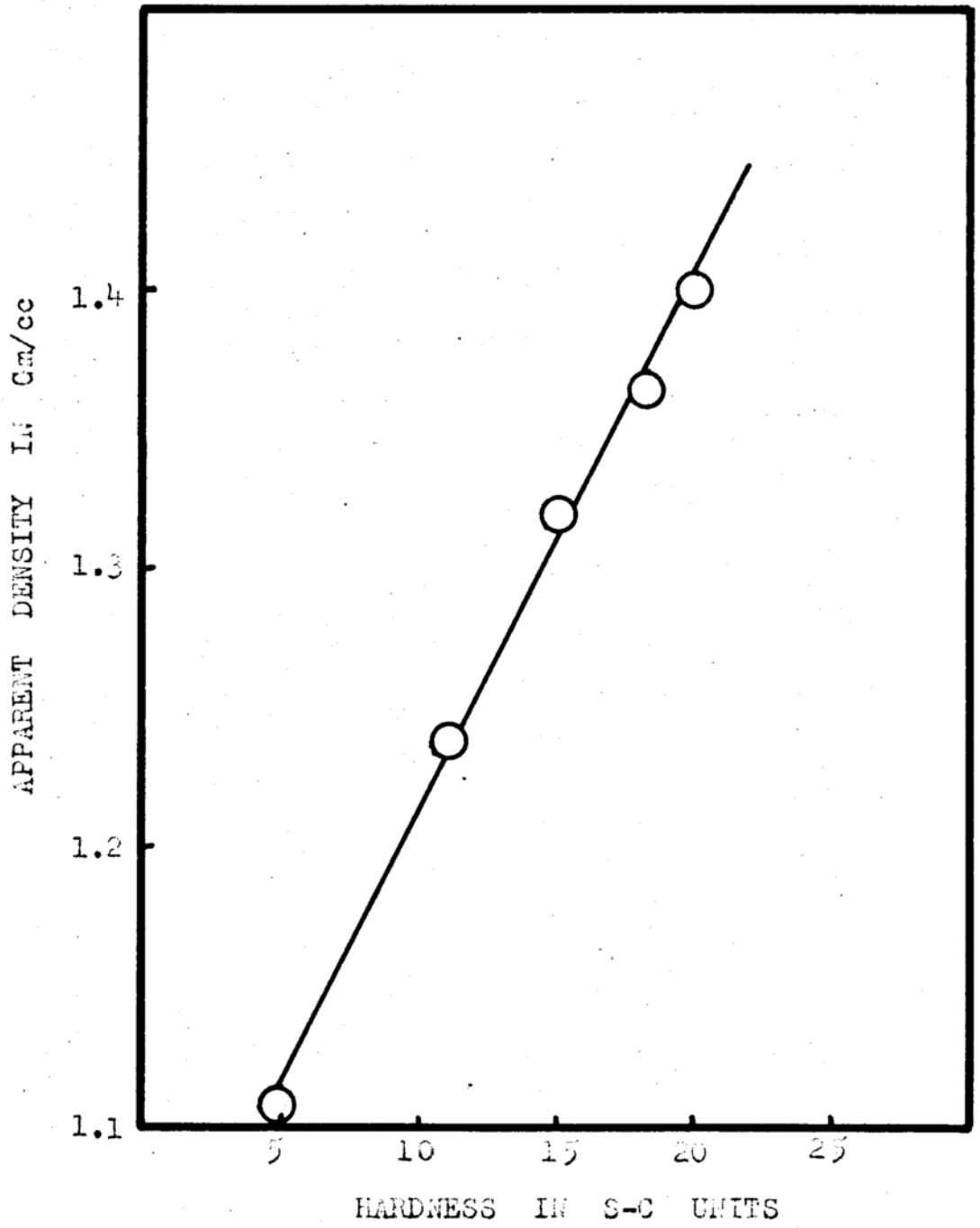


Fig. 4 . Hardness vs Apparent Density of Sulfadiazine Tablets.

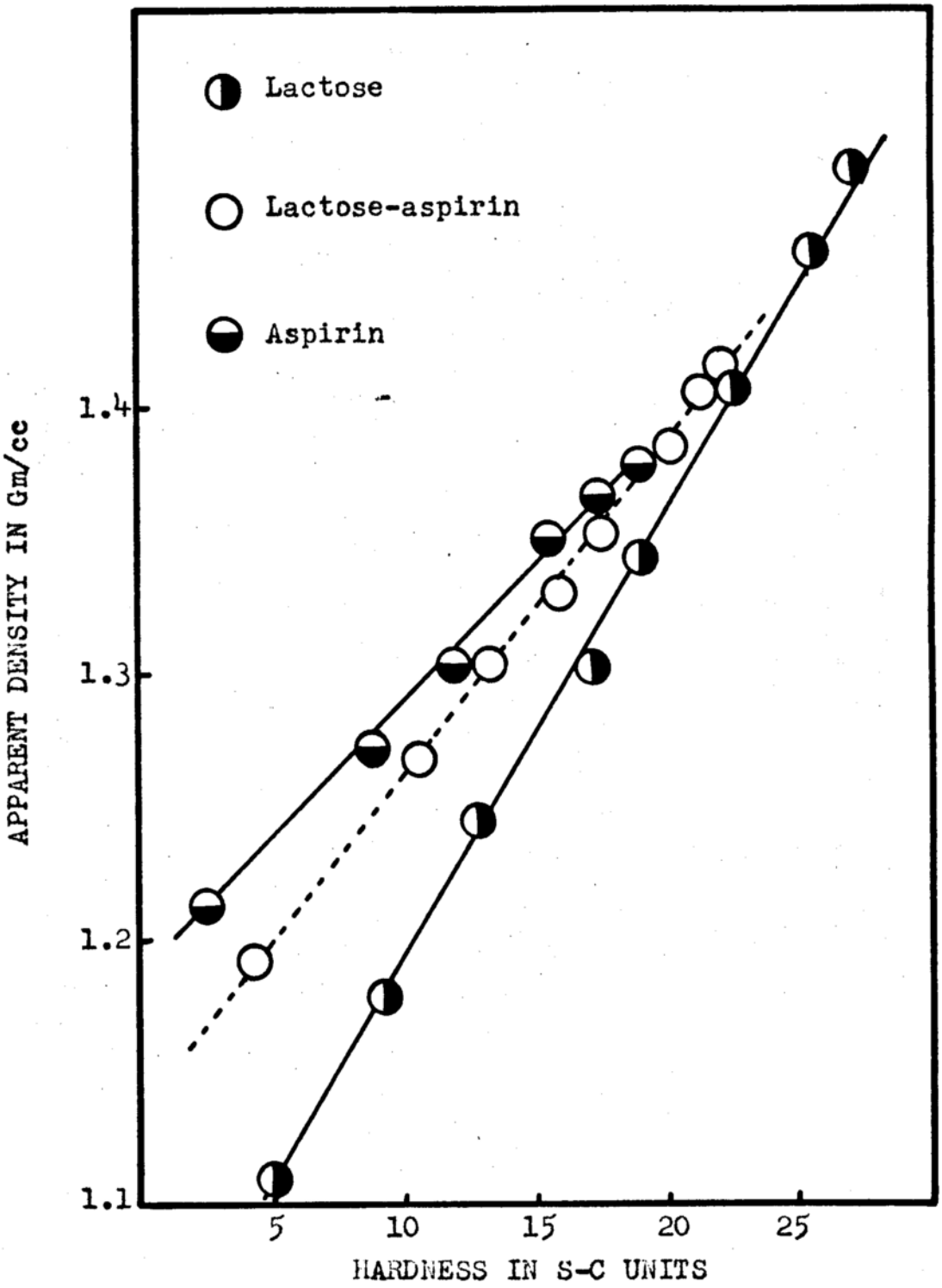


Fig. 5 . Hardness vs Apparent Density of various tablets.

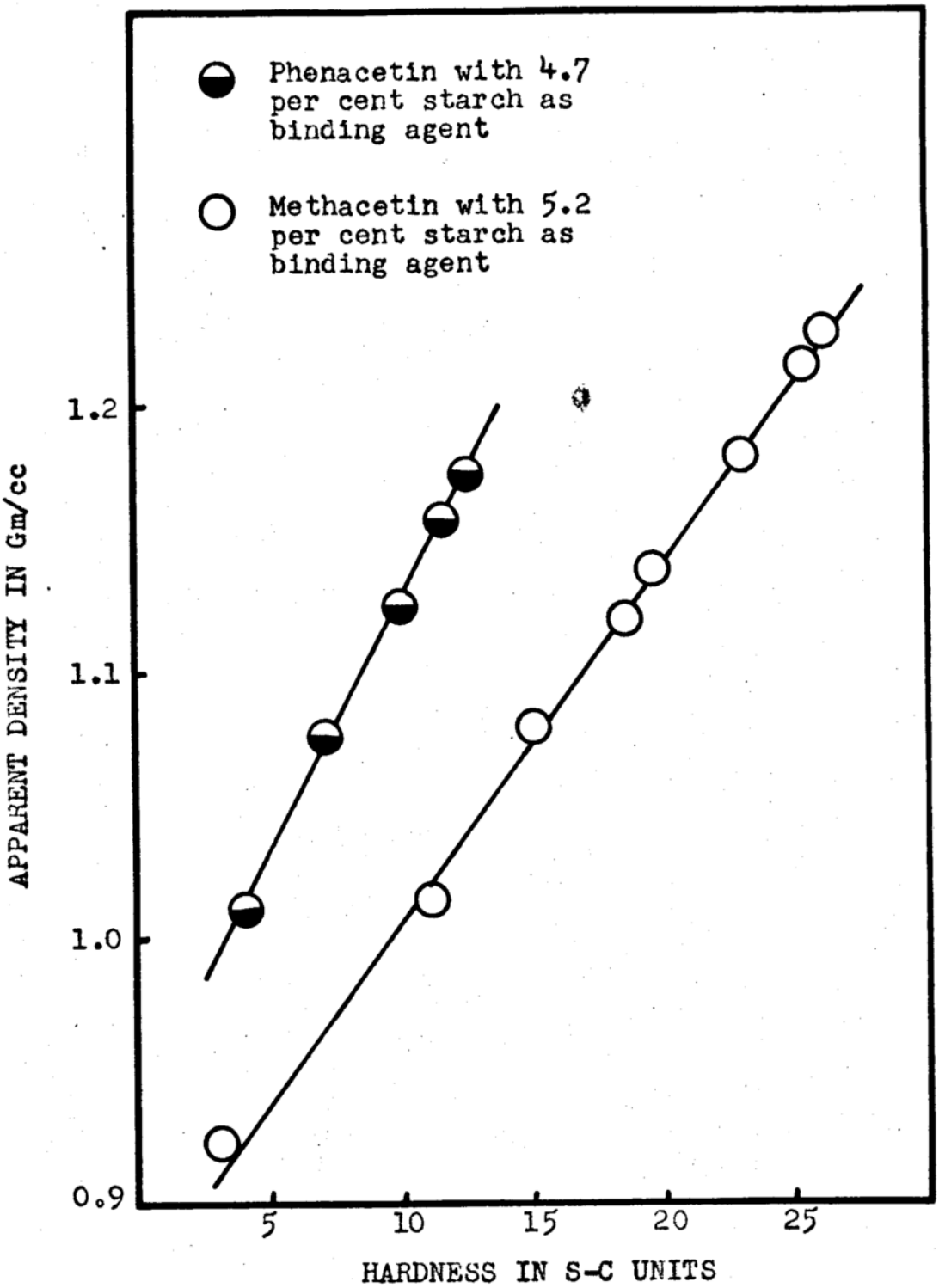


Fig. 6 . Hardness vs Apparent Density of various tablets.

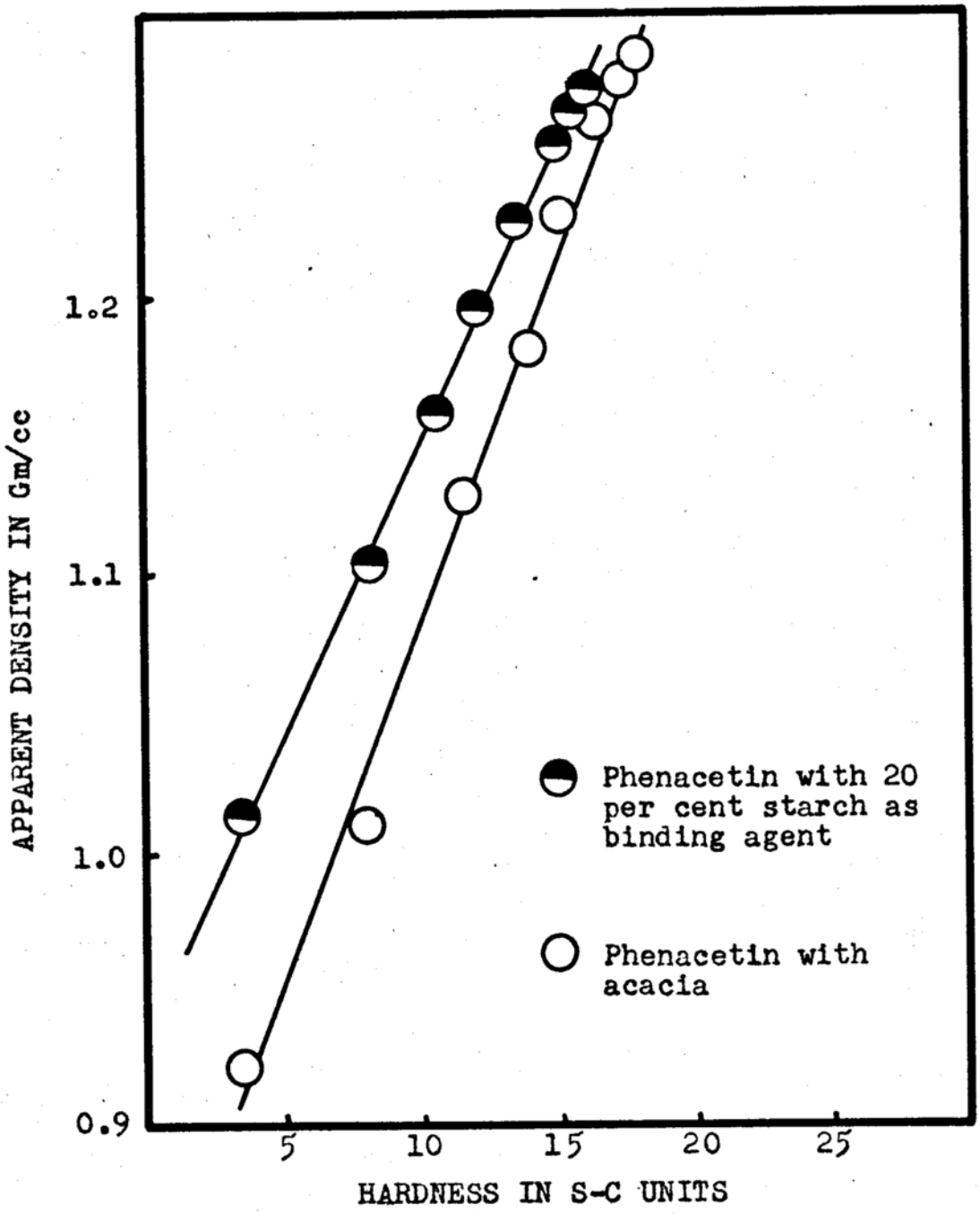


Fig. 7 . Hardness vs Apparent Density of various tablets.

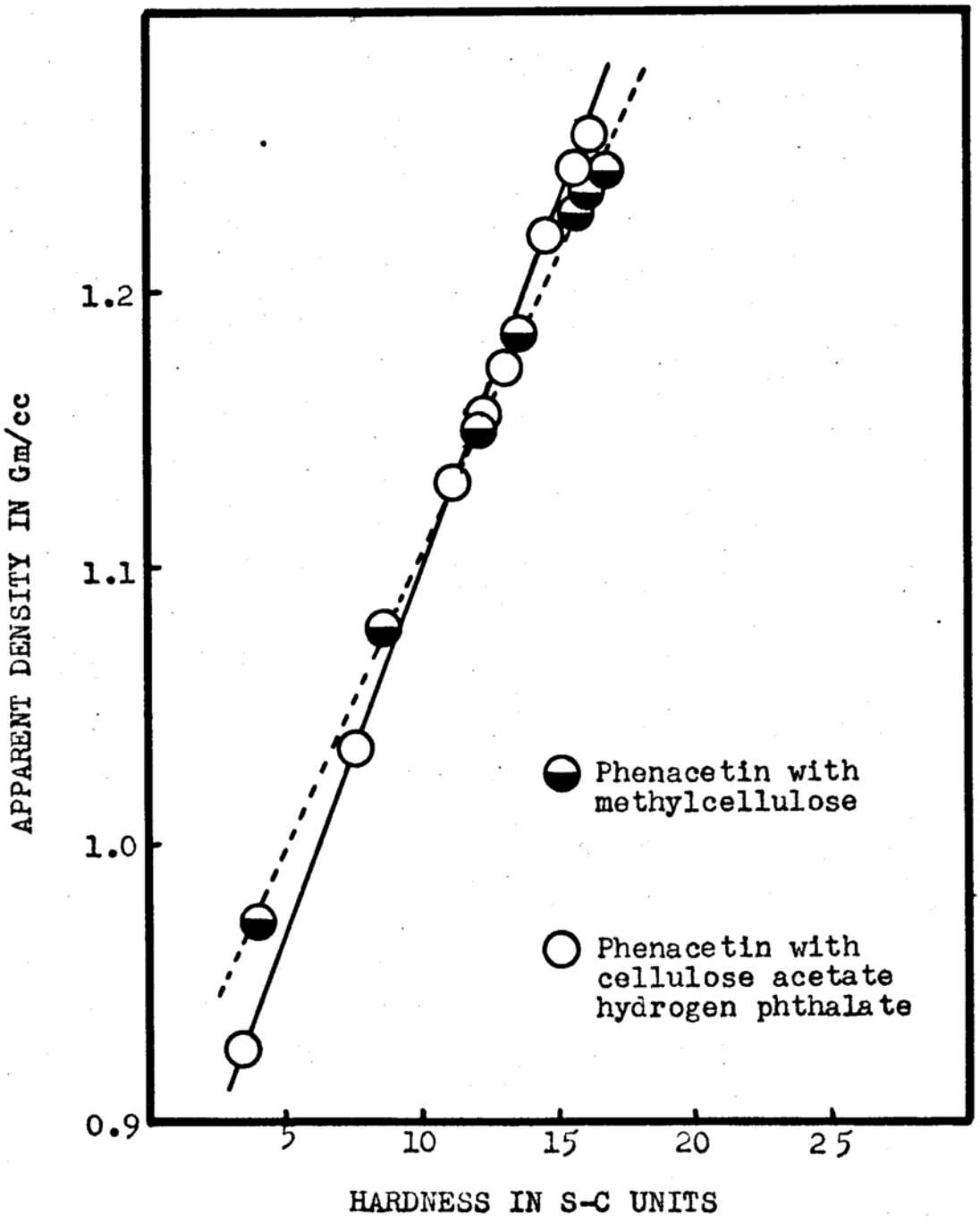


Fig. 8 . Hardness vs Apparent Density of various tablets.

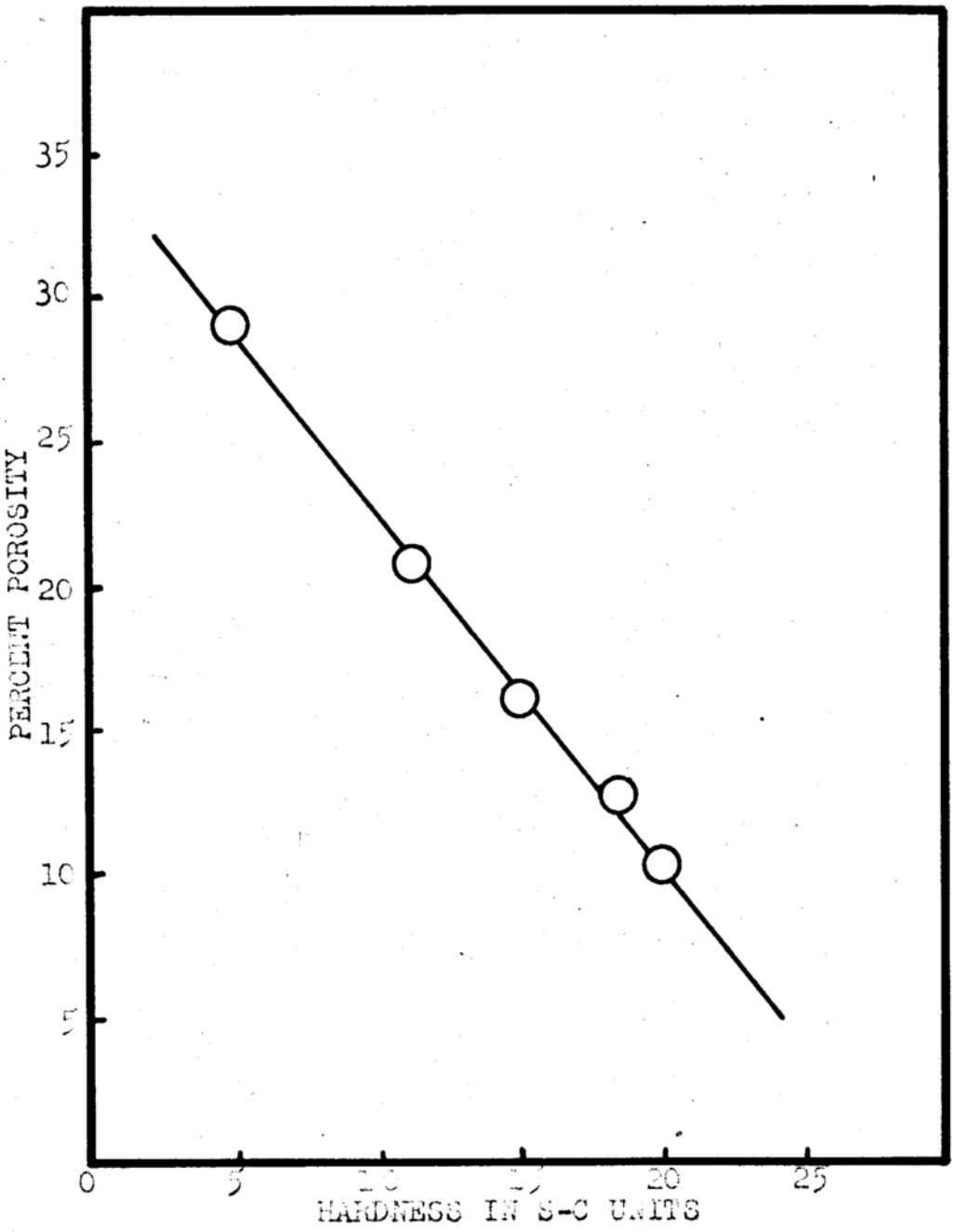


Fig. 9 . Hardness vs Porosity of Sulfadiazine Tablets.

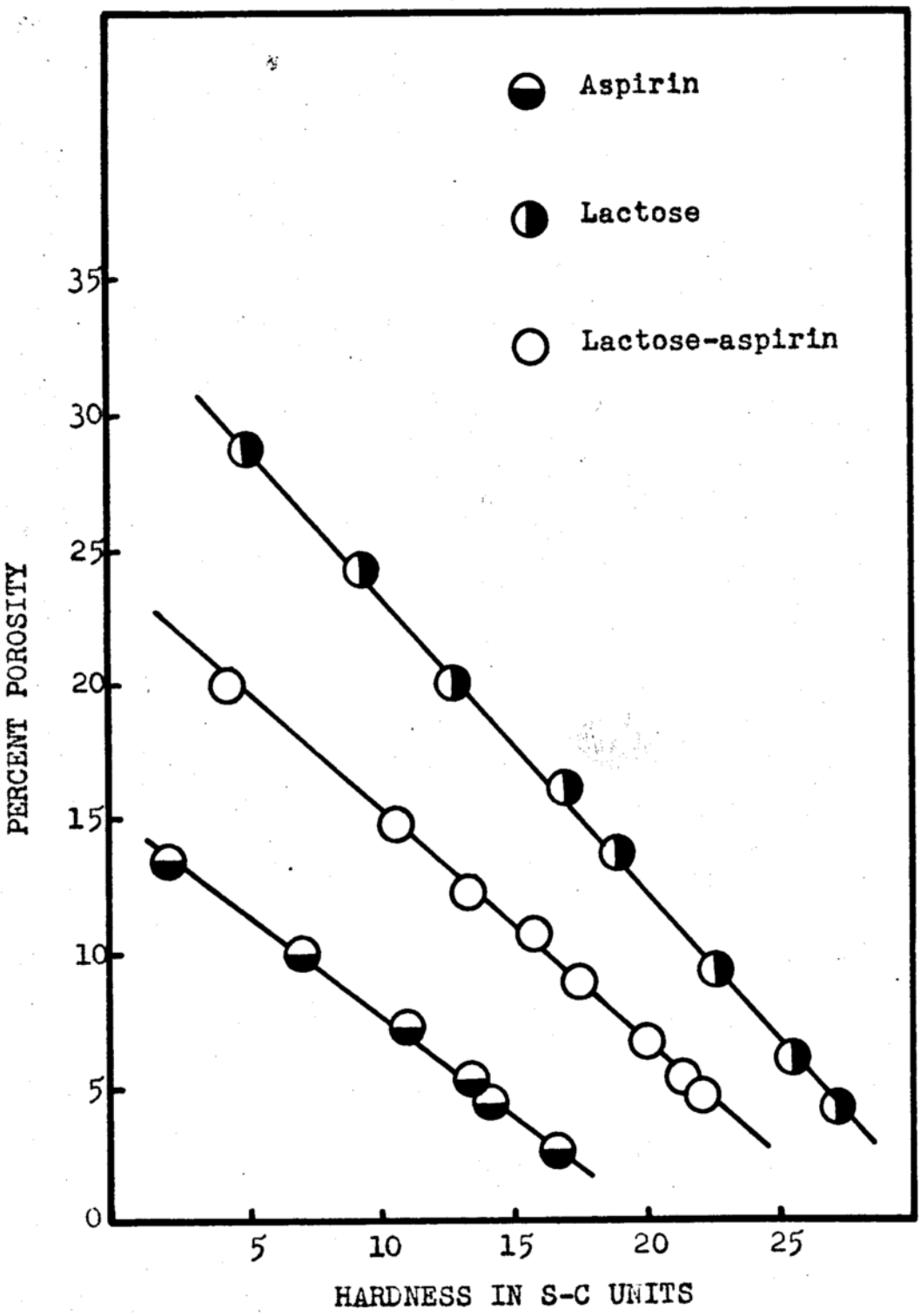


Fig. 10 . Hardness vs Porosity of various tablets.

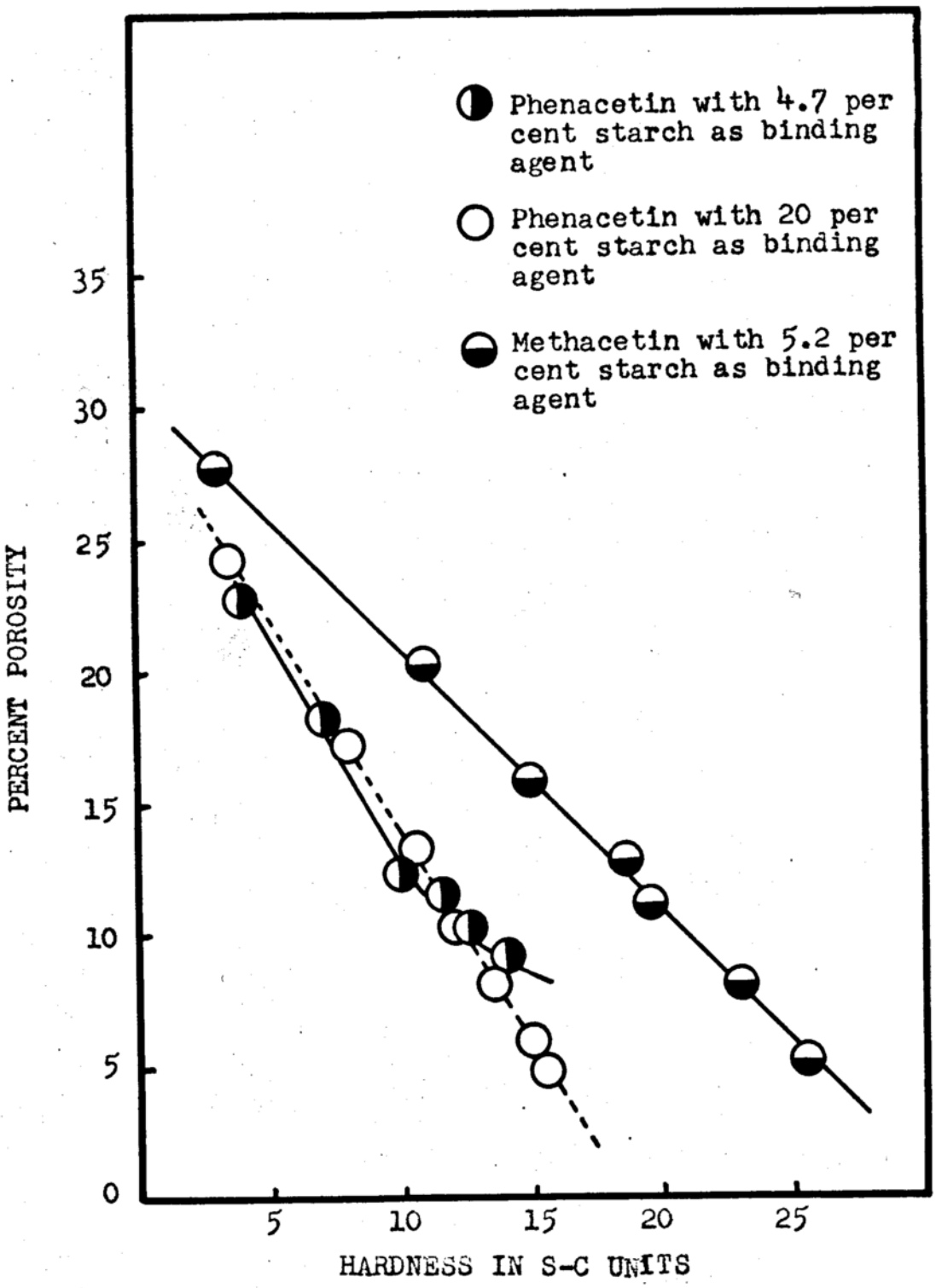


Fig. 11. Hardness vs Porosity of various tablets.

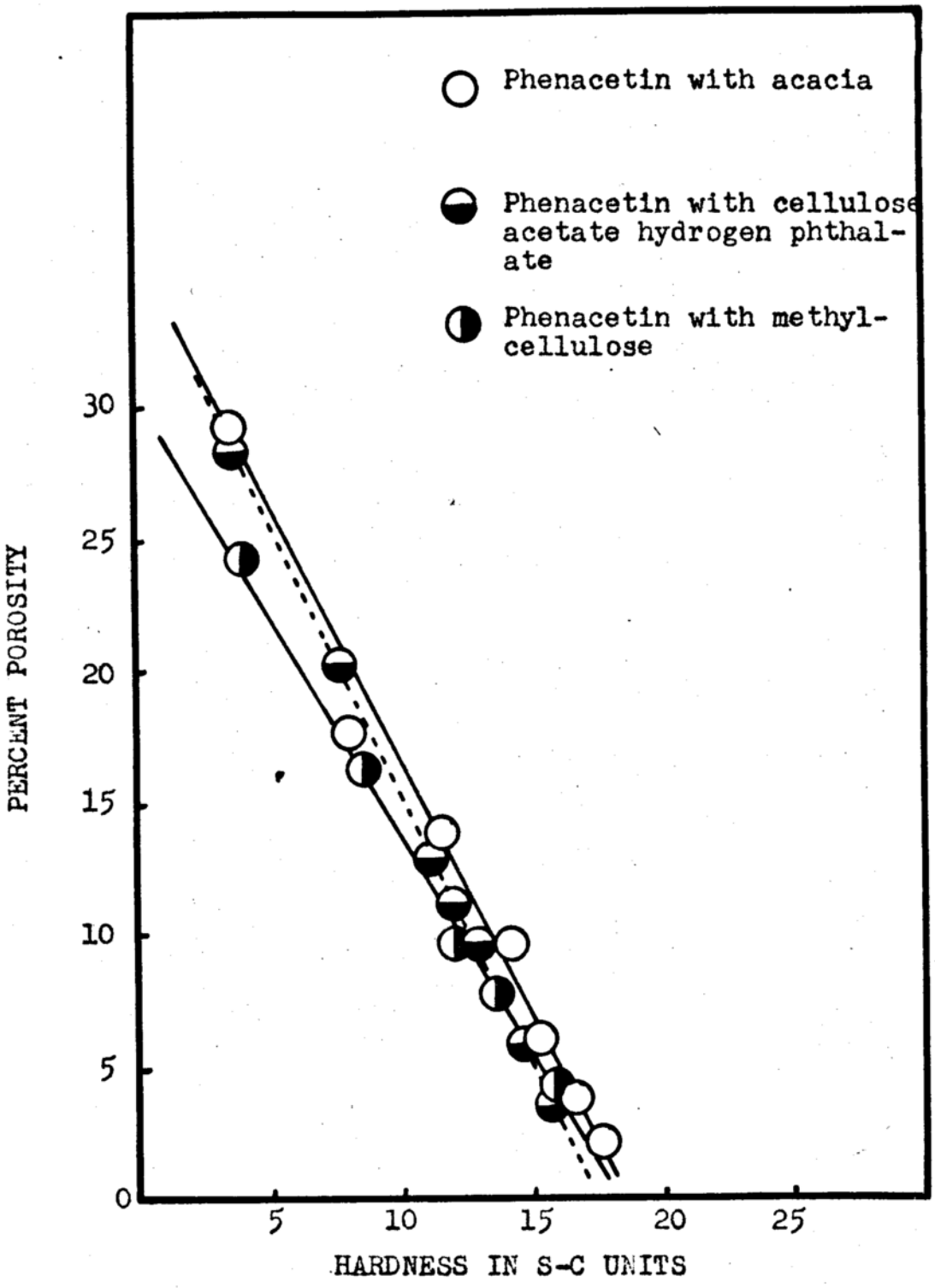


Fig. 12 . Hardness vs Porosity of various tablets.

## DENSITY GRADIENT IN COMPRESSED TABLETS

Higuchi et al (1) compressed different weights of sulfathiazole granulation and found that they obtained the same apparent density for the tablets at fixed maximal compressional forces. To investigate this point further, a more extensive study of this area was undertaken in the present work.

Three different formulations were compressed at eight various force levels using two series of weights for each formulation. It was also found desirable to measure the apparent density of whole tablets and then the apparent density of 'cores' of these tablets. These 'cores' were obtained by slicing layers from all surfaces of the tablet until approximately cubical masses of about 0.15 cm. dimensions were left at the centers. The apparent density of these 'cores' was measured pycnometrically like the whole tablets.

Tables I-III contain data obtained from measurements of the apparent density of different weight tablets made at various maximal compressional forces. The results clearly indicate that the apparent density of the tablets at corresponding force levels is the same irrespective of the weight of the tablets. This is in line with the earlier finding in the case of sulfathiazole tablets (1). Data in Tables IV-V show that 'cores' of the tablets have the same apparent densities as the parent tablets from which they were obtained.

Table I

Apparent Density of Sulfadiazine Tablets of Different Weights made at varying Compressional forces

| Force in lb. | DENSITY IN Gm/cc of TABLETS | |
|---|---|---|
| | 0.2800 Gm. | 0.3950 Gm. |
| 500 | 1.100 | 1.098 |
| 1000 | 1.231 | 1.231 |
| 1500 | 1.305 | 1.303 |
| 2000 | 1.357 | 1.356 |
| 2500 | 1.391 | 1.392 |
| 4000 | 1.428 | 1.426 |
| 6000 | 1.456 | 1.456 |
| 8000 | 1.469 | 1.469 |

Table II

Apparent Density of Aspirin Tablets of Different Weights made at varying Compressional Forces

| Force in lb. | DENSITY of TABLETS in Gm/cc | |
|---|---|---|
| | 0.2800 Gm. | 0.3575 Gm. |
| 500 | 1.213 | 1.212 |
| 1000 | 1.269 | 1.268 |
| 1500 | 1.309 | 1.308 |
| 2000 | 1.333 | 1.327 |
| 2500 | 1.346 | 1.345 |
| 4000 | 1.362 | 1.361 |
| 6000 | 1.373 | 1.372 |
| 8000 | 1.377 | 1.376 |

Table III

Apparent Density of Lactose Tablets of Different Weights made at varying Compressional Forces

| Force in lb. | DENSITY IN Gm/cc of TABLETS | |
|---|---|---|
| | 0.2800 Gm. | 0.3945 Gm. |
| 500 | 1.104 | 1.107 |
| 1000 | 1.175 | 1.176 |
| 1500 | 1.242 | 1.244 |
| 2000 | 1.299 | 1.300 |
| 2500 | 1.340 | 1.342 |
| 4000 | 1.404 | 1.406 |
| 6000 | 1.458 | 1.459 |
| 8000 | 1.486 | 1.487 |

Table IV

Apparent Density of Aspirin Tablets made at varying Compressional Forces

| Force in lb. | D E N S I T Y I N Gm/cc of Whole Tablets | Cores |
|---|---|---|
| 500 | 1.212 | 1.215 |
| 1000 | 1.268 | 1.271 |
| 1500 | 1.308 | 1.309 |
| 2000 | 1.327 | 1.327 |
| 2500 | 1.345 | 1.345 |
| 4000 | 1.361 | 1.359 |
| 6000 | 1.372 | 1.373 |
| 8000 | 1.376 | 1.375 |

Table V

Apparent Density of Phenacetin Tablets made at varying Compressional Forces

| Force in lb. | DENSITY IN Gm/cc of Whole Tablets | Cores |
|---|---|---|
| 500 | 1.003 | 1.007 |
| 1000 | 1.062 | 1.069 |
| 1500 | 1.114 | 1.109 |
| 2000 | 1.148 | 1.148 |
| 2500 | 1.166 | 1.164 |
| 4000 | 1.179 | 1.179 |
| 6000 | 1.184 | 1.185 |
| 8000 | 1.189 | 1.187 |

It would seem from the observed data that density is uniformly distributed throughout the whole volume of the tablets. However, Seeling and Wulff (3) have demonstrated the existence of a stress and a density gradient in compacting metallic powders. A stress gradient has also been showed to exist in compressed tablets in Nelson et al's work (4). In view of these facts, we are led to believe that a density gradient might also exist in compressed tablets. This is in no way in contradiction with our data, because such data can also be interpreted to indicate a density gradient in the tablets.

Since the 'cores' of tablets were selected in our study for apparent density measurements in comparison with the whole tablets, these 'cores' will apparently have an equal average apparent density as the whole tablets themselves, even though a density gradient existed.

In view of the above, our results in this area are not conclusive . They could mean either (a) density is uniformly distributed throughout the volume of the tblet or (b) there exists a density gradient in tablets.

## BIBLIOGRAPHY


1. Higuchi, T., Rao, A.N., Busse, L.W., and Swintosky, J.V., J. Am. Pharm. Assoc., 42, 194 ( 1953)

2. Goetzel, C.G., " Treatise on Powder Metallurgy ", Interscience Publishers, Inc., New York, 1950

3. Seeling, R.P., and Wulff, J., Trans. Am. Inst. Mining Met. Engrs., Metals Division, 166, 492 (1946)

4. Nelson, E., Naqvi, S., Busse, L.W., and Higuchi, T., J. Am. Pharm. Assoc., in press.

## GENERAL CONCLUSIONS

1. It became apparent from the results obtained in the present study and in the earlier investigation of sulfathiazole tablets that certain general qualitative relationships between maximal compressional force and the different physical properties of the tablets exist in all cases studied. While these relationships follow the same qualitative pattern in all instances, they differ quantitatively with the various formulations.
2. In addition to the qualitative similarity between sulfathiazole and sulfadiazine tablets in regard to the effect of maximal compressional force on their physical properties, a good quantitative agreement was also obtained in the values of corresponding properties of the two formulations. No such quantitative agreement was found, however, during the comparative study of phenacetin and methacetin granulations. It is evident, therefore, that, before any conclusions can be drawn regarding correlation of structure and compressional behavior, a more detailed investigation of this area of study has to be carried out.
3. Phenacetin granulation containing 4.7 per cent partially hydrolyzed starch as binding agent gave defective tablets showing splitting and capping at high compressional forces. The incorporation of a higher percentage

of the same binding agent, and other binding agents, in the formulation yielded good tablets upon compression.

4. The similar qualitative relationships observed in all cases can be summarized as follows:

(a) The specific surface area of the tablets increases with increased compressional force to a maximum, and then decreases.

(b) Apparent density and hardness of the tablets vary directly, and porosity inversely, with the logarithm of the maximal compressional force, up to a force level well above that used in ordinary compression of tablets.

(c) Hardness varies directly with the apparent density and inversely with the porosity of tablets.

(d) The logarithm of the disintegration time of tablets varies directly with maximal compressional force. Higher rates of disintegration are produced by increasing the proportions of disintegrating agents.

(e) In some instances, in the presence of high proportions of disintegrating agents, a minimum in the disintegration time of the tablets is observed as the compressional force increases up to an optimum point. After this point has been passed, the ordinary relationship of disintegration time with compressional force is then manifested.

(f) A density gradient has been found to exist throughout the volume of the tablets.

5. Because essentially the same type of relationships has been found to apply in the similar and dissimilar formulations studied, it is reasonable to conclude that the general application of these relationships to all tablet systems has been established.

## GENERAL SUMMARY

### Analysis of the Physical Characteristics of Compressed Tablets

A quantitative study of the compressional behavior and the physical properties of compressed tablets is a rather complicated project in view of the many variables that exist in the different stages of their manufacture. It is not surprising, therefore, to find that, until recently, most of the work done in this field has been in the form of empirical approaches to various isolated aspects of tablet characteristics. As compressed tablets have become one of the most commonly used dosage forms of medication today, the need for standardized methods for their manufacture and control is now generally recognized in pharmaceutical manufacturing circles. Such a standardization can be achieved only through quantitative studies of the physical properties of compressed tablets and their correlation with the different variables encountered during the manufacturing process. Recently, in this direction, some quantitative measurements of the static characteristics of compressed tablets have been made, along with an investigation into their dynamic compressional behavior. The results obtained from these studies, being limited in nature to a single formulation, cannot be of any real practical value

until the same kind of investigation has been extended to other systems to test whether the quantitative relationships observed are of general or limited application.

The present work comprises results obtained from such a horizontal extension of the investigation over several tablet formulations. An attempt is made to analyze, interpret and compare the findings with the purpose of arriving at some general conclusions regarding the compressional behavior of tablets.

In tablet making, one of the easiest variables to alter and control is compressional force; its influence on several physical properties of tablets was studied. The investigation covered true and apparent densities, porosity, hardness, disintegration time and specific surface area of tablets made from aspirin, lactose, lactose-aspirin, sulfadiazine, methacetin and phenacetin granulations.

The specific surface area of tablets was obtained by means of the B.E.T. low temperature nitrogen adsorption apparatus. In all cases, the tablets showed increasing specific surface area with rising force of compression. This increase continued until a certain maximum was reached after which further increases in compressional force resulted in declining specific surface areas. This maximum appeared in all formulations studied; its magnitude and position along the compressional scale, however, seems to be a characteristic of each individual formula.

The true and apparent densities were obtained by means of a helium densitometer and a mercury displacement tablet pycnometer, respectively, while porosity was calculated from their values at corresponding force levels. The apparent density increased, and the porosity decreased, linearly with the logarithm of the compressional force, the true density remaining constant.

Correlation of porosity and specific surface area of the tablets revealed that the maximum in the specific surface area curve occurred generally at that compressional force level where the tablets retained approximately ten per cent porosity.

A Strong-Cobb Tablet Hardness Tester was used to measure the resistance to breaking offered by the different tablets. Here again, hardness increased linearly with the logarithm of compressional force, with a significant leveling off as the relatively high forces of 5000 lb. and over were reached. This effect was also noticed in the case of apparent density, and it can be explained by the fact that the latter approaches the true density of the tablets as a limit at high force levels.

A linear relationship exists between hardness and porosity and, therefore, between hardness and apparent density.

Two separate methods based on the U.S.P. XIV and the B.P. 1932 ( seventh addendum ) were employed for the measure-

ment of disintegration times of the tablets. A linear relationship was obtained between the logarithm of the disintegration time and the compressional force, the rate of disintegration increasing with higher percentage of dried starch.

A possible explanation was sought for the frequent occurrence of splitting and capping in phenacetin tablets during the process of compression. Different binding agents in varying proportions were used in the preparation of phenacetin granulations for the purpose of a comparative study of their compressional behavior. From an analysis of the results obtained, the following explanation can be offered: phenacetin particles are very resistant to crushing as partly evidenced by the comparatively lower increase in the specific surface area of phenacetin tablets over that of the granules. It is believed that phenacetin particles undergo reversible elastic deformation when subjected to high pressures. If the binding agent, in the proportion in which it is present, is sufficient to overcome the tendency of the deformed particles to assume their original shapes as the pressure is released, good tablets will be obtained. On the other hand, an insufficient proportion of the binding agent used will allow the deformed particles to bounce back upon release of the pressure. This could find a relief in capping or splitting of the tablets.

In an attempt to correlate structure and compressional behavior, tablets were prepared from methacetin (p-methoxyacetanilide), a compound closely related in structure to phenacetin which is the p-ethoxyacetanilide. The tablets of methacetin were expected to show similar capping and splitting with low proportions of binding agents, but, unlike phenacetin tablets, they were all well formed with no signs of physical defects. Thus, with these two compounds, no apparent correlation of structure and physical characteristics was obtained. Such a correlation was, however, found in the comparative investigation of sulfathiazole and sulfadiazine tablets. It is evident, therefore, that this area of study must be investigated in detail before any conclusions can be drawn.

From the results of the present study, it is found that, although differing in magnitude, the same qualitative relations between compressional force and the various physical properties of tablets studied have been obtained for all formulations used in this investigation. Because the same relationships were obtained for similar and dissimilar systems, it is reasonable to conclude that these relationships are of general application to all tablet formulations.

APPROVED: Louis W. Busse

Professor of Pharmacy

DATE: May 28, 1954