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STUDIES ON CARBOXYMETHYLCELLULOSE AND STARCH AS TABLET DISINTEGRANTS

by

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ACKNOWLEDGEMENT

The writer wishes to sincerely thank Dr. J.V. Swintosky for initiating and guiding this study. Gratitude is also expressed to Drs. T. Higuchi and L.W. Busse for helpful advice given throughout the investigation's duration.

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INTRODUCTION

As is usual in articles concerning tablet studies, this paper may also begin by pointing out that in the past tableting has been accomplished and improved only through empirical approaches. Just how empirical some of these approaches have been is illustrated by the following statement concerning the degree of compression needed to obtain a good hypodermic tablet (1):

> "The pellets can be easily made by any pharmacist having the necessary pill press, but should not be compressed with too much force (a tap with a light wooden mallet usually suffices), else the solutions will not be rapidly enough obtained."

Hypodermic tablets are no longer called soluble compressed pellets, and neither are such blatantly empirical and unprecise directions found in formulation procedures today. Yet this shows on how very empirical a basis tableting has rested at one time. Improvement in departing from empirical approaches has been slow. Rao (2) points out that, "...very few attempts at the correlation of the basic factors influencing tablets have been undertaken as late as 1950."

Since 1950 the trend has been toward the acquisition of precise quantitative measurements in tablet studies. This paper is a report on part of this broad program of study which is aimed at studying and correlating both the static and the dynamic factors which enter into successful tablet formulation, manufacture, and utilization. Several articles which have clearly defined the problems and offered methods and data toward their solution have appeared recently (3,4,....,16,17).

A study and comparison of the value of potato starch and alginic acid as disintegrating agents in phenacetin, thyroid, digitalis, barbital, and phenobarbital tablets has been previously reported (5). In the present investigation a study of the free acid form of carboxymethylcellulose and of corn starch has been undertaken. Sulfathiazole tablets have been made at various compressional force levels and with various amounts of starch as the disintegrant for some tablets and carboxymethylcellulose as the disintegrating agent for others. The objective was to determine the affects of disintegrant concentration on tablet disintegration time and hardness when the tablets were prepared at different known compressional forces.

The commercially available form of carboxymethylcellulose is the sodium salt and is designated CMC. The material used in this study is the free acid form made by replacing the sodium atoms with hydrogen atoms. This product will be henceforth designated CMCA in this manuscript.

Extensive studies on the toxicity of CMC have been made by Massatsch and Steudel (18), Brown and Houghton (19), Werle (20), Letzig (21), Shelanski and Clark (22), and Rowe, Spencer, Adams, and Irish (23). No toxicity was observed when CMC was given orally as food to various test animals and human beings. The product was not attacked by any of the digestive juices and appeared quantitatively and unchanged in the feces. Hueper (24) has demonstrated toxicity when CMC was injected intravenously.

EXPERIMENTAL

Source of CMCA and Starch

The properties and preparation of CMCA as a water dispersible powder have been previously described (25). The method of preparation used here was modified only in the ion exchange procedure.

The CMC used was that of the Hercules Powder Company, Wilmington, Delaware. It was Premium Low Viscosity-Type 70. A 2% solution was ion exchanged as follows:

Eight 4000 cc. Erlenmeyer flasks formed a series of resin beds. Each flask contained 1 Kg. of the sulfonic acid cation exchange resin, Amberlite IR-120 (26). The resin was charged by adding 300 cc. concentrated hydrochloric acid and 700 cc. distilled water to each flask with periodic shaking over a period of several hours. Then the HCl solution was decanted and a series of washings by decantation followed. Usually at least six such washings were necessary before the decanted water showed no acidity to litmus paper. Then about 3L. of the 2% CMC solution was added to flask #1, shaken periodically for 15-20 minutes, decanted into #2 after the resin settled, where the process was repeated, serially until the material had been transferred through all eight flasks. About 10L. was run through the series before the flasks were recharged and washed.

The CMCA solution obtained was then spray dried by atomizing it into a 230°C. chamber of a Bowen Spray Drier (27). A white powder, very similar to cornstarch in appearance was produced.

The corn starch used in this study was a food grade Argo corn starch.

Preparation of the Granulations

The granulation for the starch formulations was made by adding 30 Gm. of 10% starch paste to each 97 Gm. of sulfathiazole (U.S.P. XIII Powder, Mallinckrodt). The mixed mass was then pushed through a #10 mesh stainless steel wire sieve, and the resulting granules were dried at 45°C. for four hours. The dried granules were then pushed through a #20 mesh sieve and collected on a #60 mesh sieve. The granules used to make tablets were those which passed through the former but which were too large to pass through the latter. These granules, now containing 97% sulfathiazole, constituted the master granulation. Portions of it were used to make seven other granulations simply by mixing with proper amounts of dry starch powder to get granules for compression containing 1%, 2%, 4%, 8%, 15%, 30%, and 60% of dry starch.

The material for compression containing CMCA was made by adding the CMCA to the sulfathiazole powder, mixing, adding starch paste with some additional water, granulating, and drying. Granule size was standardized with #20 and #60 mesh sieves also. The preparation of the six CMCA-sulfathiazole granulations is summarized in Table I.

Table I: Preparation of CMCA-Sulfathiazole Granulations

% CMCA in Granulation	1%	2%	4%	8%	15%	30%
Sulfathiazole, gm.	96	95.1	93.1	89.2	82.4	67.9
10% Starch Paste, gm.	30	29	29	28	26	21
CMCA, gm.	1	2	4	8	15	30
Additional Water, cc.	14	14	23	27	36	60

Table I (cont.)

Drying Time, 45°C., hrs.	2	2	2	2	2	1.5

The granulations containing 15% and 30% CMCA became slightly tan during the drying process. This seemed to have been caused either by an unnecessarily protracted drying time or by a slightly excessive drying temperature. These granulations dried very rapidly.

Compressing the Tablets

Seven sulfathiazole granulations employing dry starch powder as disintegrant and six employing CMCA as the disintegrant were used for compression into tablets. Portions of 0.330 Gm. each were weighed and compressed into tablets one by one using a special 3/8 inch punch and die set and a mechanical lever machine previously described (3). The ten compressional forces used were 500, 1000, 1500, 2000, 2500, 3000, 4000, 5000, 6500, and 8000 pounds per tablet. Each of the thirteen granulations was compressed into tablets at these respective force levels. Twenty tablets from each of the starch-sulfathiazole granulations and twelve tablets from each of the CMCA-sulfathiazole granulations were punched at each force level. The tablets were stored in screw-cap vials with cotton plugs below and above them. The sulfathiazole tablets containing the dry starch were sixty days old when subjected to disintegration and hardness tests; those containing CMCA were two days old when these determinations were made. Half of each separate group of tablets was used for the disintegration time determinations and half for the hardness tests.

Hardness Test

Tablet hardness was determined with a pneumatic tablet hardness tester developed by Strong, Cobb Co., Inc. This tester has been previously mentioned and described (4,28). Its recording scale was calibrated with a compression tank and gauge, and the resulting straight line plot is shown in Figure 45. For each tablet the reading on the recording scale was noted at the breaking point.

Disintegration Time Determinations

The method used for determining the disintegration times of the tablets was essentially that of the U.S.P. XIV (29) with some modifications. The basket rack contained four compartments instead of the six recommended in the U.S.P. A 20L. Pyrex glass crock was used to hold the disintegration fluid (water), and the temperature of the water was maintained at 37°C. by an electrically controlled heater and thermoregulator. The basket rack was attached by a cord to a variable speed motor which raised and lowered the submerged assembly through approximately a 5 cm. range thirty-one times a minute. A tablet was considered disintegrated when all of its fragments passed through the #8 mesh screen floor of its compartment in the basket rack. Disintegration times were recorded in seconds.

DATA

The results of the disintegration time and hardness tests are tabulated in Tables II, III, IV, and V. The median values are the ones shown in these tables. Median values are used because the number of tablets in each group tested was so small that the occasional widely variant value encountered would affect the mean value to an extent not commensurate with its own significance.

Results are also shown graphically in Figures 1-50. The coordinates used were chosen after an inspection of a previously reported investigation (4). The graphs may be divided as follows into groups for purposes of explanation.

1. Figures 1-6: The logarithm of disintegration time vs. the compressional force at each percentage of starch used as disintegrant.

2. Figures 7-12: The logarithm of disintegration time vs. the compressional force at each percentage of CMCA used as disintegrant.

3. Figures 13-22: The logarithm of disintegration time vs. the logarithm of the percentage of starch used as disintegrant at each force level used.

4. Figures 23-32: The logarithm of disintegration time vs. the logarithm of the percentage of CMCA used as disintegrant at each force level used.

5. Figures 33-38: The hardness vs. the logarithm of the compressional force at each percentage of starch used as disintegrant.

6. Figures 39-44: The hardness vs. the logarithm of the

compressional force at each percentage of CMCA used as disintegrant.

7. Figure 45: Strong, Cobb hardness tester readings vs. compressed air gauge readings.

8. Figure 46: A plot of disintegration time vs. compressional force for 4% CMCA tablets.

9. Figures 47-50: Summary graphs combining where possible Figures 1-44 in appropriate groups.

Graphs of Figures 1-44 are plotted logarithmically with smooth curves or straight lines because the maxmin exemplified in Figure 46 are not completely significant statistically because of probable errors:

The probable error of the mean in a series of n measures $a_1, a_2, a_3, \ldots a_n$, where m is the mean is given by the expression (30):

$$E = \frac{0.6745}{\sqrt{n(n-1)}} \sqrt{(m-a_1)^2 + (m-a_2)^2 + \ldots + (m-a_n)^2}$$

The following approximate equation is a convenient form for computation:

$$E = 0.8453 \frac{\Sigma d}{n\sqrt{n-1}}$$

, where Σd represents the arithmetrical sum of the deviations.

The probable errors figured for this data on the basis of mean values (not tabulated) had values between 2-15%. Since median values were used for the tables and graphs, the errors should be less than the calculated errors because widely divergent results are eliminated by using median values. Hence the maxmin (as in Figure 46) essentially lose their significance.

The tables and graphs follow.

Compressional Force	% Dry Starch In Tab					
	1	2	4	8	15	30
500	78	40	33	20	16	10
1000	215	104	56	32	18	13
1500	424	196	131	45	22	12
2000	899	343	153	49	19	12
2500	1406	575	143	45	22	11
3000	3197	965	116	35	18	12
4000	4615	1128	309	40	22	13
5000	3850	944	170	41	18	14
6500	5986	525	107	24	14	14
8000	10304	1037	95	19	15	14

Table II. Disintegration times (median values) in seconds are shown at various compressional forces with varied concentrations of starch in tablets.

Compressional Force	% CMC Ac. In Tab					
	1	2	4	8	15	30
500	96	52	48	36	31	12
1000	463	111	69	42	34	15
1500	712	162	72	41	35	15
2000	1020	358	138	42	47	17
2500	1192	461	155	55	45	20
3000	1586	365	119	44	49	23
4000	2151	650	195	62	83	28
5000	5660	449	95	81	79	31
6500	2100	422	80	81	88	32
8000	14000	244	81	84	98	34

Table III. Disintegration times (median values) in seconds are shown at various compressional forces with varied concentrations of CMCA in tablets.

Compressional Force	% Dry Starch In Tab					
	1	2	4	8	15	30
500	3.0	2.4	2.2	2.0	1.5	0
1000	6.3	6.2	5.4	4.5	3.8	0.6
1500	10.9	9.9	10.2	10.3	6.0	1.2
2000	13.1	13.5	11.4	11.9	9.2	2.9
2500	15.5	15.9	14.0	15.0	10.5	4.3
3000	18.2	13.4	15.7	17.5	13.6	5.0
4000	15.7	18.1	16.8	20.8	17.2	7.2
5000	17.4	20.7	19.3	22.4	16.5	7.9
6500	17.2	21.7	23.5	22.9	19.3	8.1
8000	17.3	22.7	20.5	23.1	24.0	7.8

Table IV. Hardness in Strong-Cobb units (median values) are shown at various compressional forces with varied concentrations of starch in tablets.

Compressional Force	% CMC Ac. In Tab 1	2	4	8	15	30
500	3.9	3.0	3.8	2.6	2.3	2.2
1000	8.0	8.0	8.0	6.4	6.2	5.4
1500	8.7	11.9	12.9	9.3	10.4	8.0
2000	14.2	15.5	14.3	13.9	15.4	12.0
2500	16.1	17.1	14.6	17.3	18.8	11.8
3000	21.8	22.2	22.6	16.8	19.6	17.0
4000	21.0	21.5	16.0	22.5	27.5	18.8
5000	19.3	26.1	18.7	24.7	26.3	21.0
6500	22.3	27.1	23.4	23.0	26.0	20.4
8000	21.4	>30	26.0	22.6	30.0	23.9

Table V. Hardness in Strong-Cobb units (median values) are shown at various compressional forces with varied concentrations of CMCA in tablets.

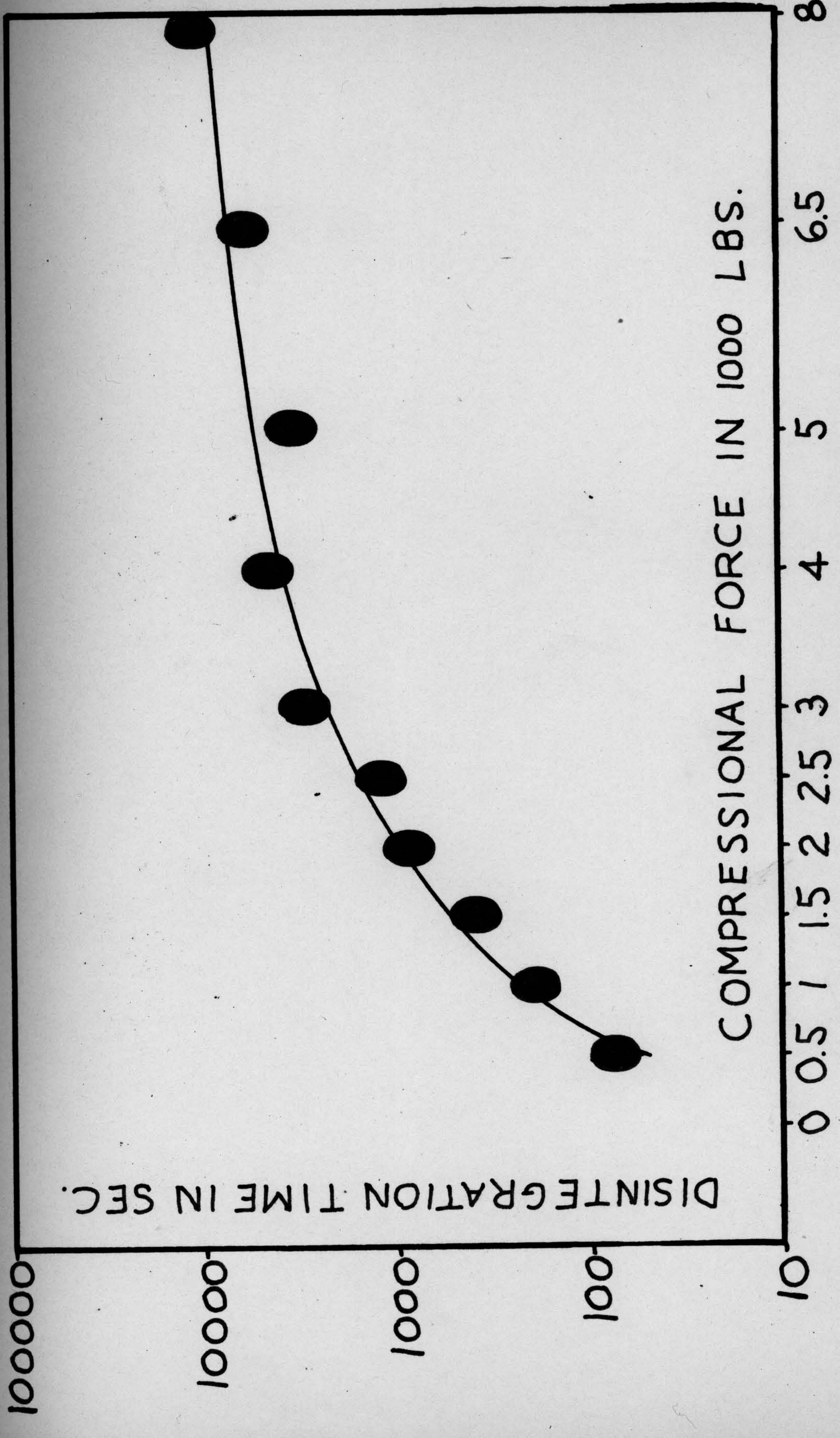


FIG. 1 STARCH 1%

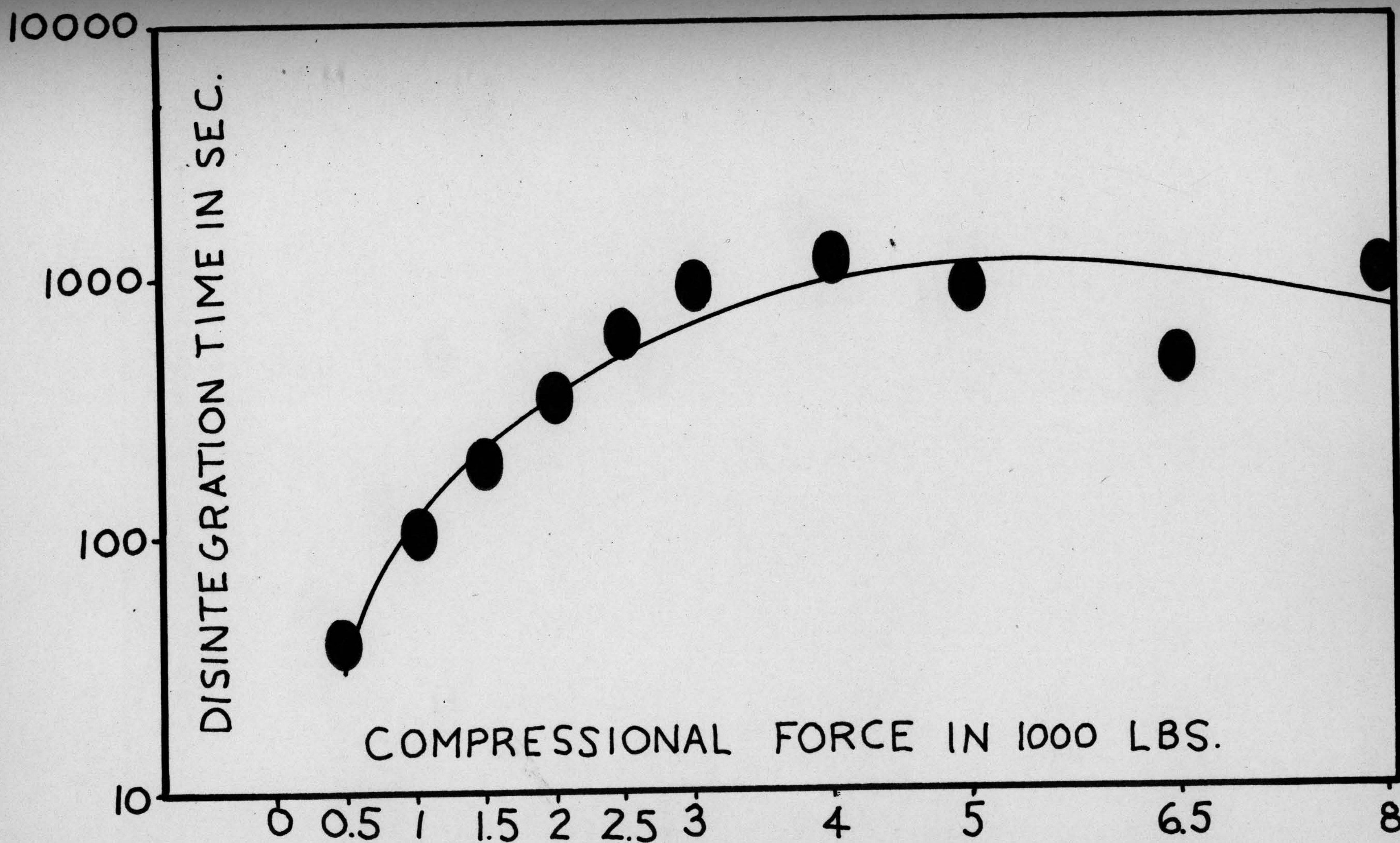


FIG. 2 STARCH 2 %

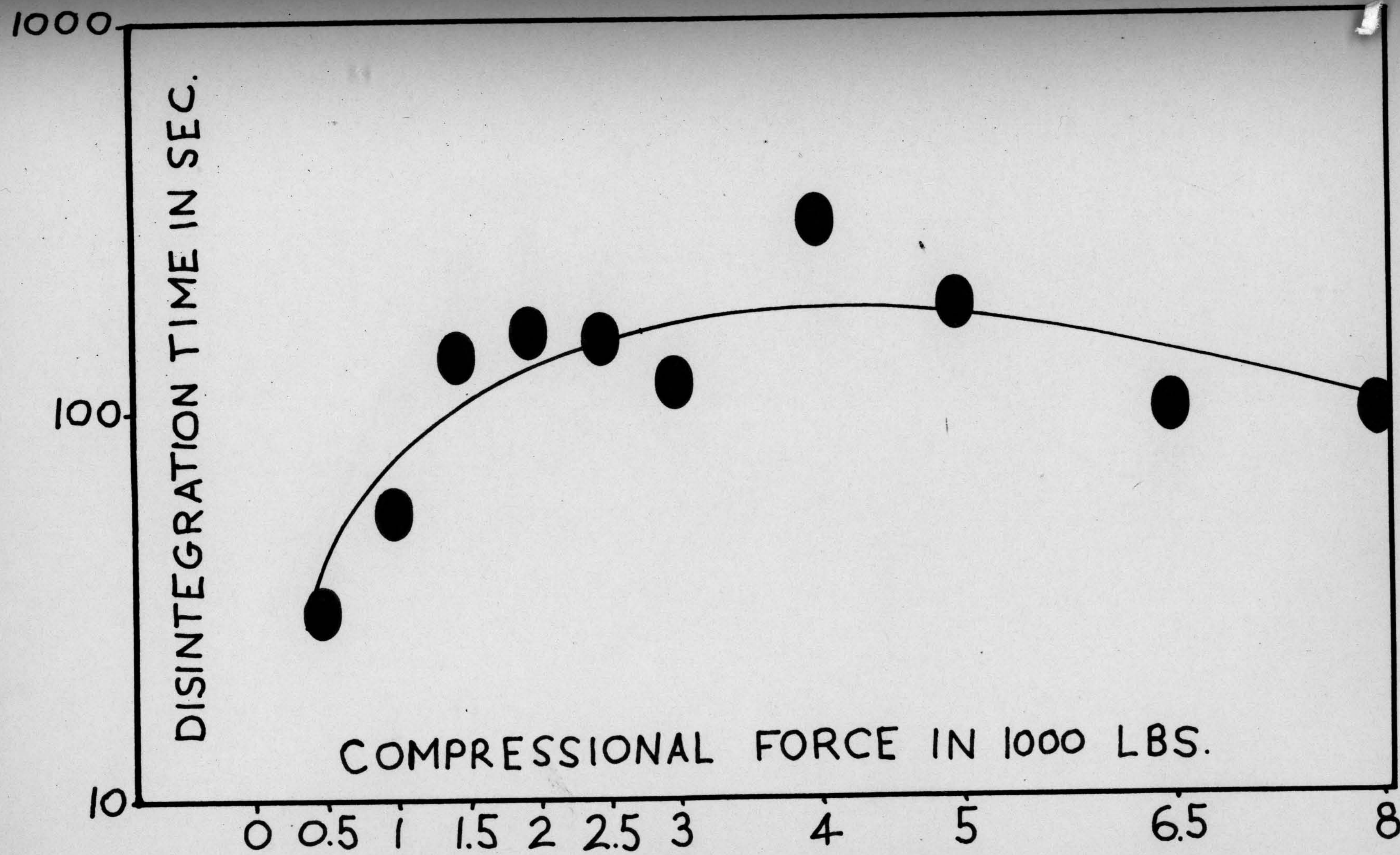


FIG. 3 STARCH 4 %

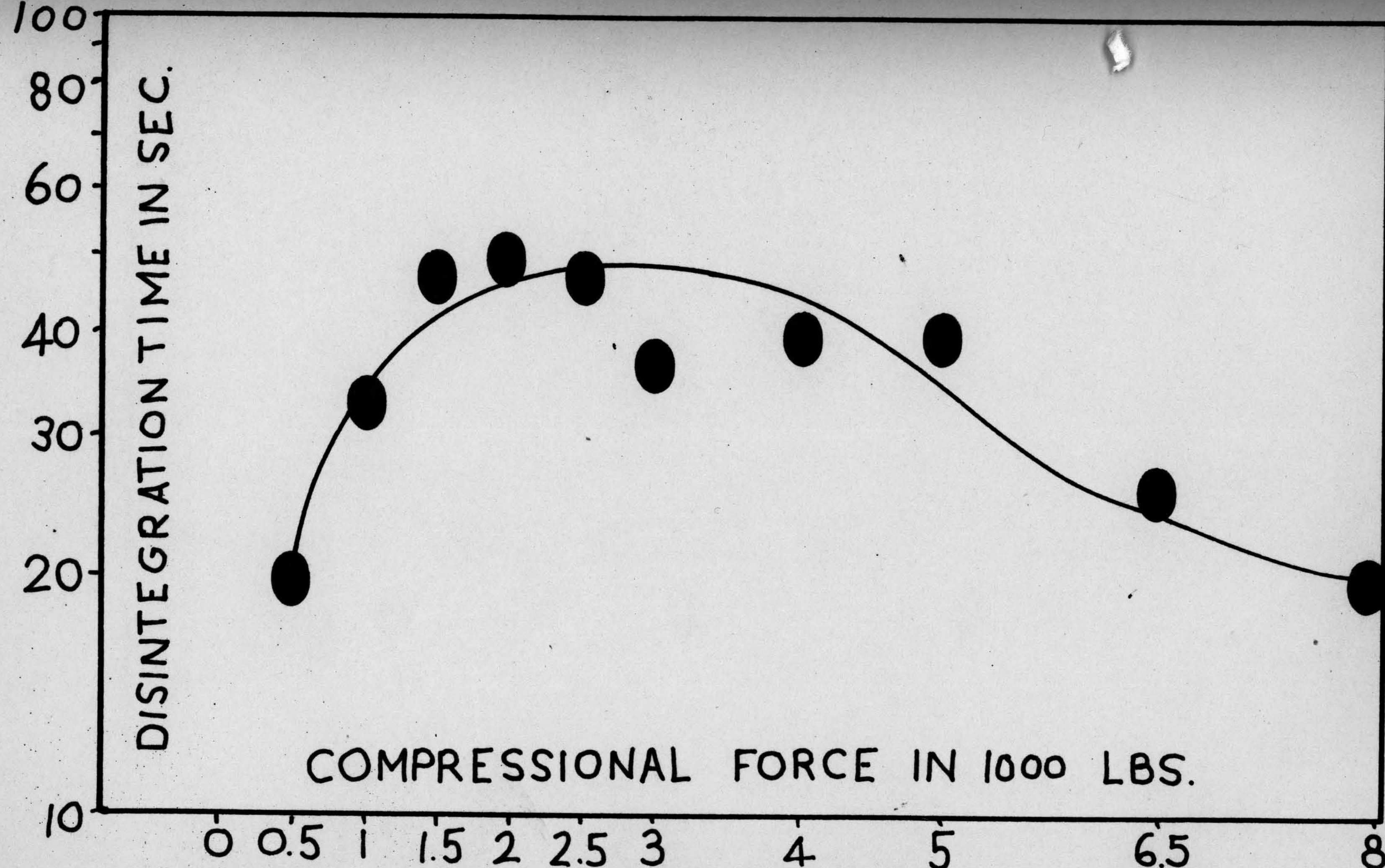


FIG. 4 STARCH 8%

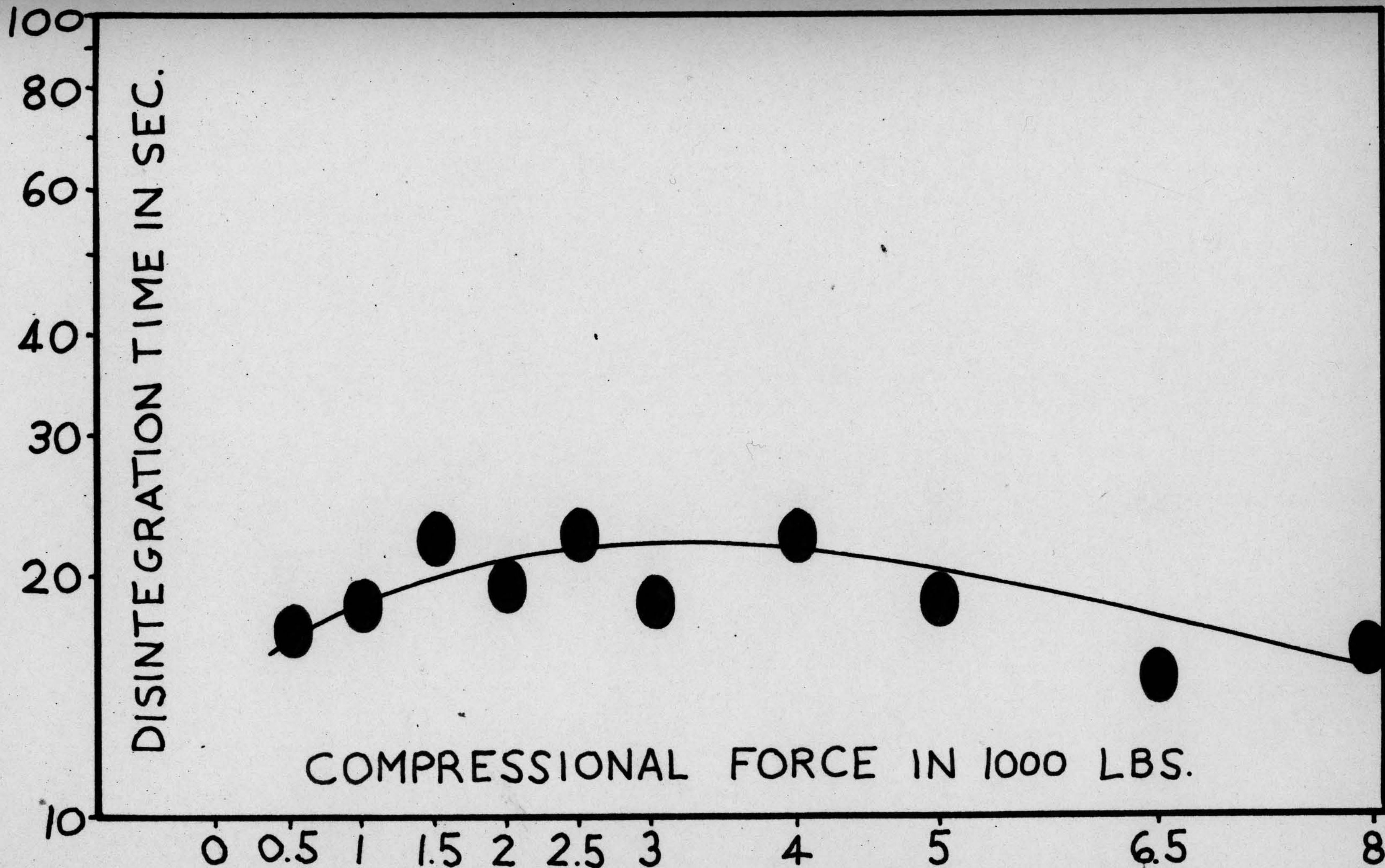


FIG. 5 STARCH 15 %

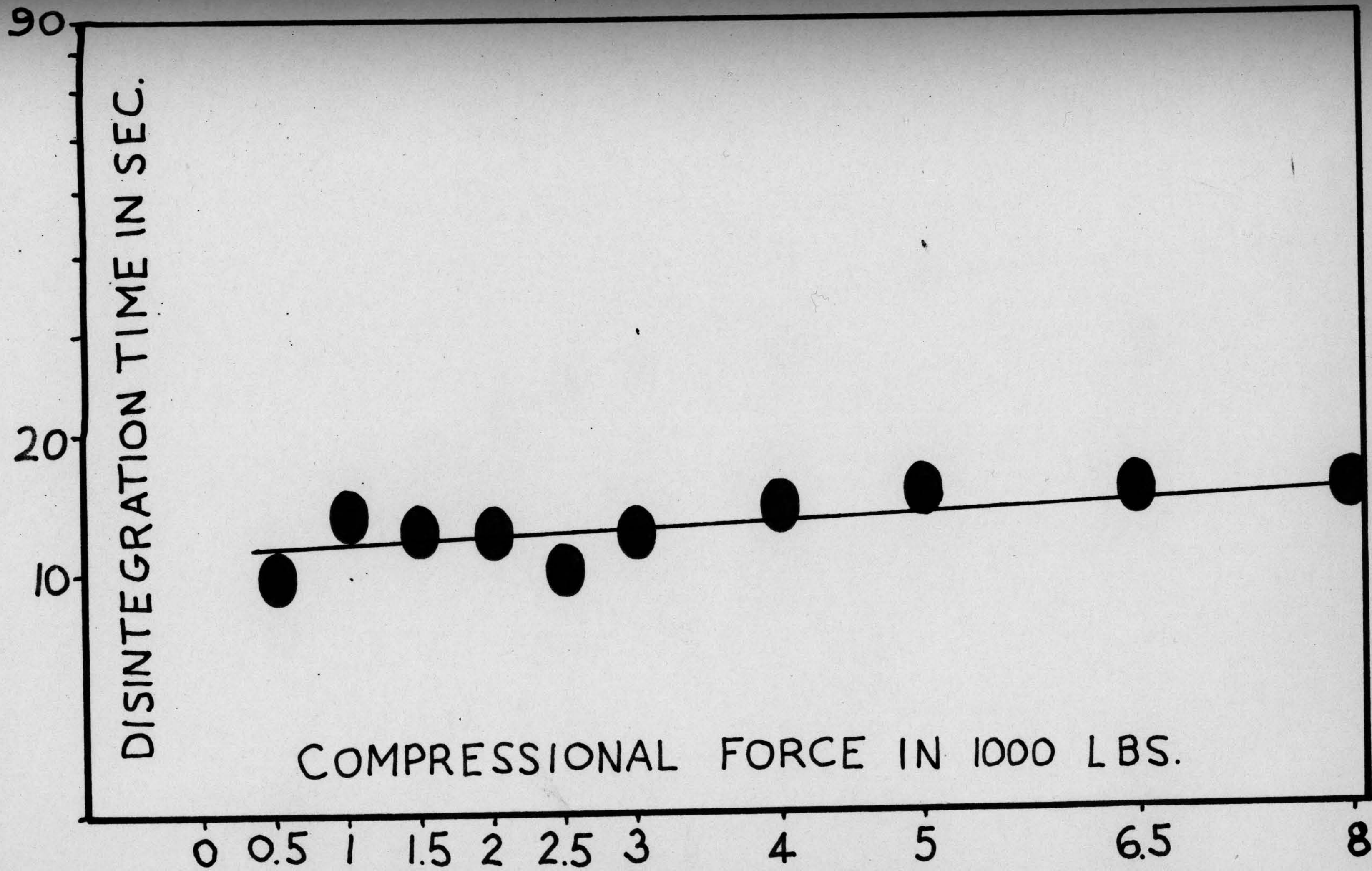
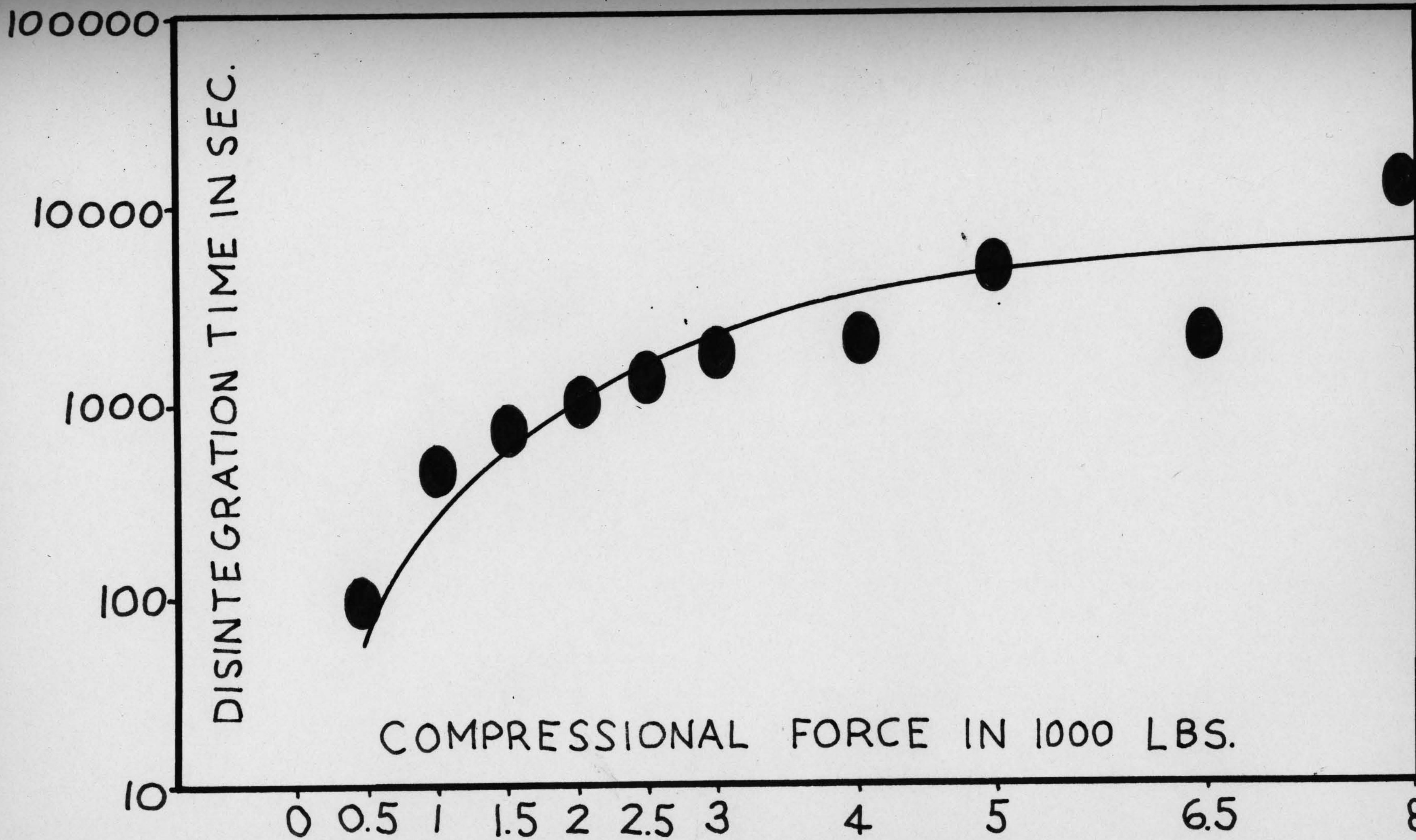


FIG. 6 STARCH 30%



100000
10000
1000
100
10
DISINTEGRATION TIME IN SEC.
COMPRESSIONAL FORCE IN 1000 LBS.
0
0.5
1
1.5
2
2.5
3
4
5
6.5
8

FIG. 7 CMCA 1%

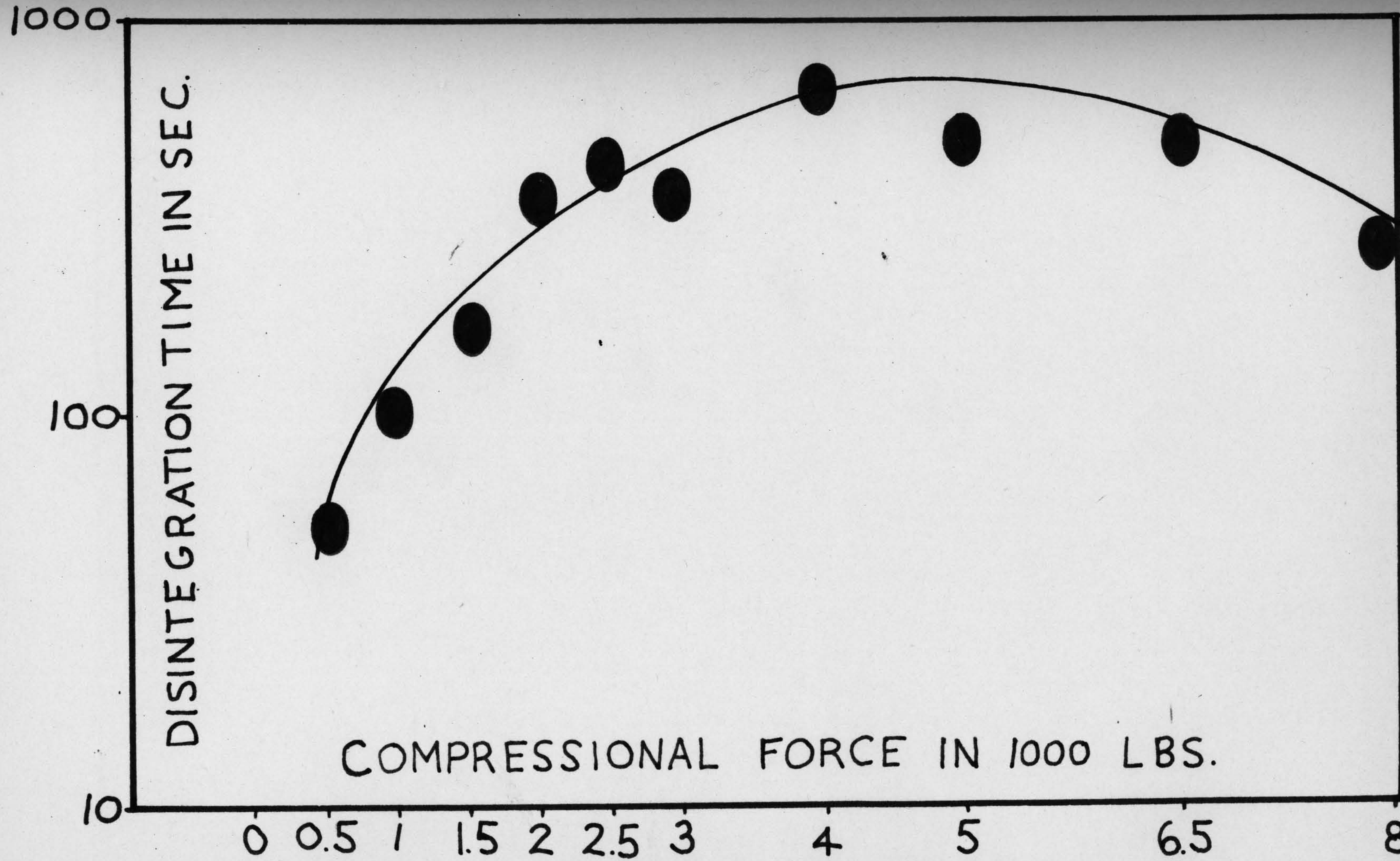

1000
100
10
DISINTEGRATION TIME IN SEC.
COMPRESSIONAL FORCE IN 1000 LBS.
0 0.5 1 1.5 2 2.5 3 4 5 6.5 8

FIG. 8 CMCA 2%

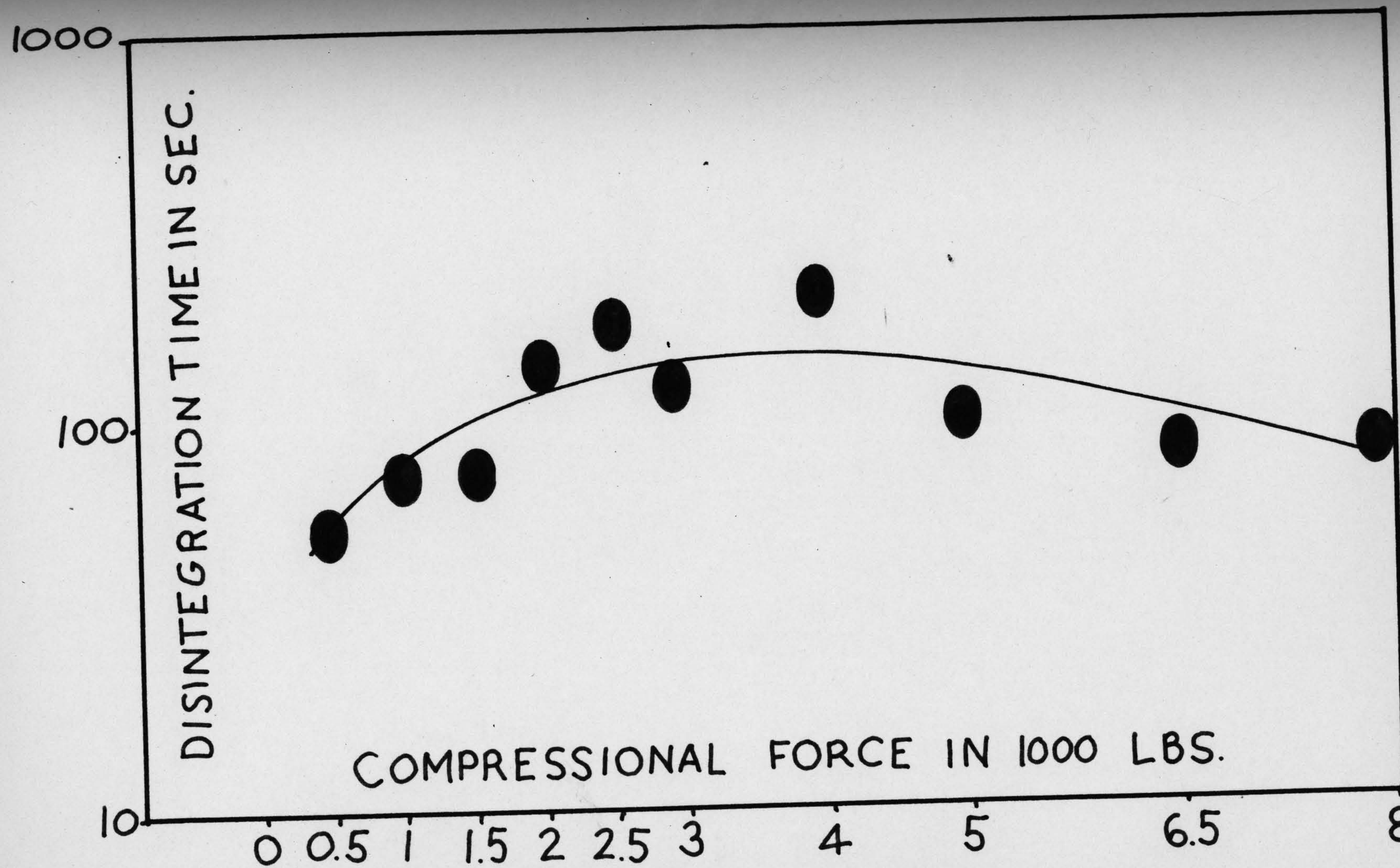
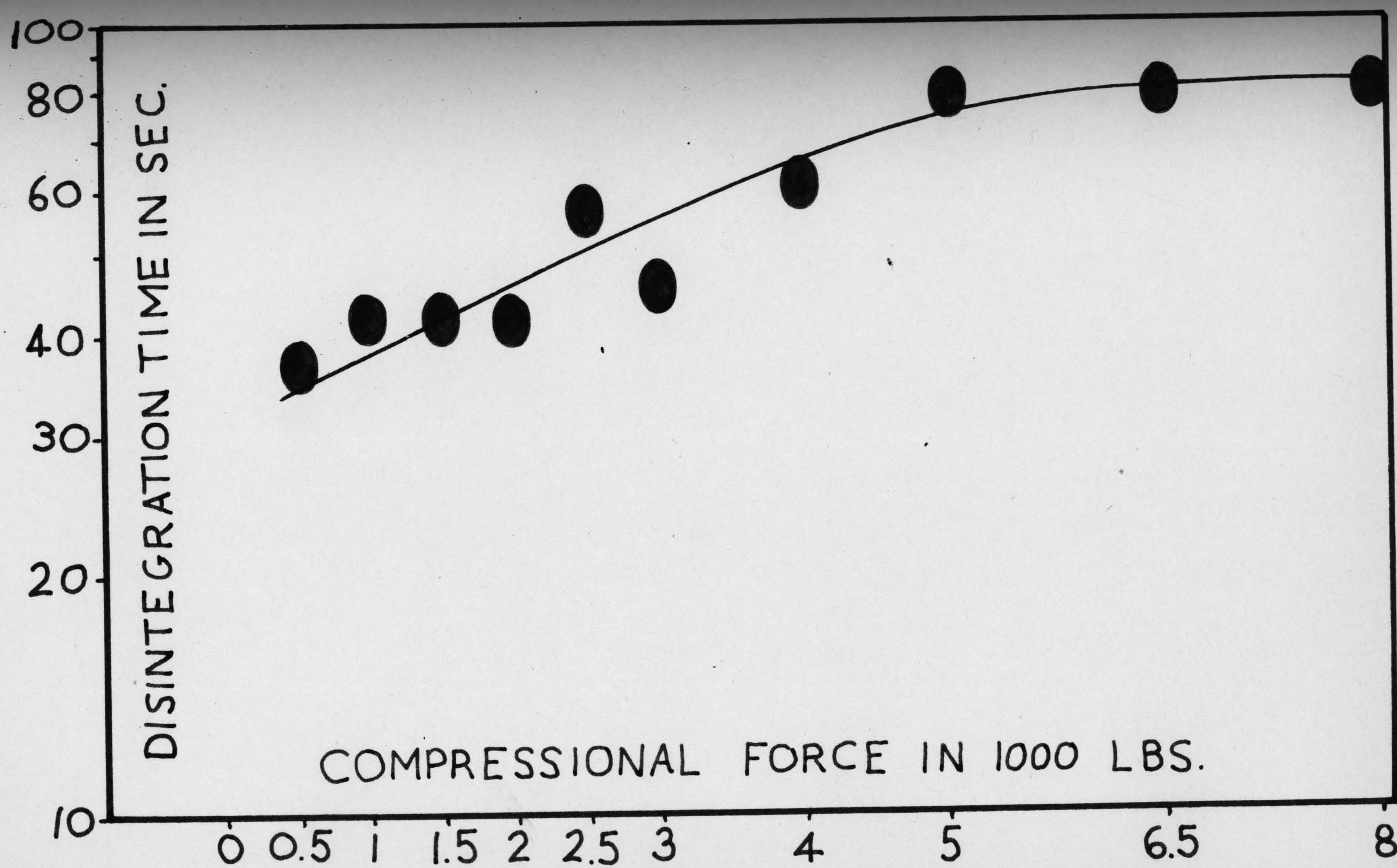

1000
100
10
DISINTEGRATION TIME IN SEC.
COMPRESSIONAL FORCE IN 1000 LBS.
0
0.5
1
1.5
2
2.5
3
4
5
6.5
8

FIG. 9 CMCA 4%



100
80
60
40
30
20
10
DISINTEGRATION TIME IN SEC.
COMPRESSIONAL FORCE IN 1000 LBS.
0
0.5
1
1.5
2
2.5
3
4
5
6.5
8

FIG. 10 CMCA 8%

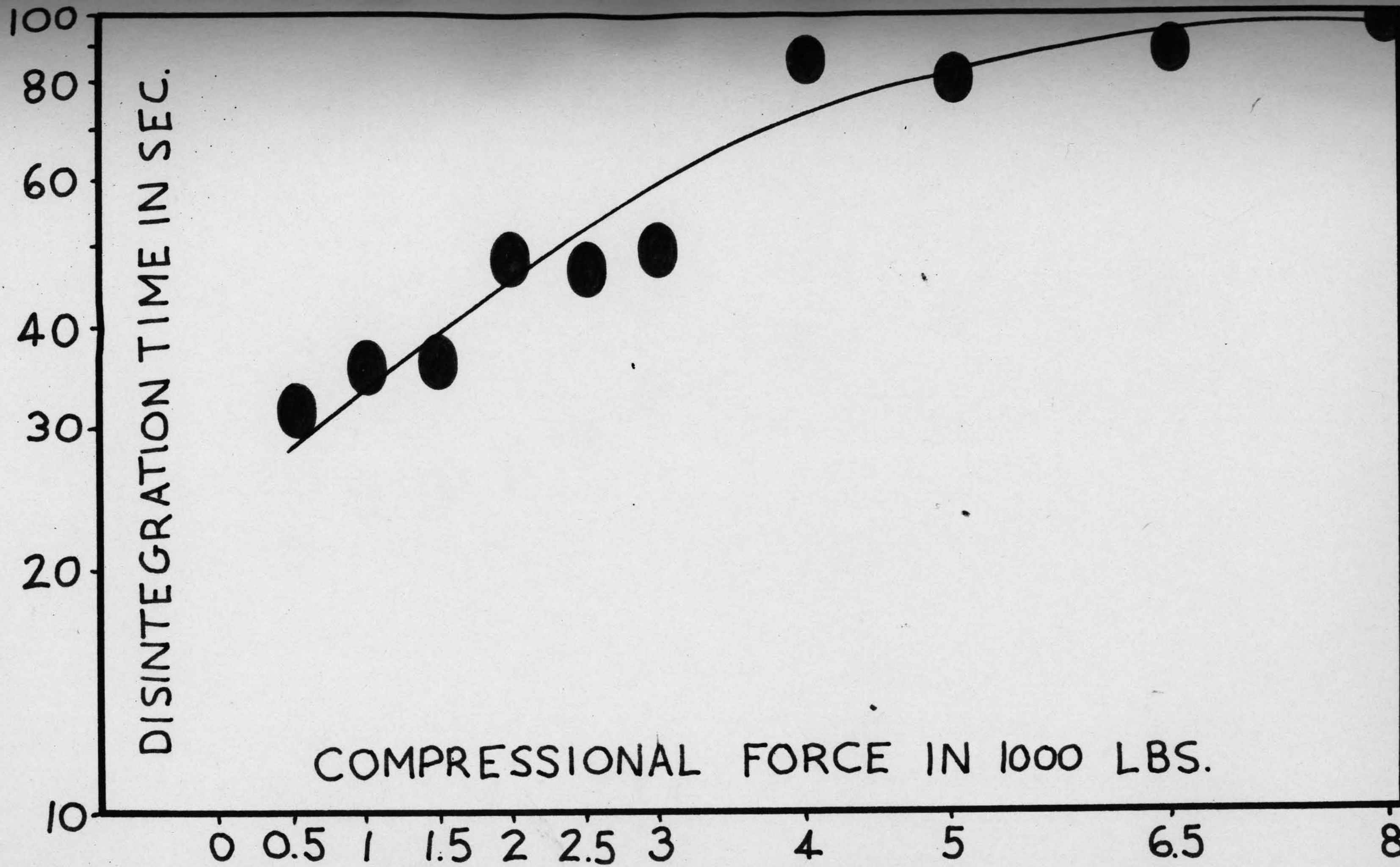


FIG. 11 CMCA 15%

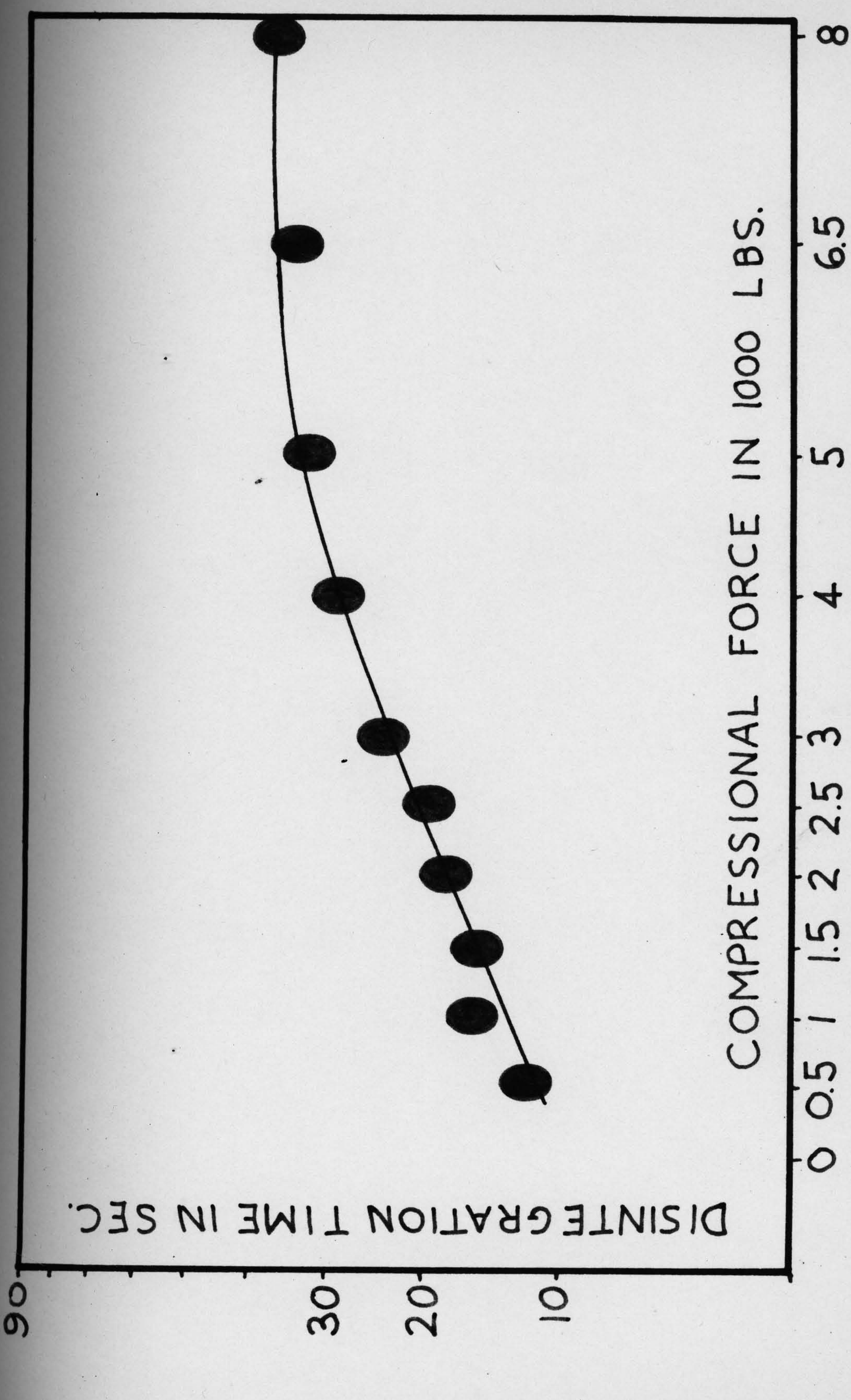


FIG. 12 CMCA 30%

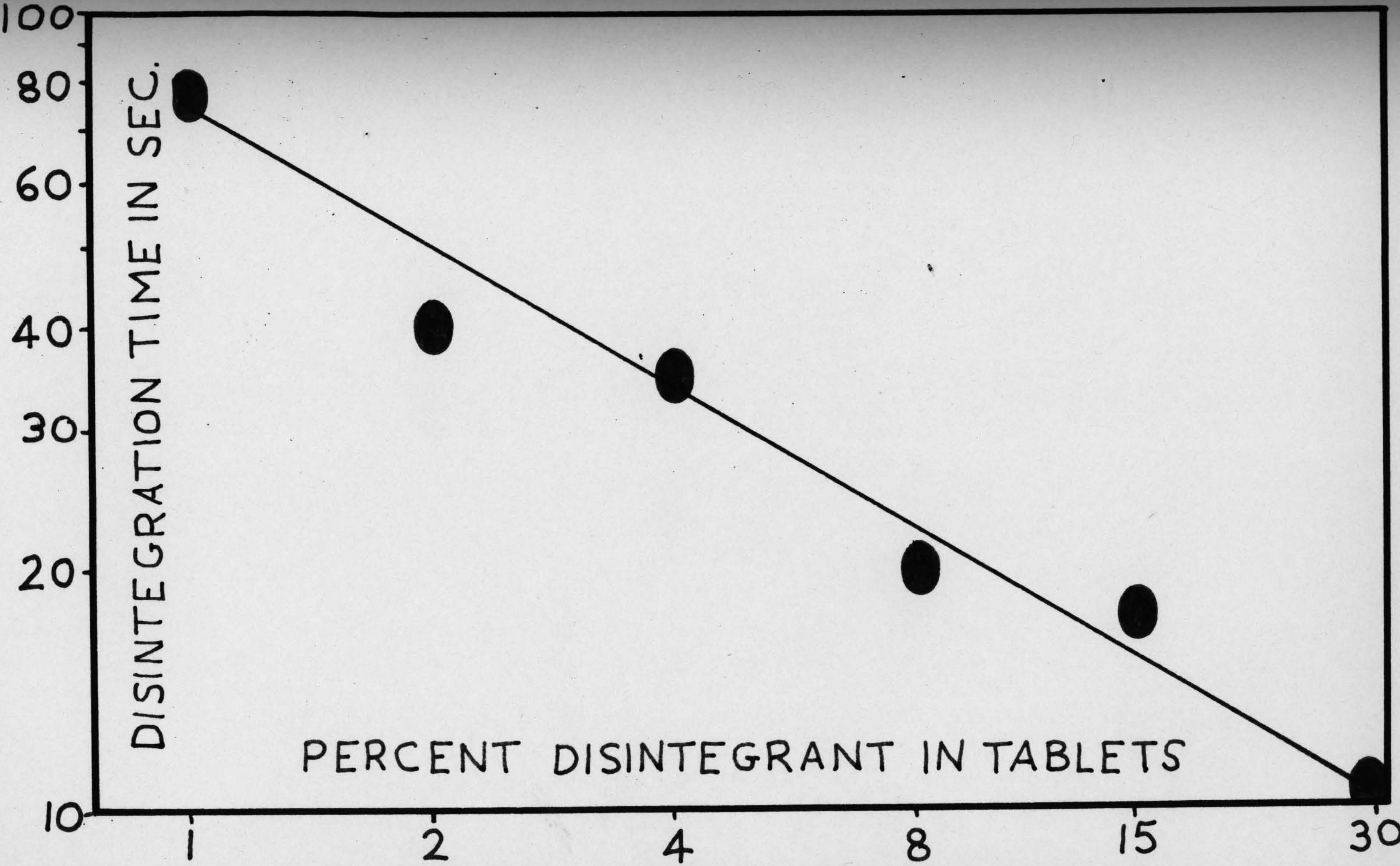


FIG. 13 STARCH-FORCE: 0.5

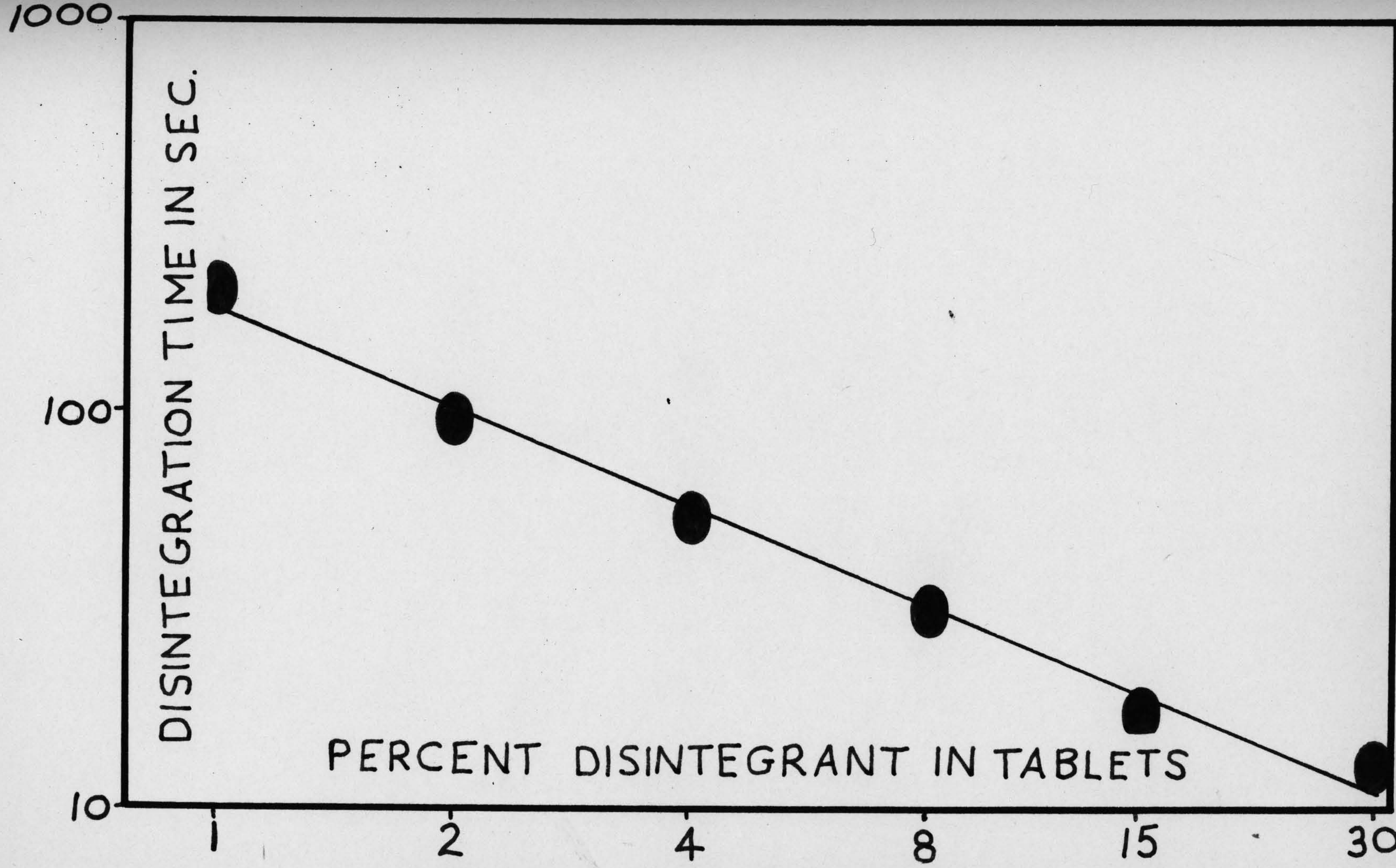


FIG. 14 STARCH-FORCE: 1

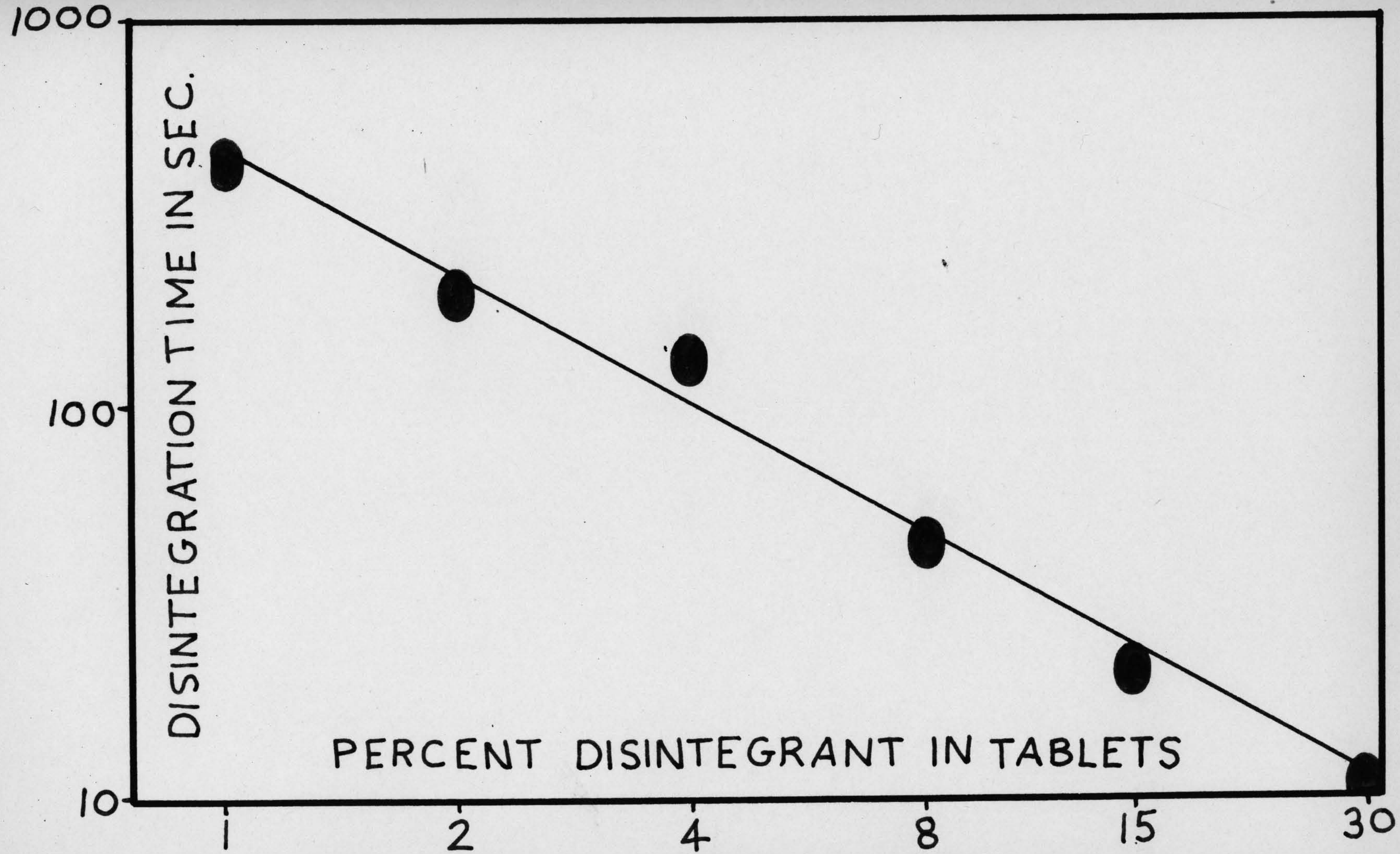


FIG. 15 STARCH-FORCE: 1.5

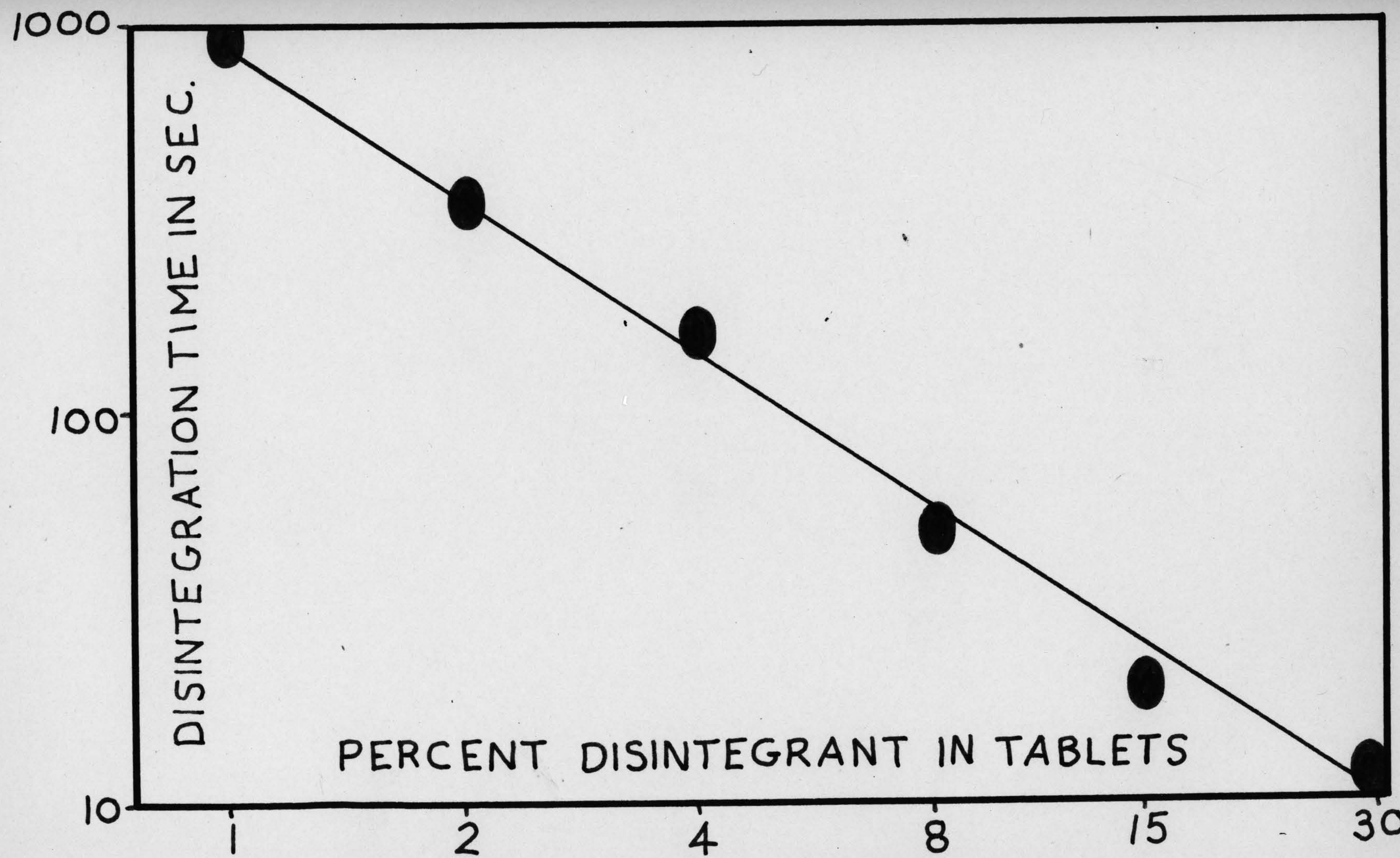


FIG. 16 STARCH-FORCE: 2

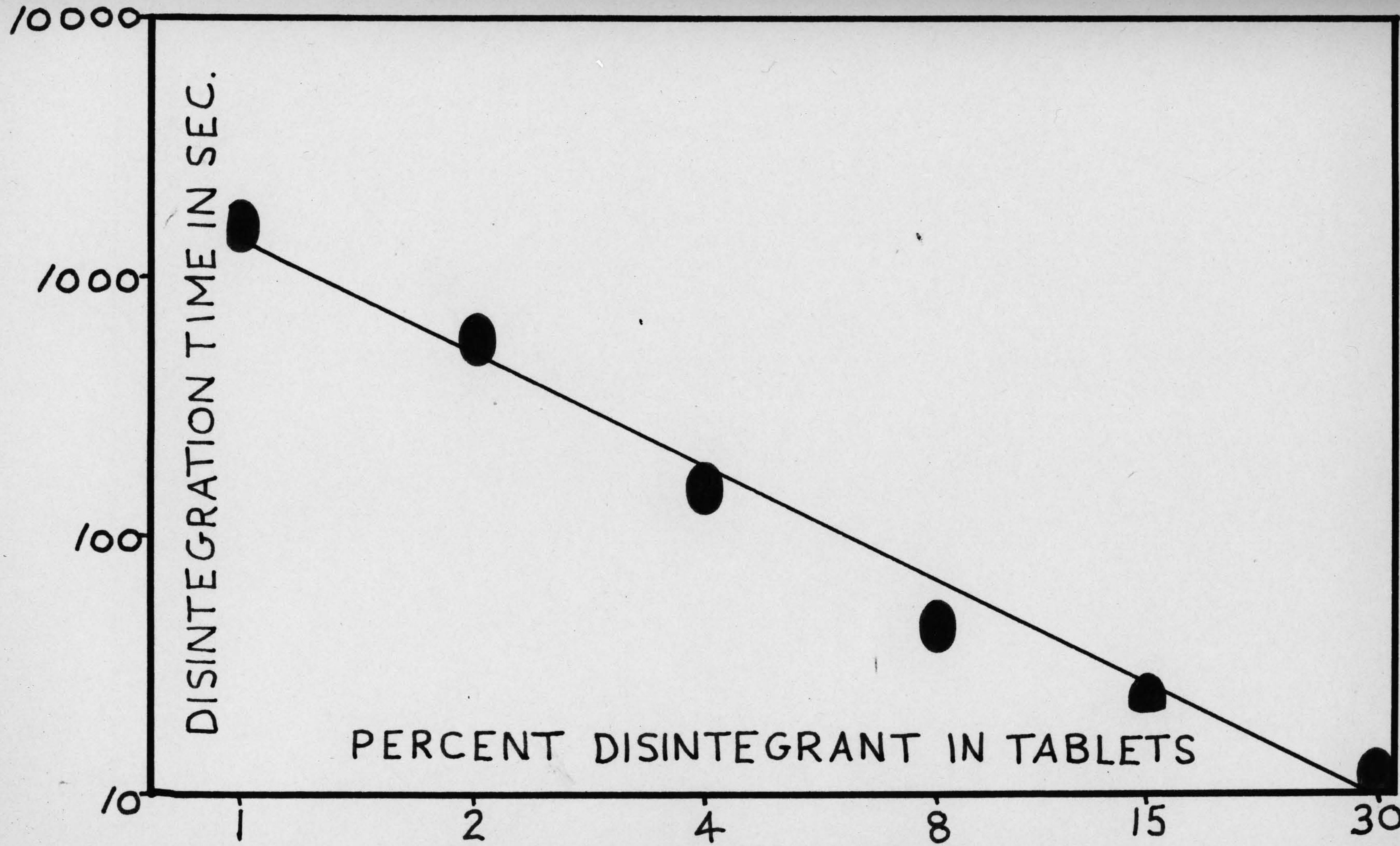


FIG. 17 STARCH-FORCE: 2.5

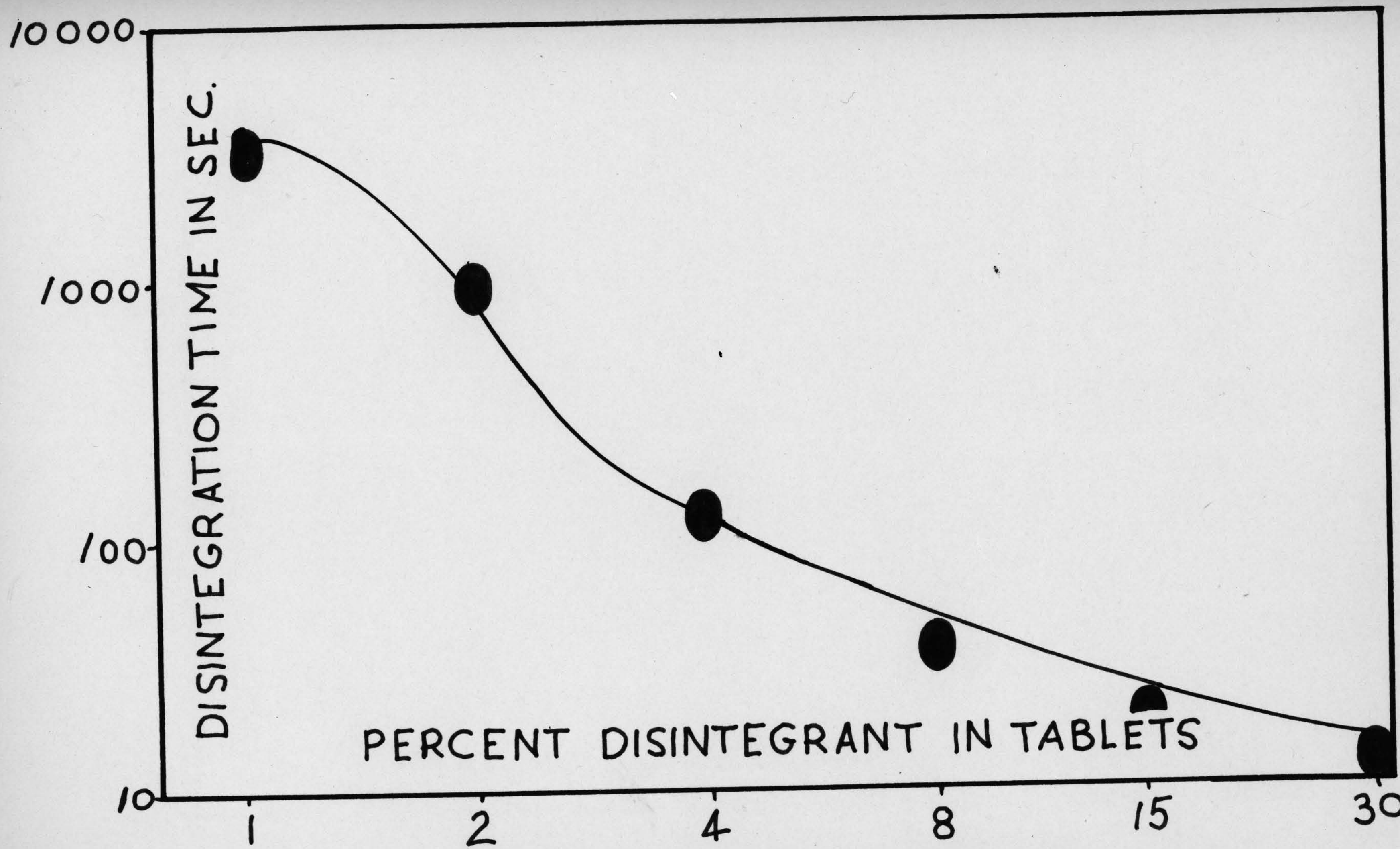


FIG. 18 STARCH-FORCE: 3

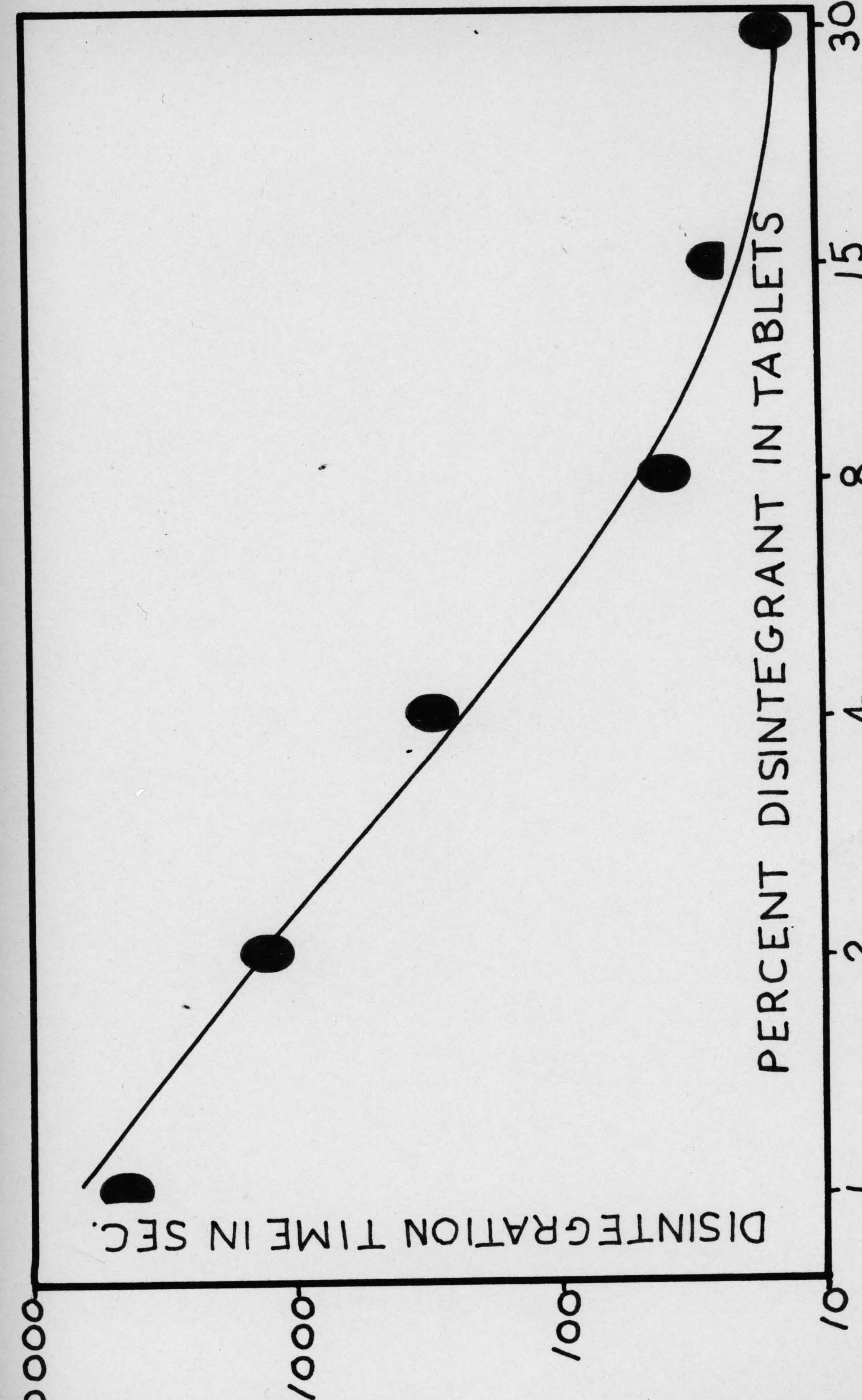


FIG 19 STARCH-FORCE: 4

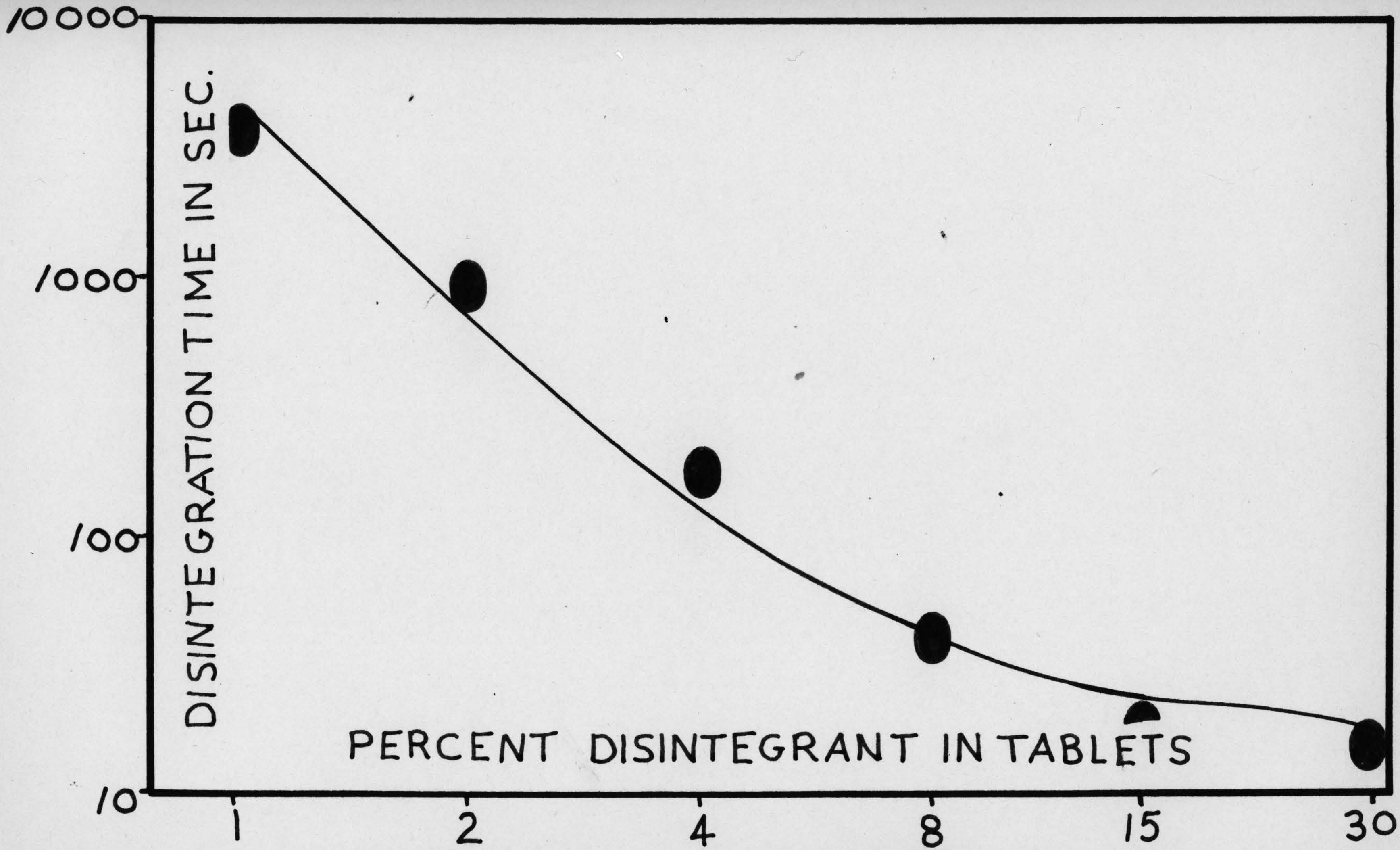


FIG. 20 STARCH-FORCE: 5

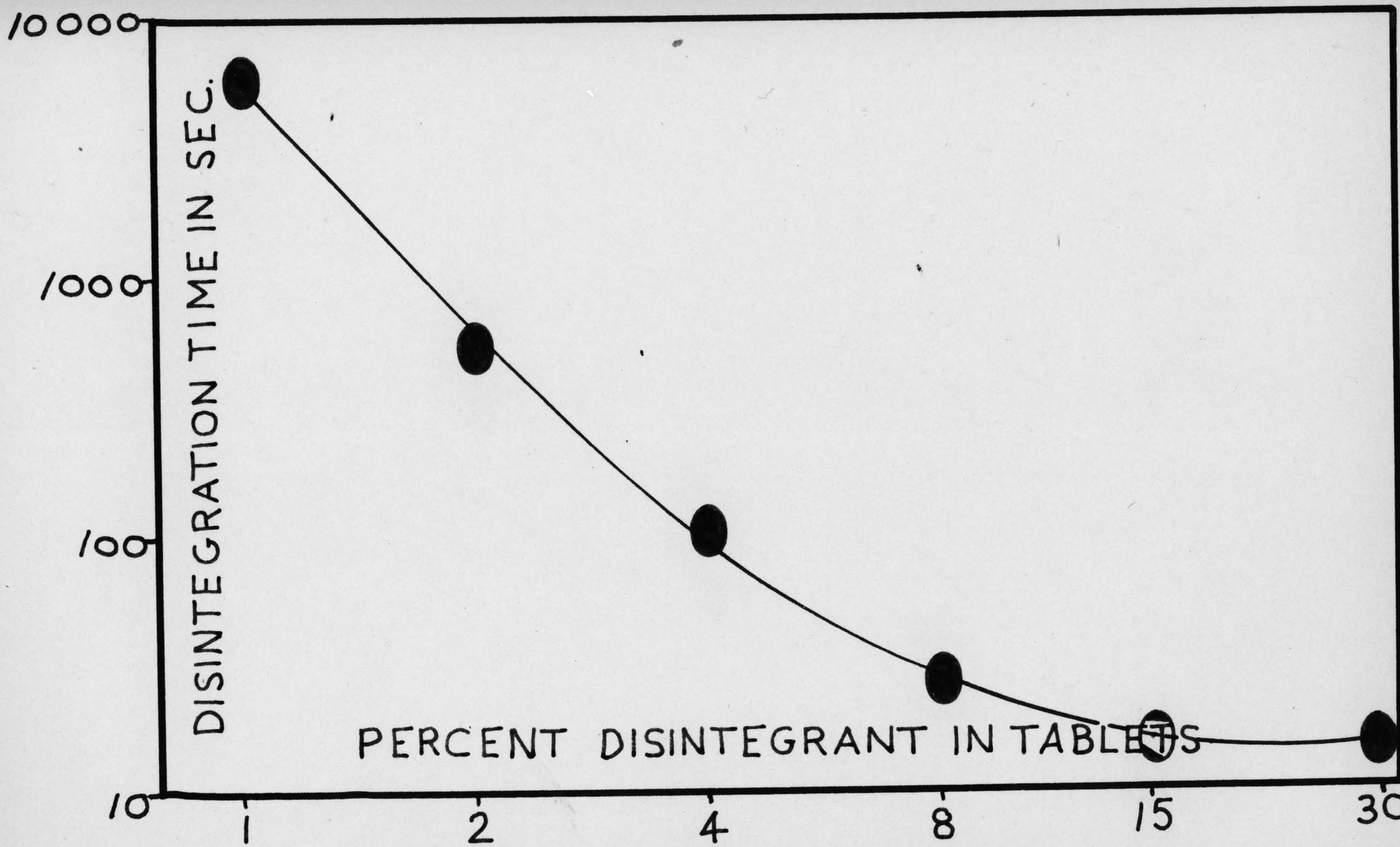


FIG. 21 STARCH-FORCE: 6.5

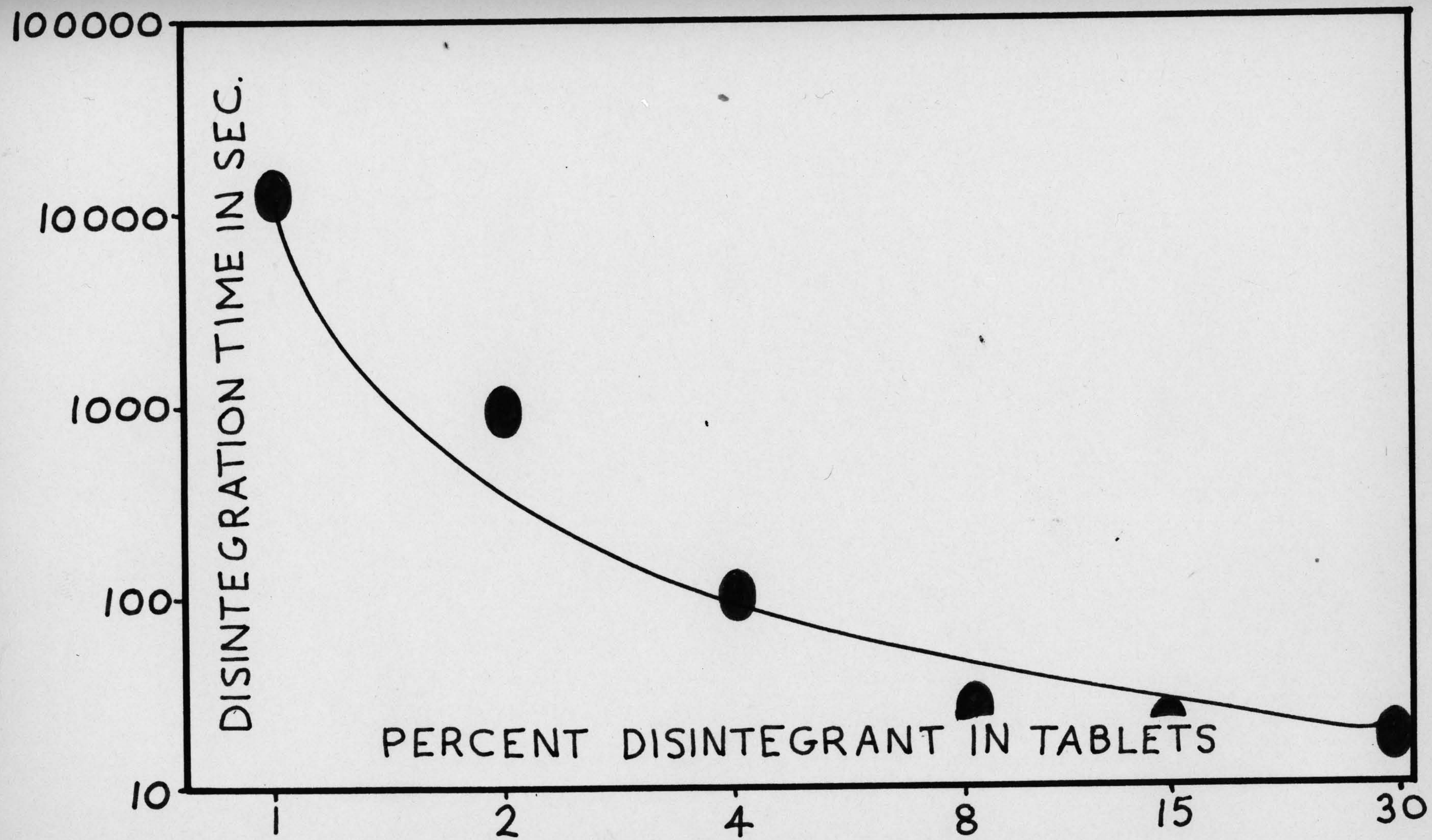


FIG. 22 STARCH-FORCE: 8

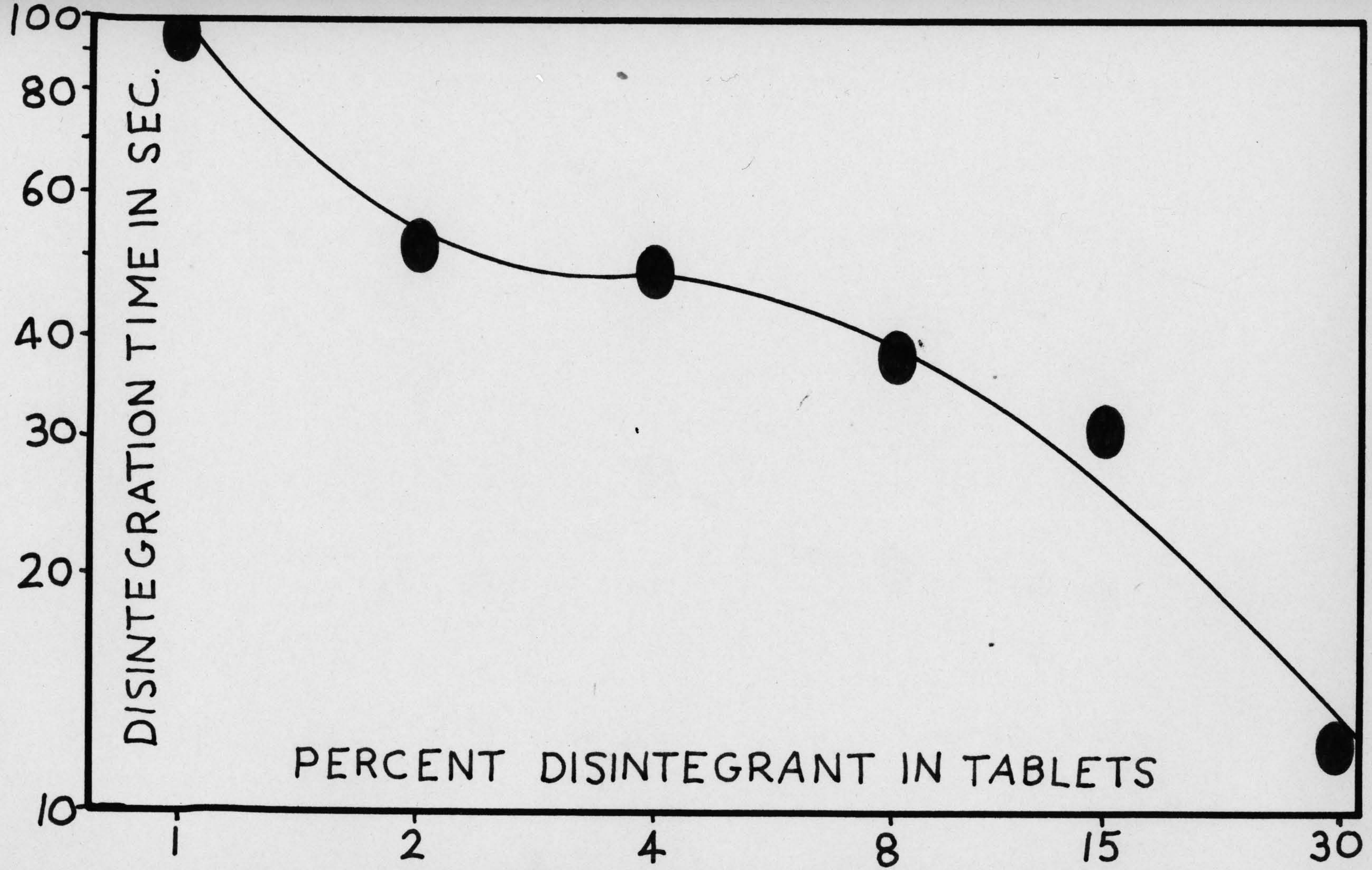


FIG. 23 CMCA-FORCE: 0.5

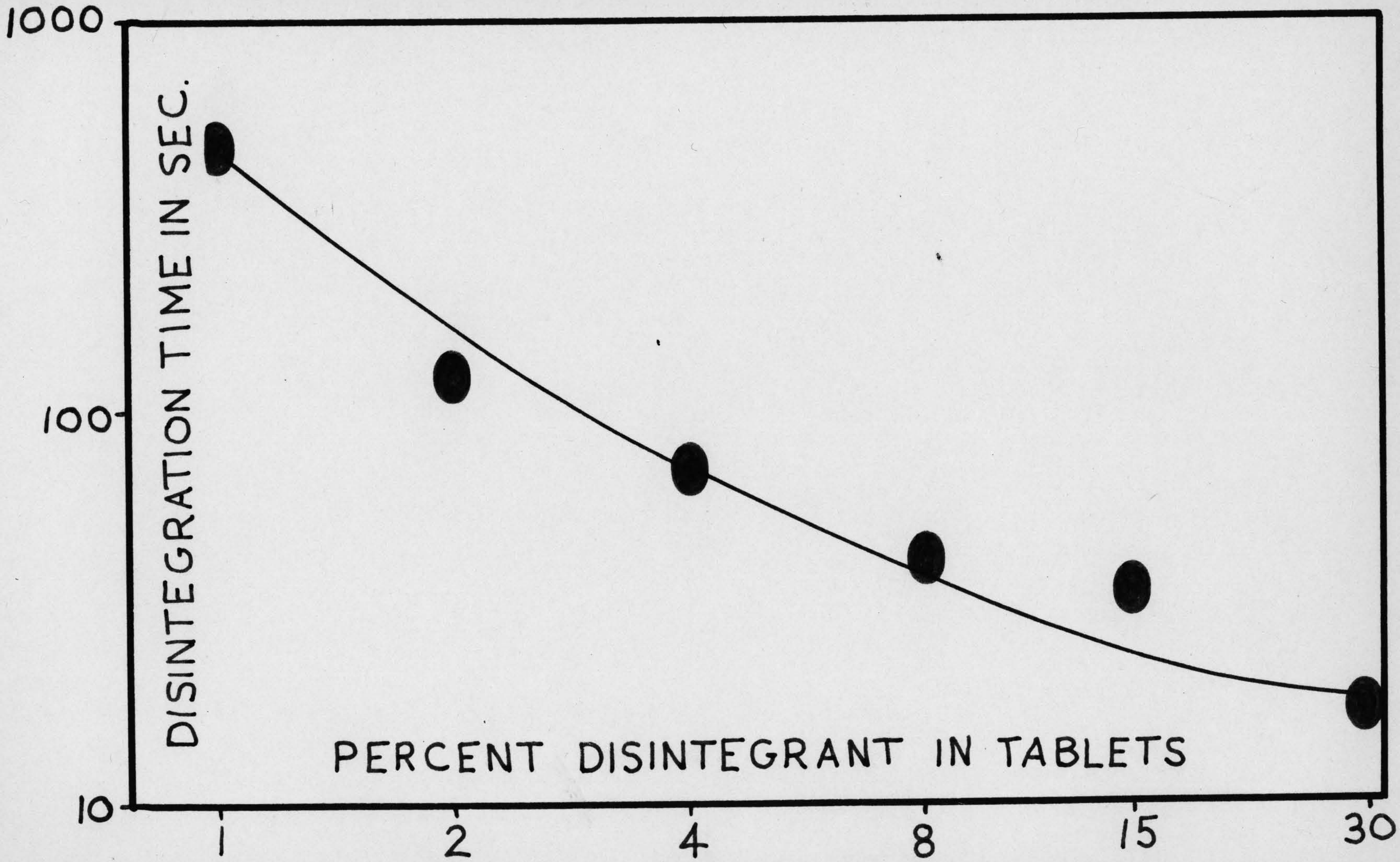


FIG. 24 CMCA-FORCE: 1

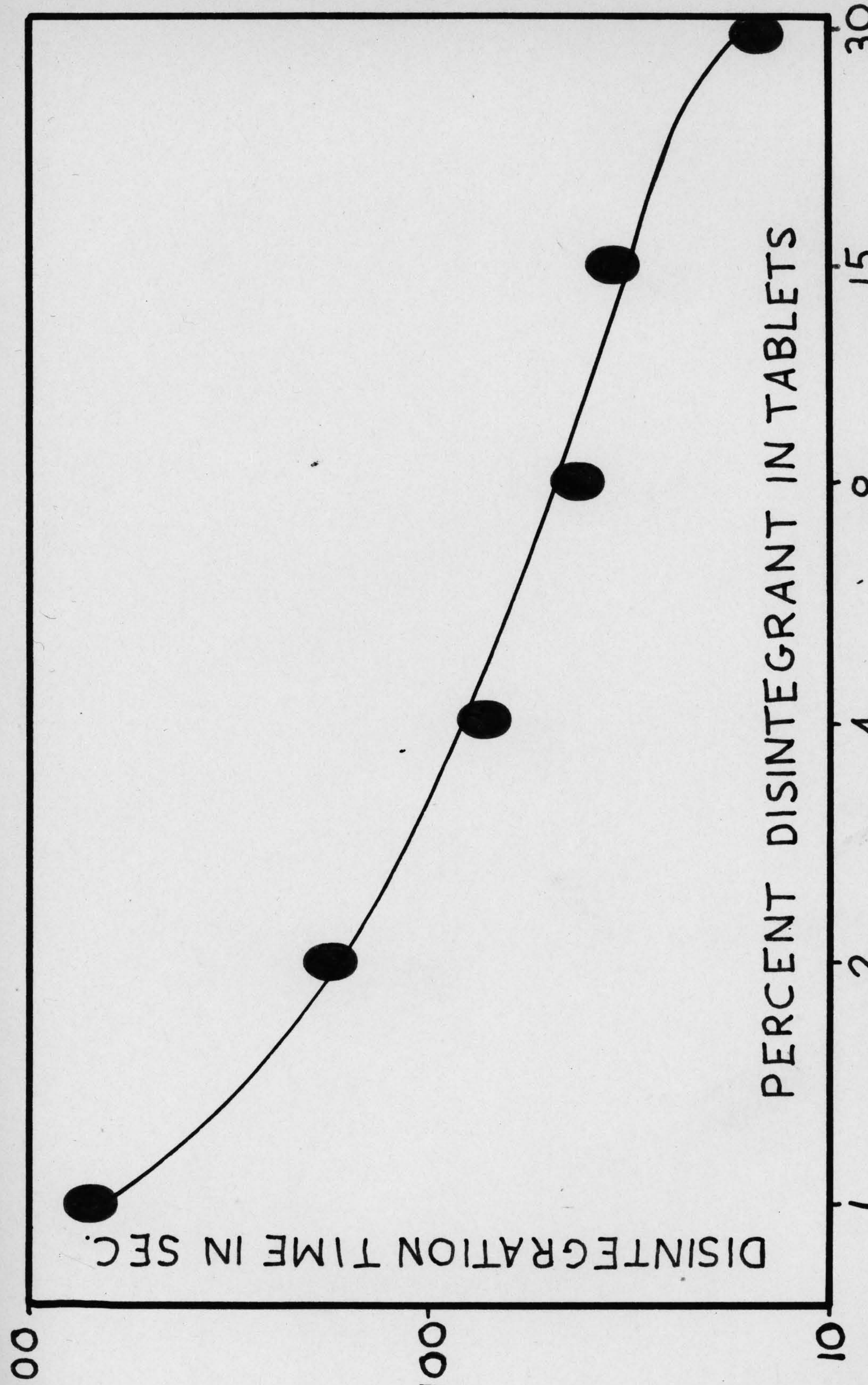


FIG. 25 CMCA-FORCE: 1.5

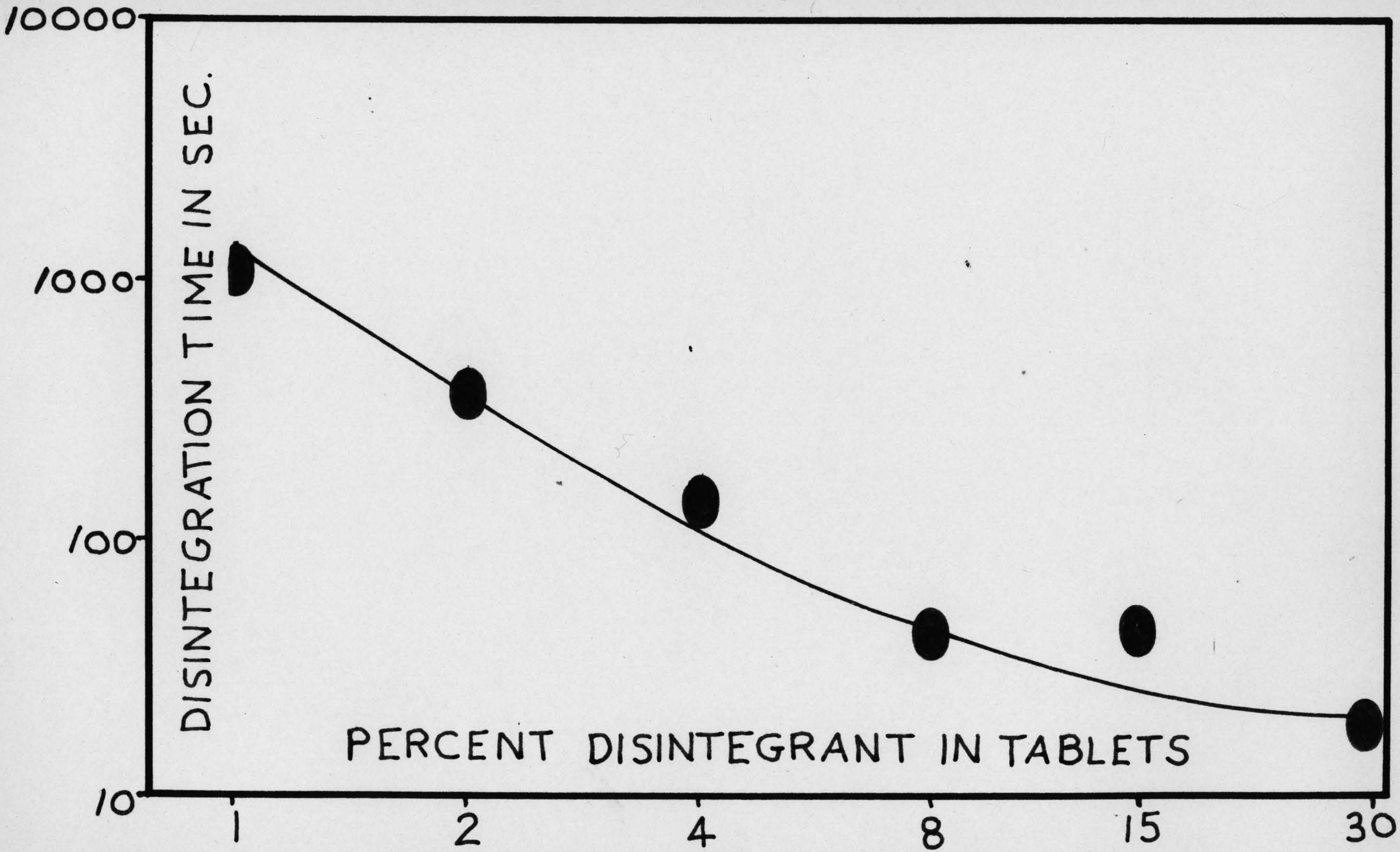


FIG. 26 CMCA-FORCE: 2

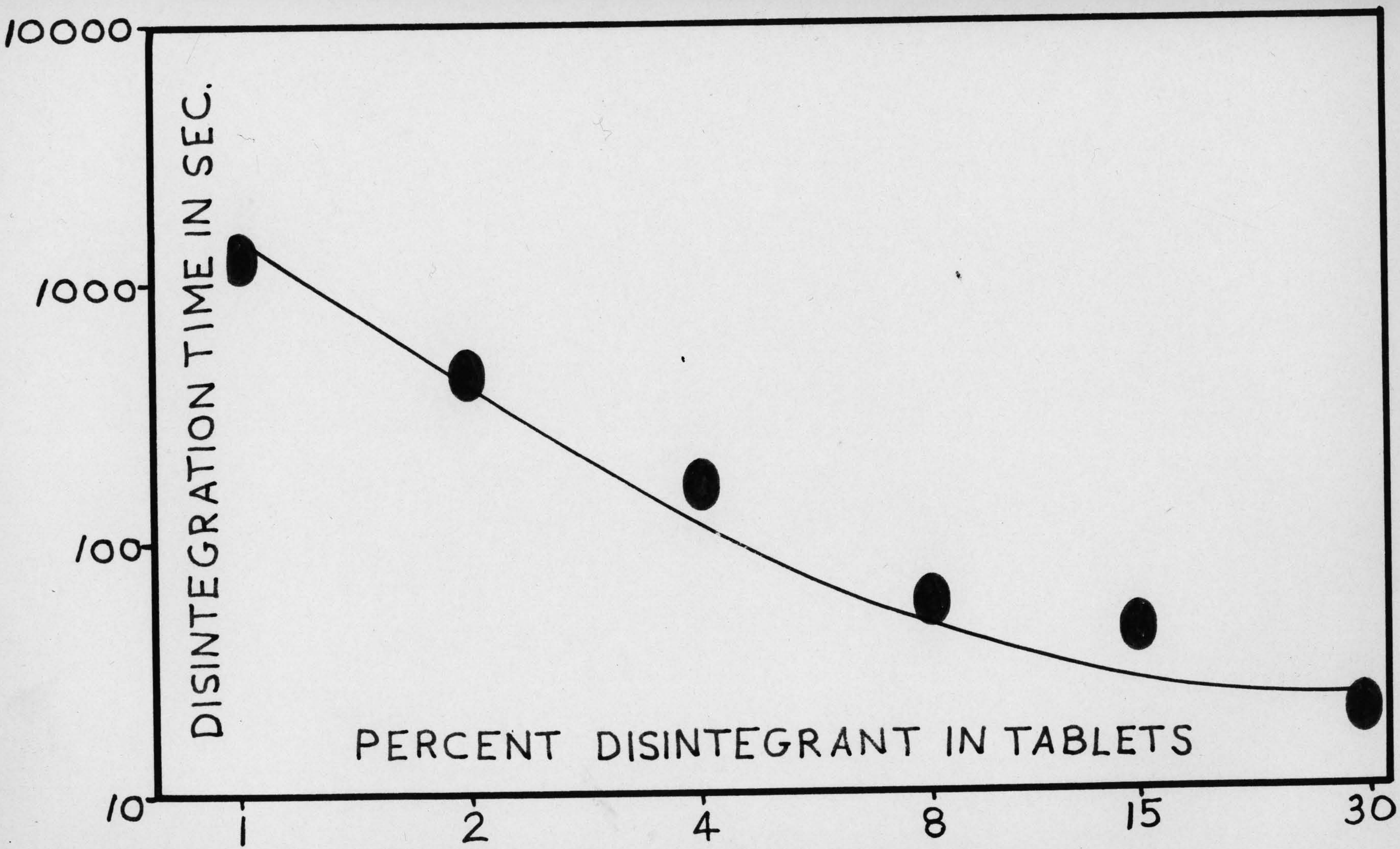


FIG. 27 CMCA-FORCE: 2.5

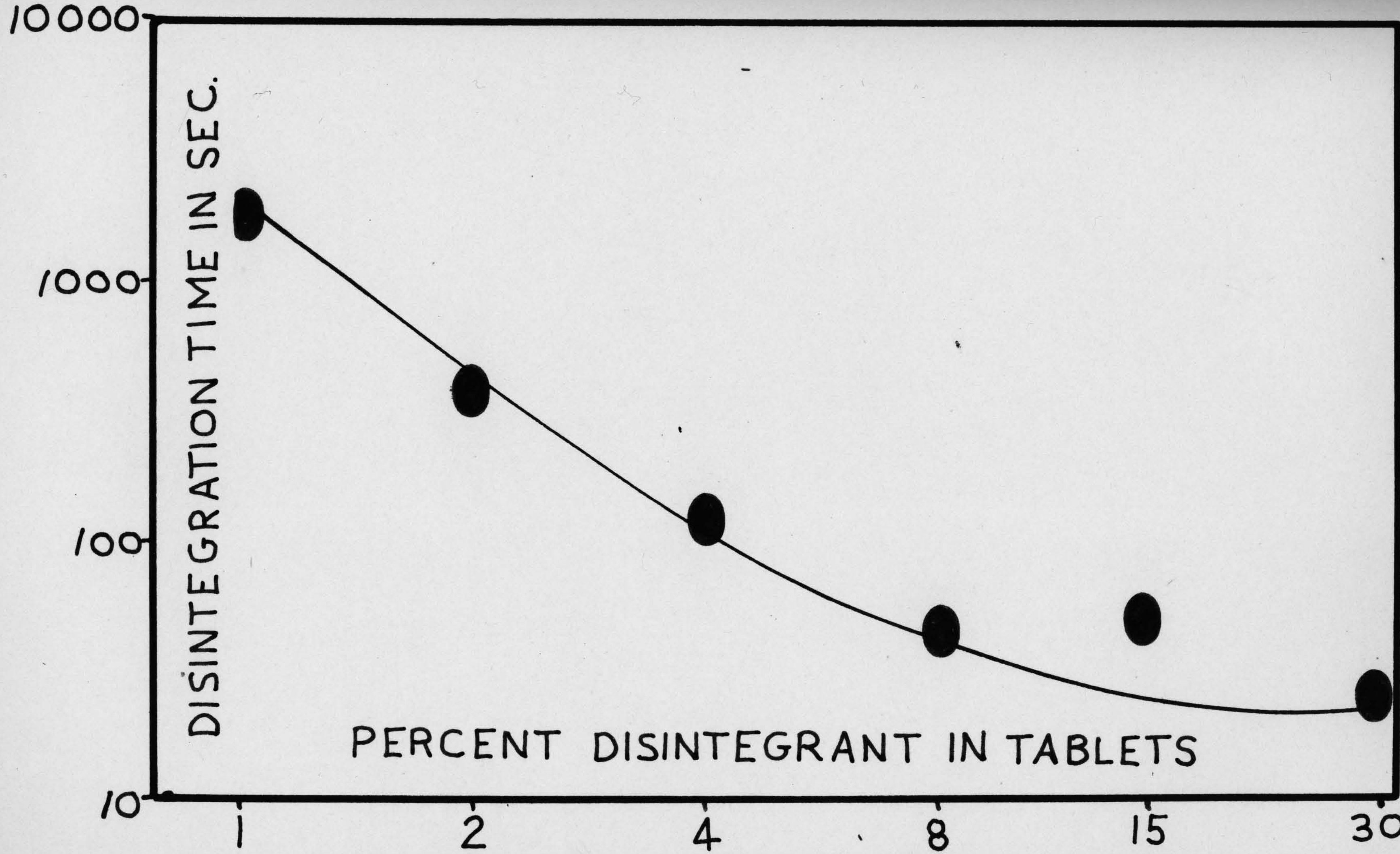


FIG. 28 CMCA-FORCE: 3

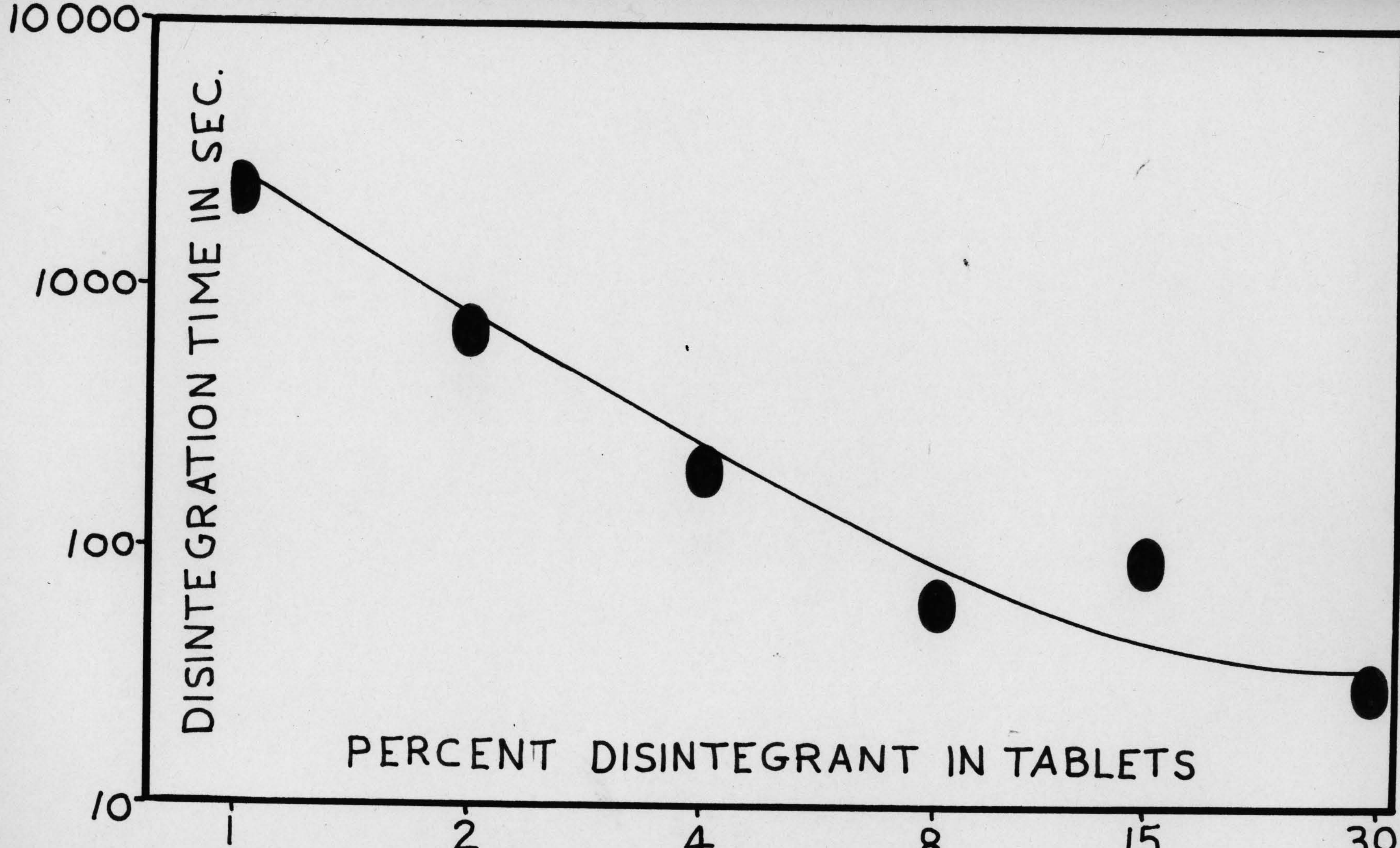


FIG. 29 CMCA-FORCE: 4

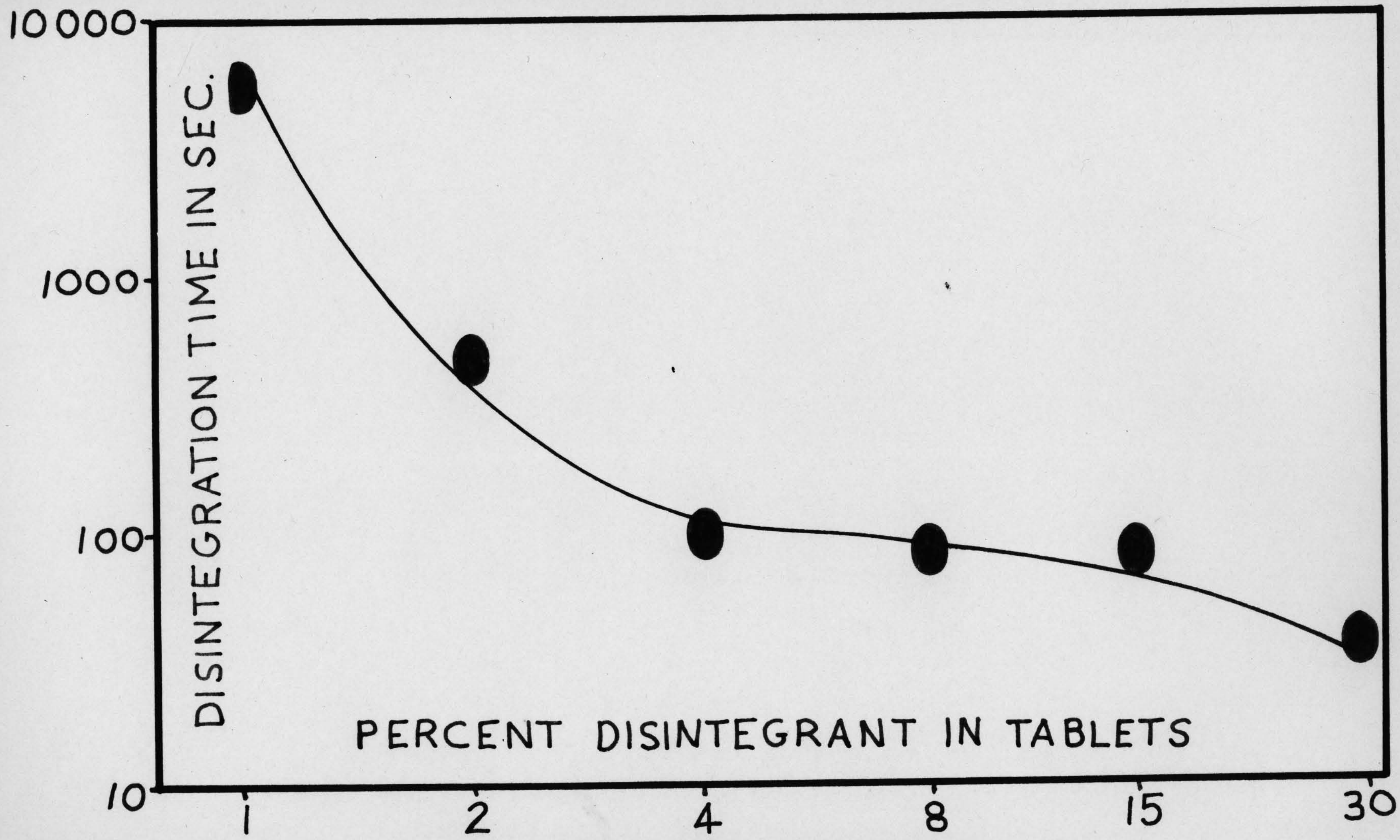


FIG. 30 CMCA-FORCE: 5

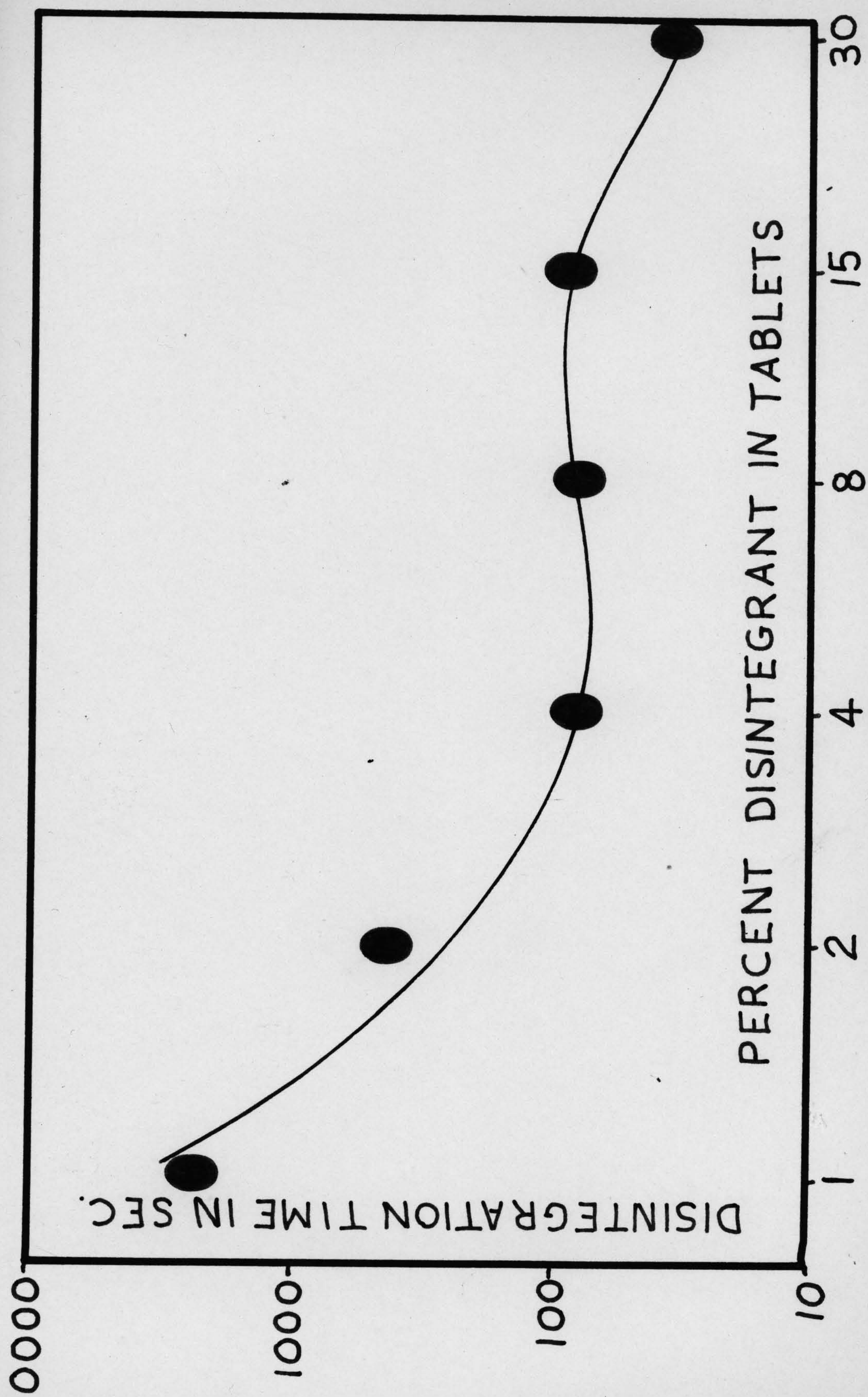


FIG. 31 CMCA-FORCE: 6.5

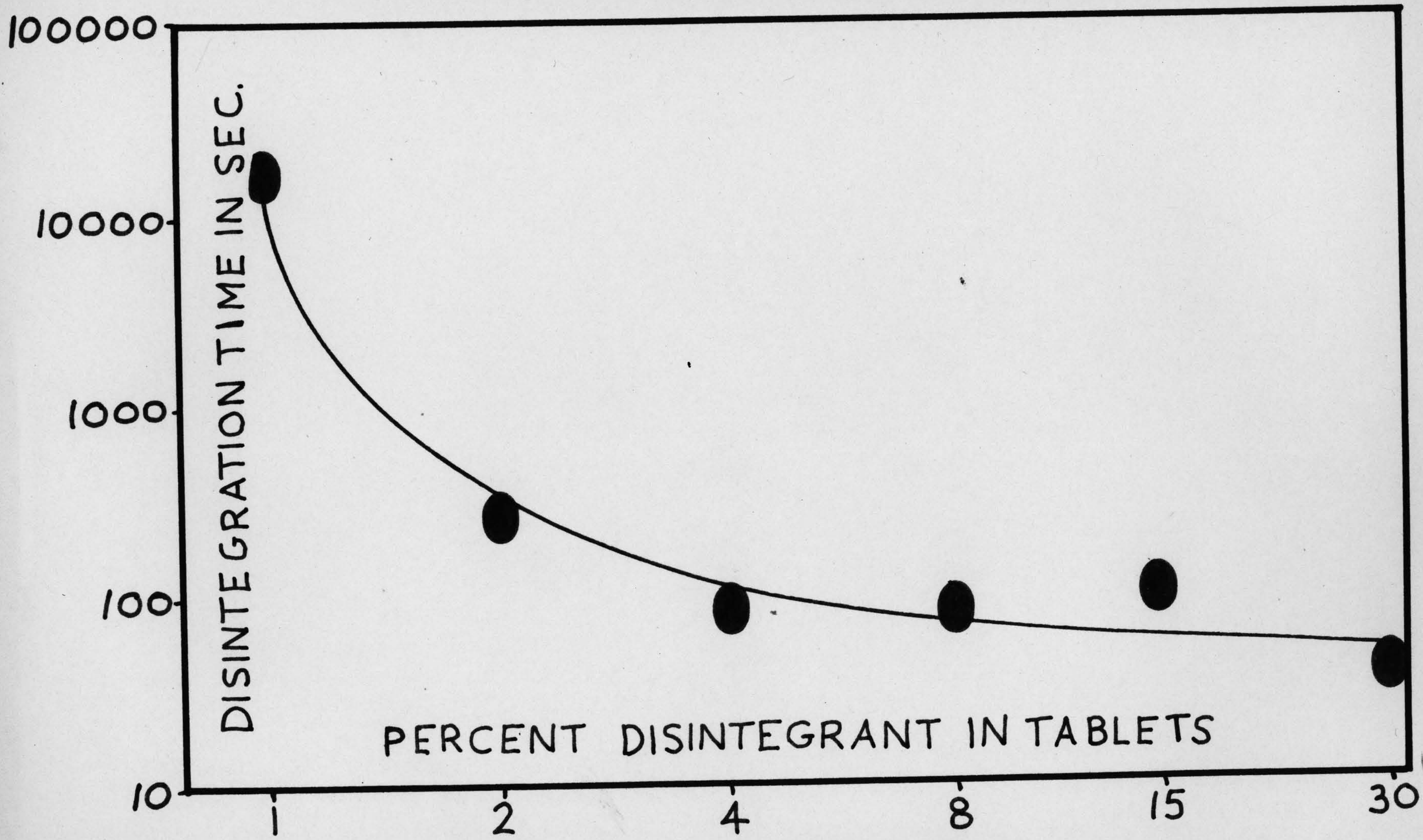


FIG. 32 CMCA-FORCE: 8

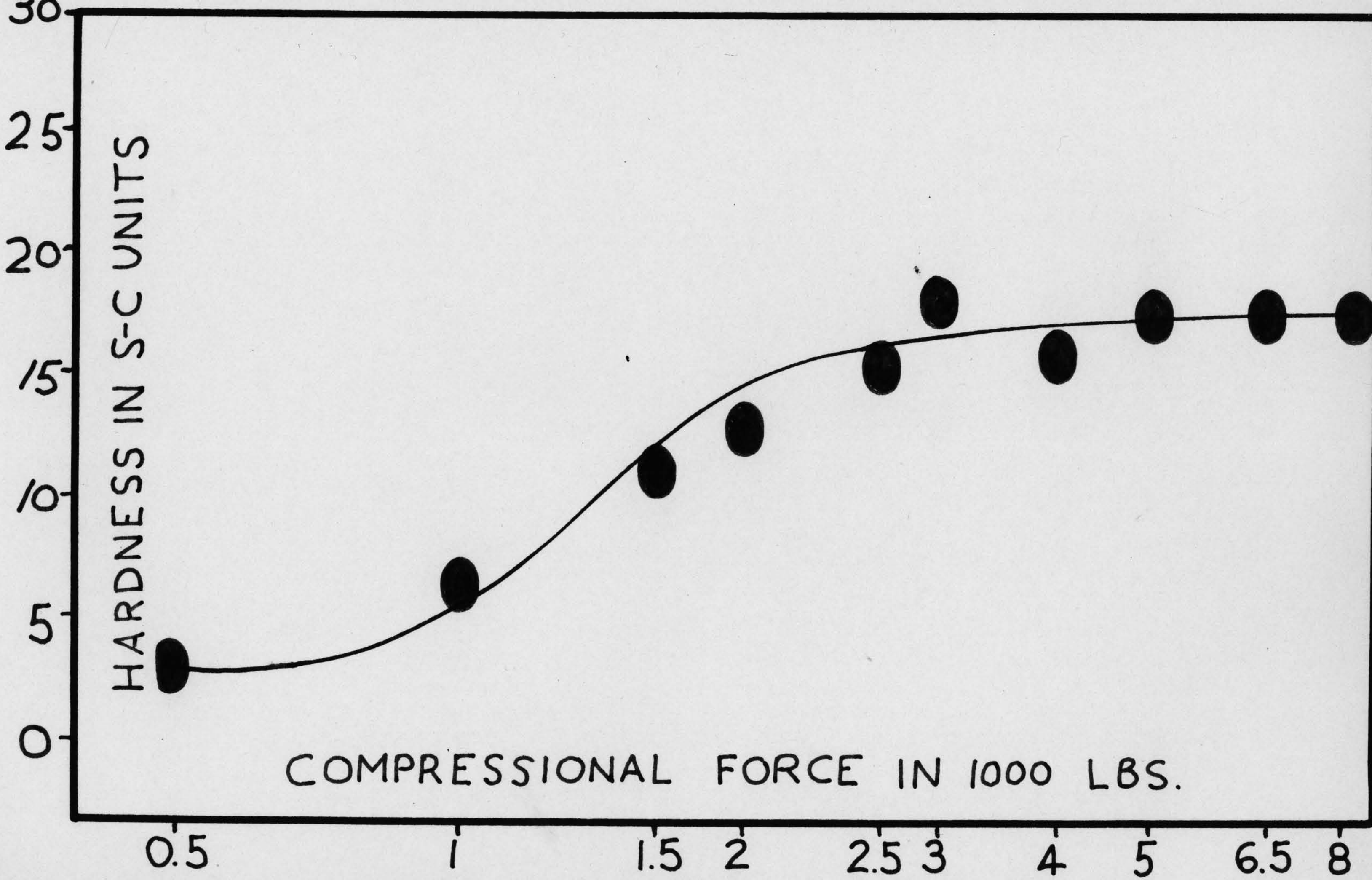


FIG. 33 STARCH 1%

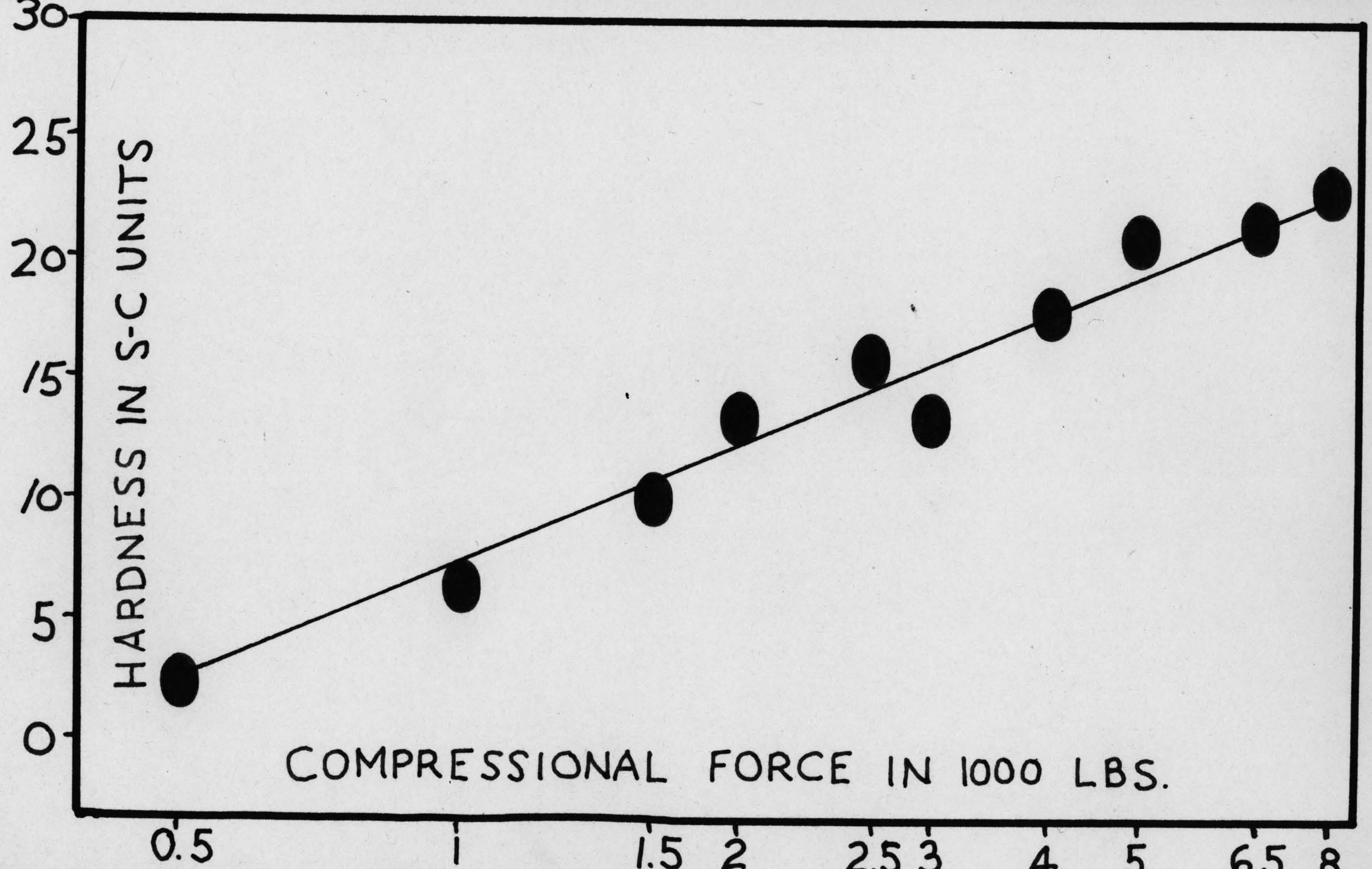


FIG. 34 STARCH 2%

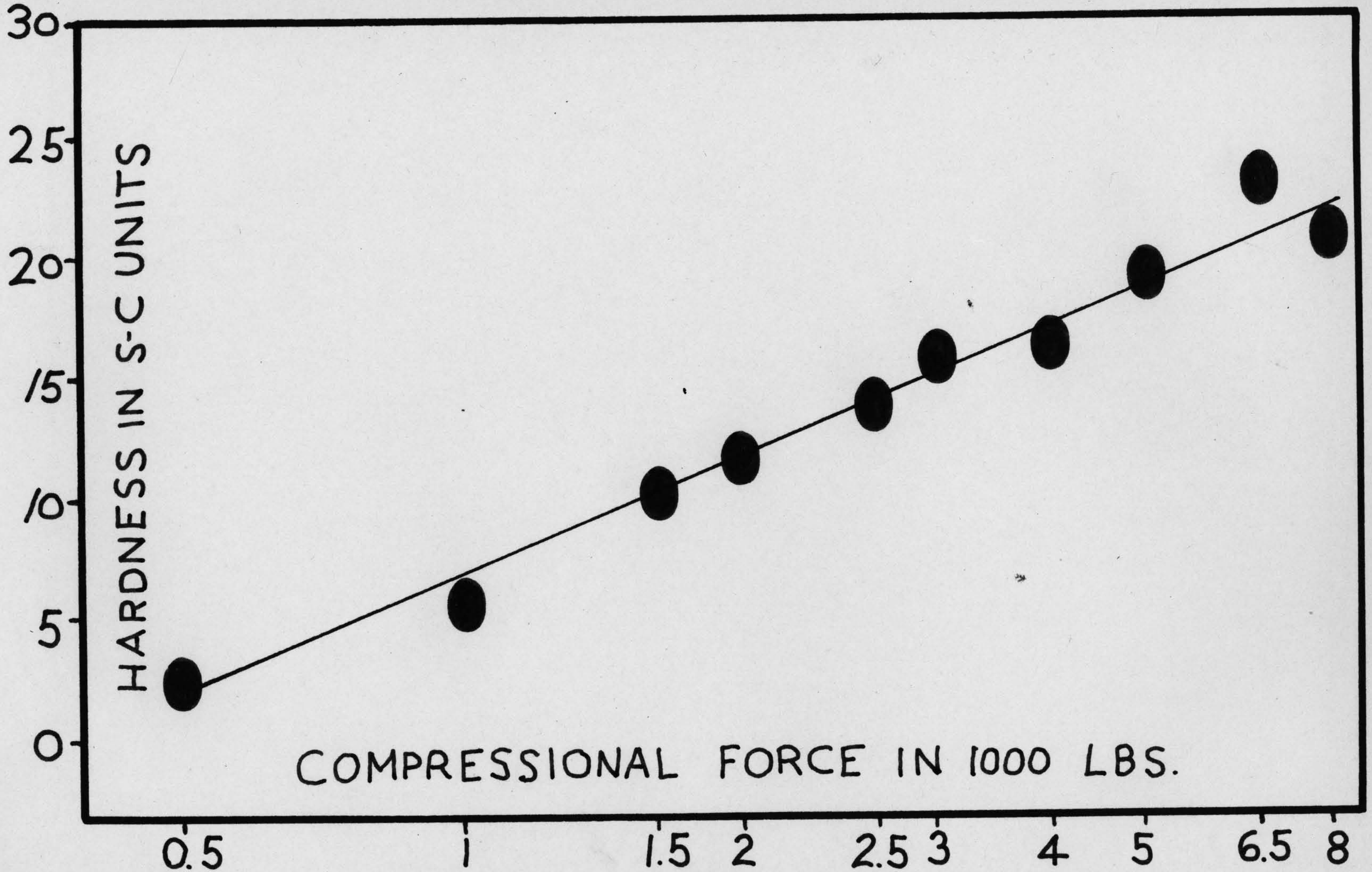


FIG. 35 STARCH 4%

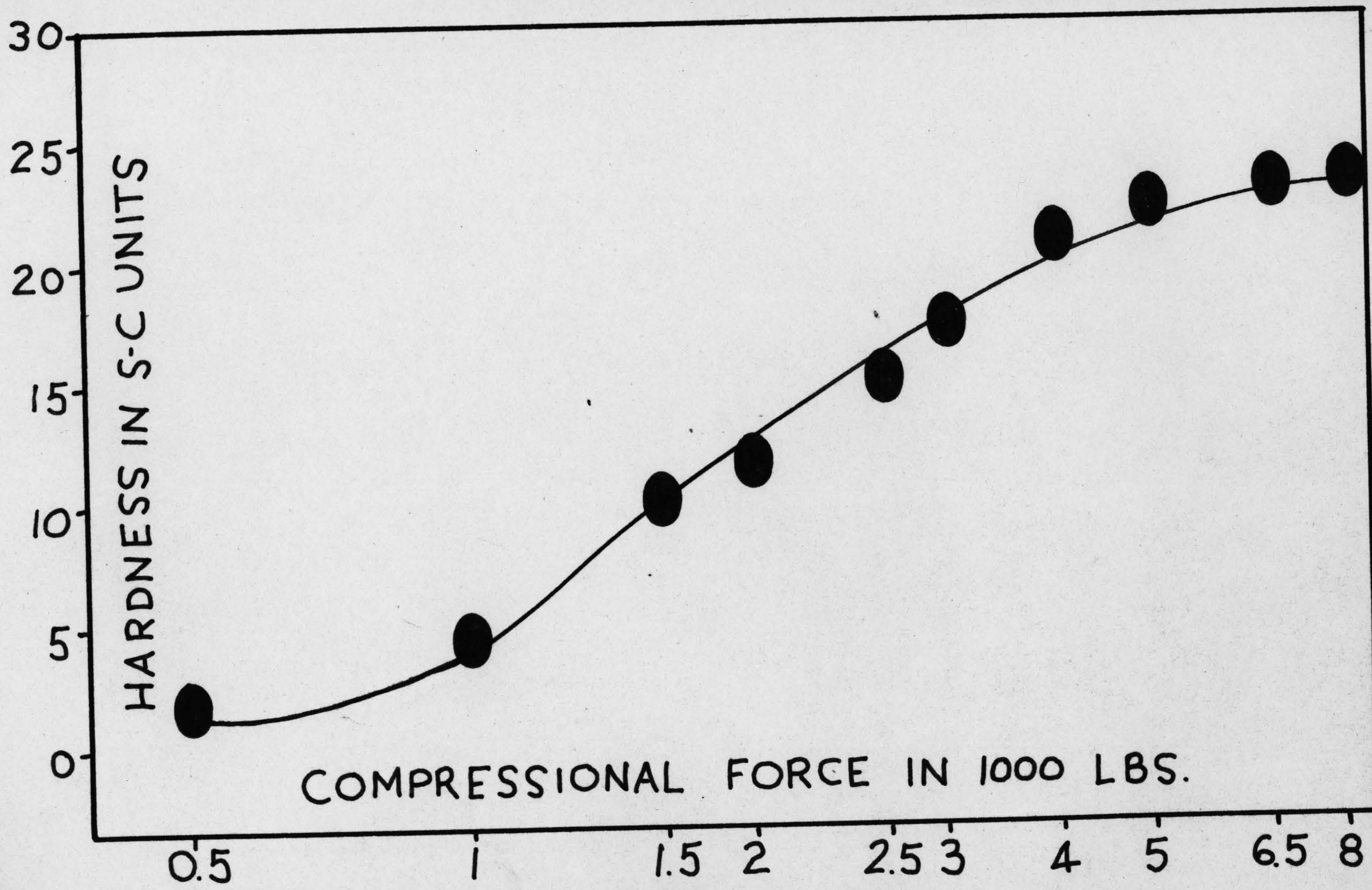


FIG. 36 STARCH 8%

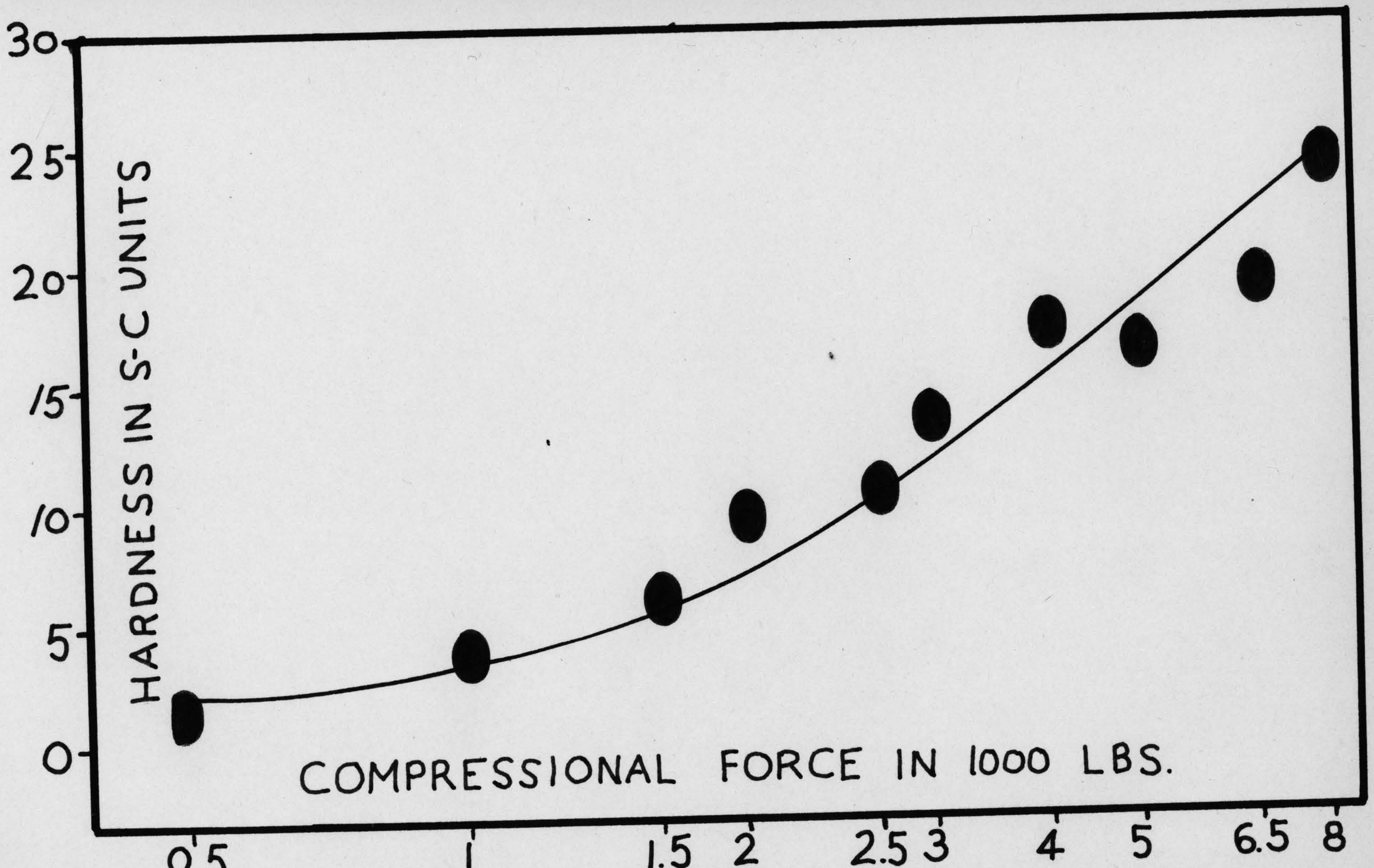


FIG. 37 STARCH 15 %

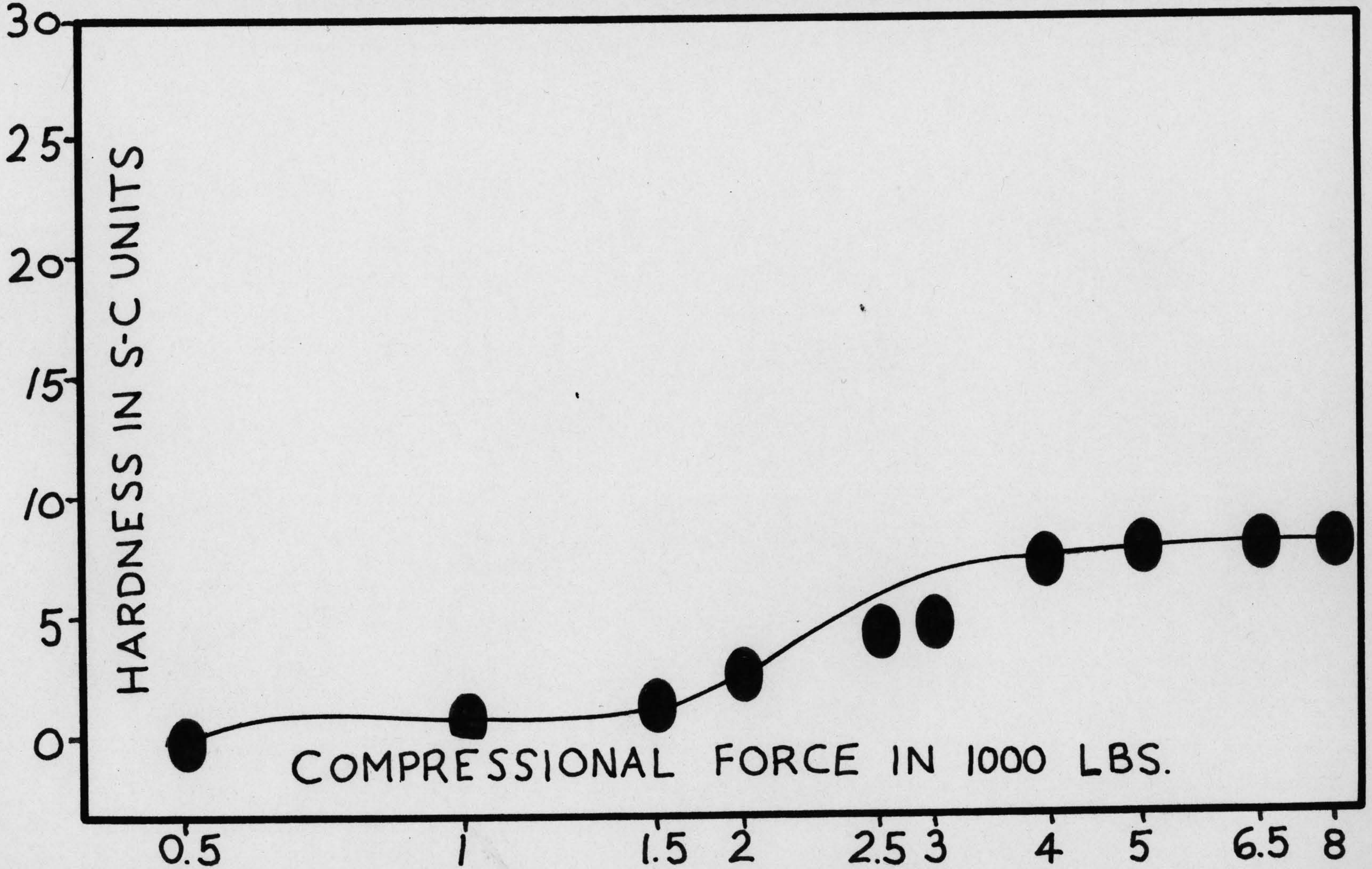


FIG. 38 STARCH 30%

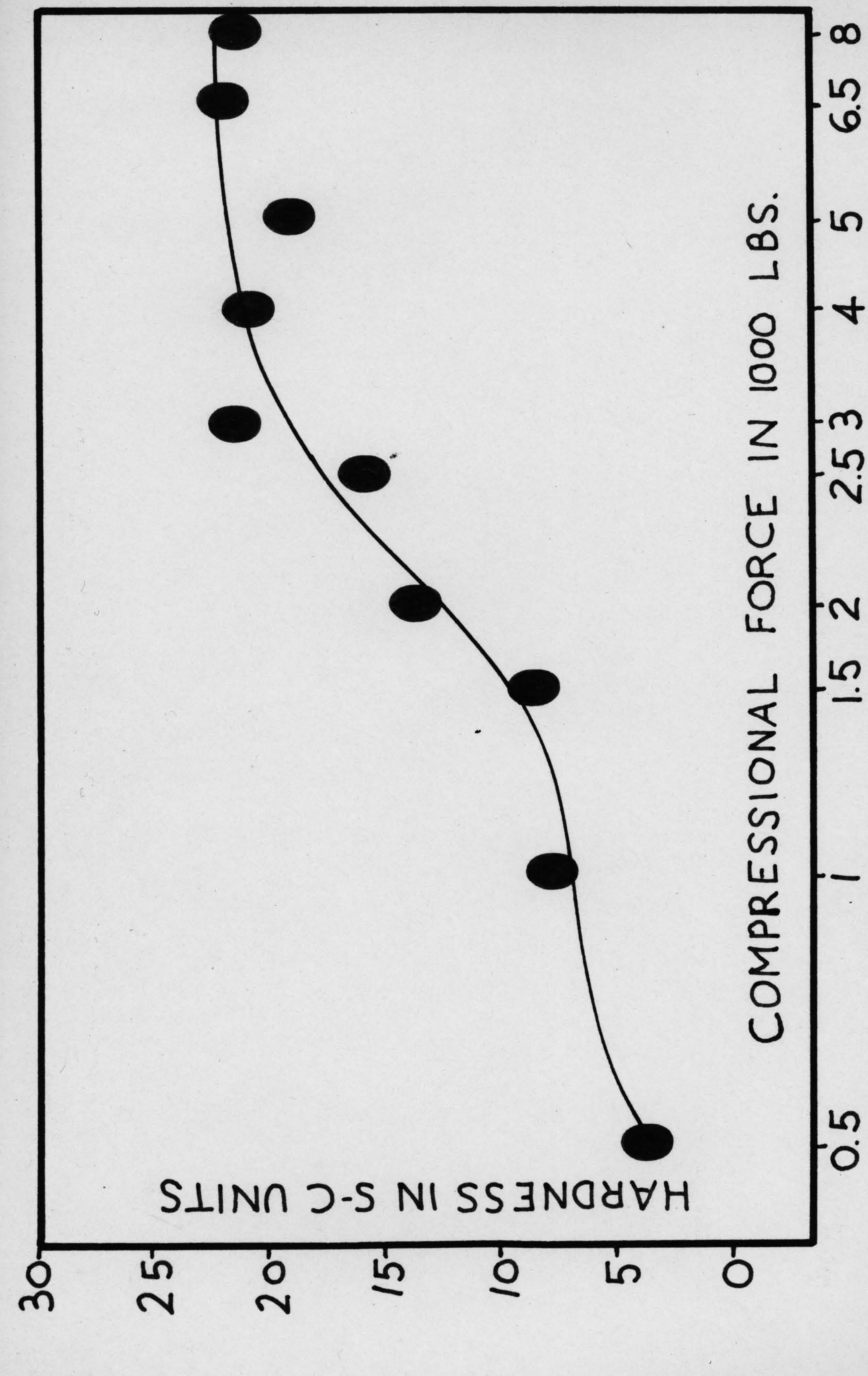

HARDNESS IN S-C UNITS
0
5
10
15
20
25
30
0.5
1
1.5
2
2.5
3
4
5
6.5
8
COMPRESSIONAL FORCE IN 1000 LBS.

FIG. 39 CMCA 1%

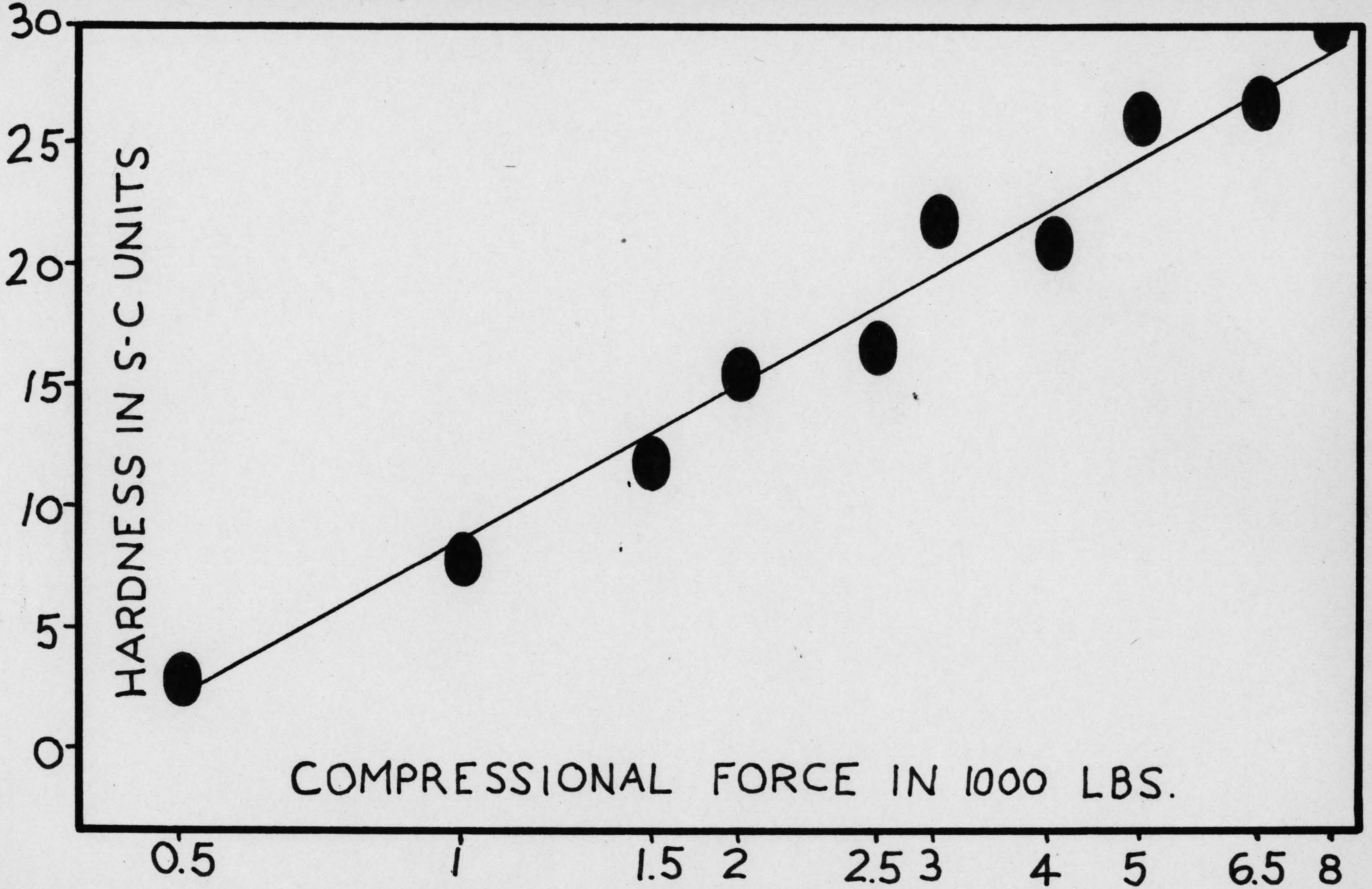

30
25
20
15
10
5
0
HARDNESS IN S-C UNITS
COMPRESSIONAL FORCE IN 1000 LBS.
0.5
1
1.5
2
2.5
3
4
5
6.5
8

FIG. 40 CMCA 2%

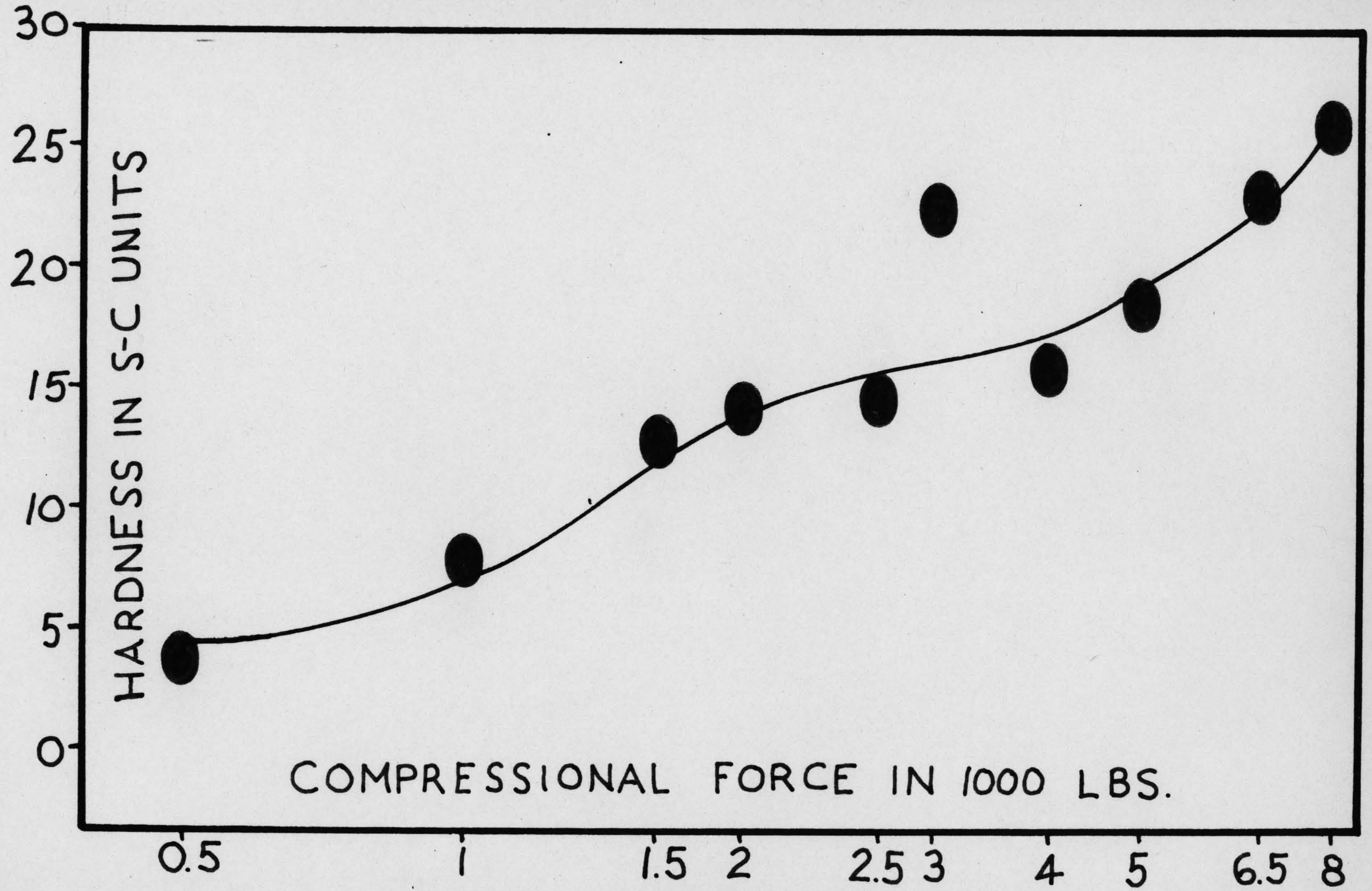

30
25
20
15
10
5
0
HARDNESS IN S-C UNITS
COMPRESSIONAL FORCE IN 1000 LBS.
0.5
1
1.5
2
2.5
3
4
5
6.5
8

FIG. 41 CMCA 4 %

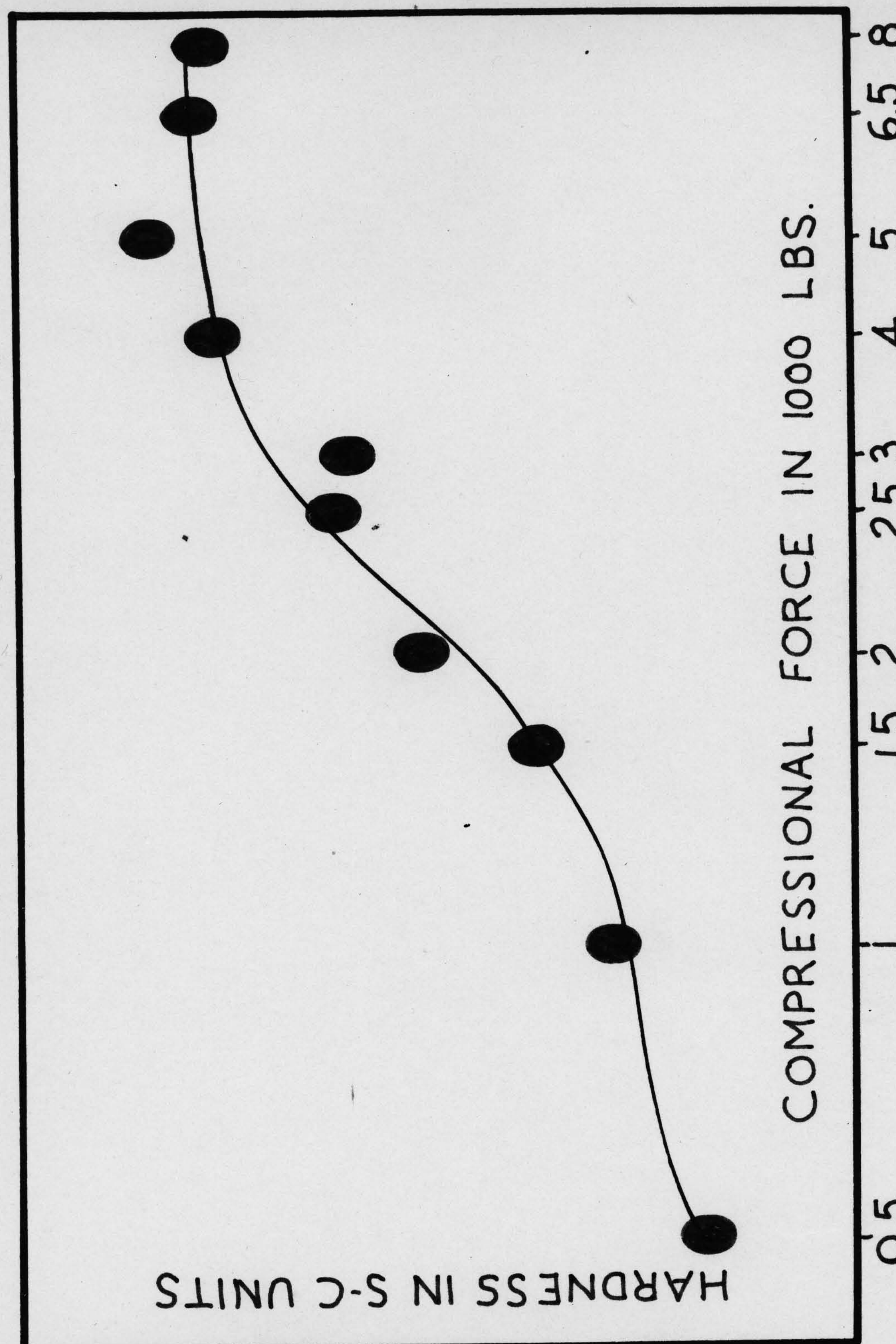

30
25
20
15
10
5
0
HARDNESS IN S-C UNITS
0.5
1
1.5
2
2.5
3
4
5
6.5
8
COMPRESSIONAL FORCE IN 1000 LBS.

FIG. 42 CMCA 8 %

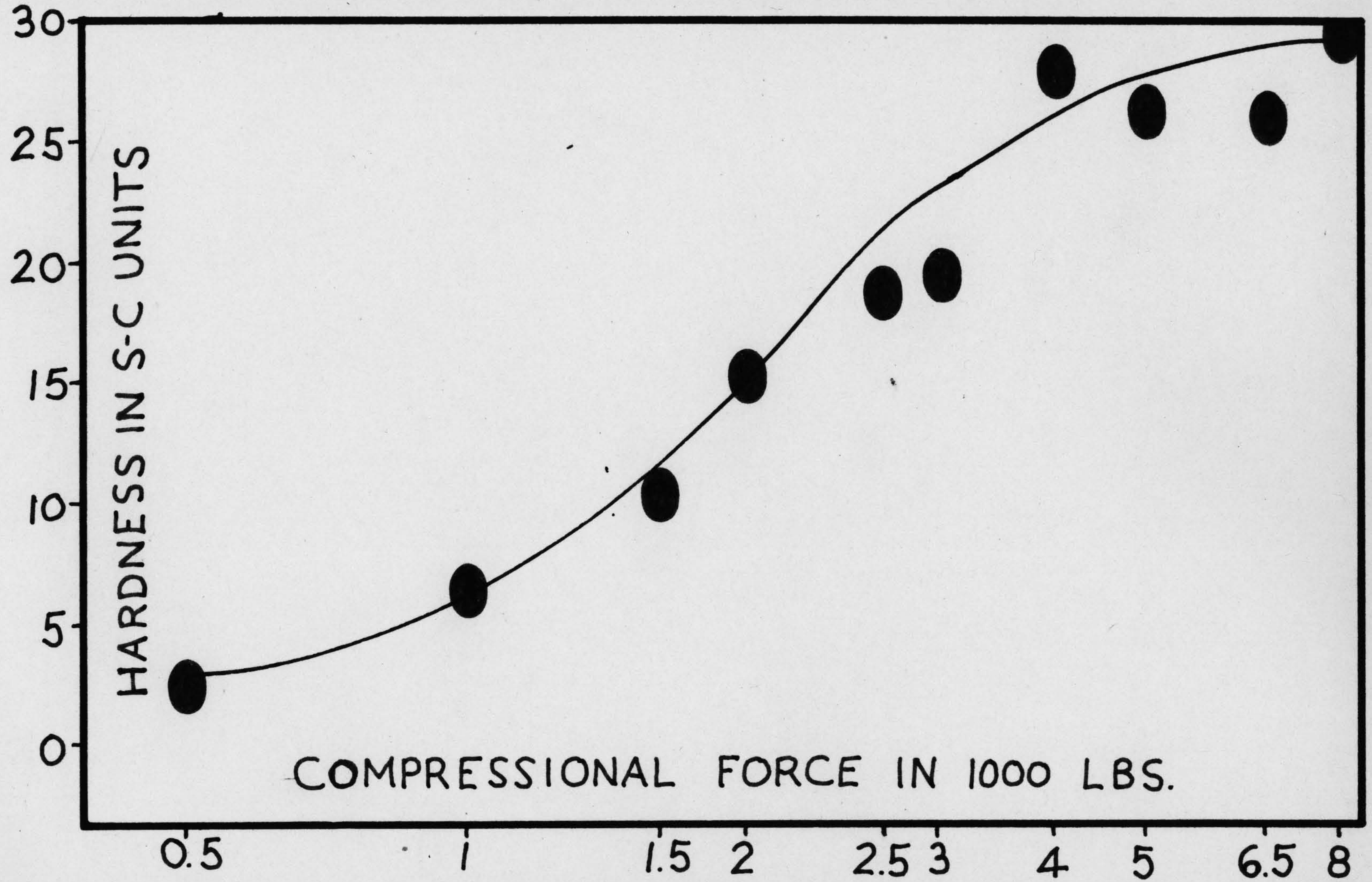


FIG. 43 CMCA 15%

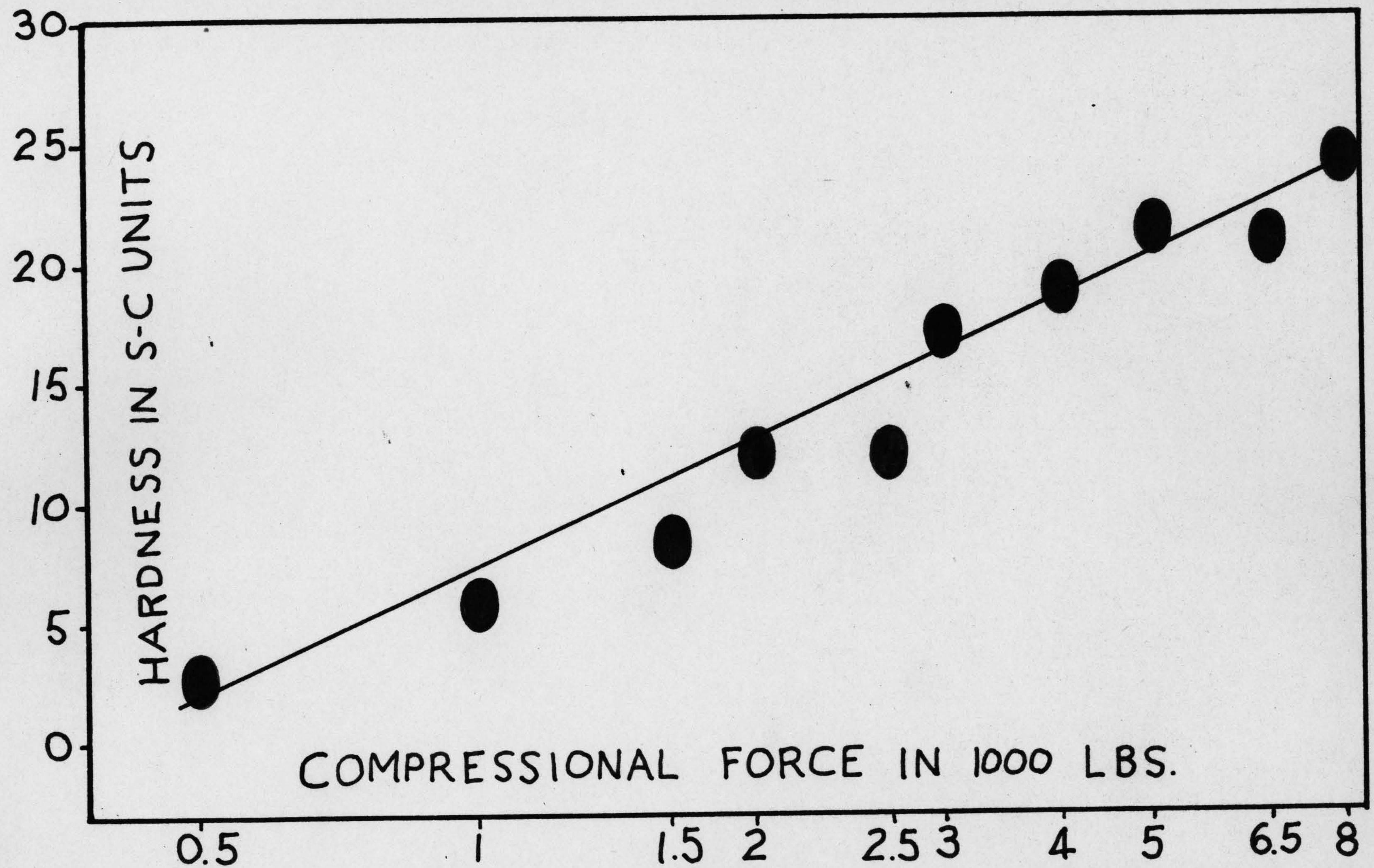


FIG. 44 CMCA 30 %

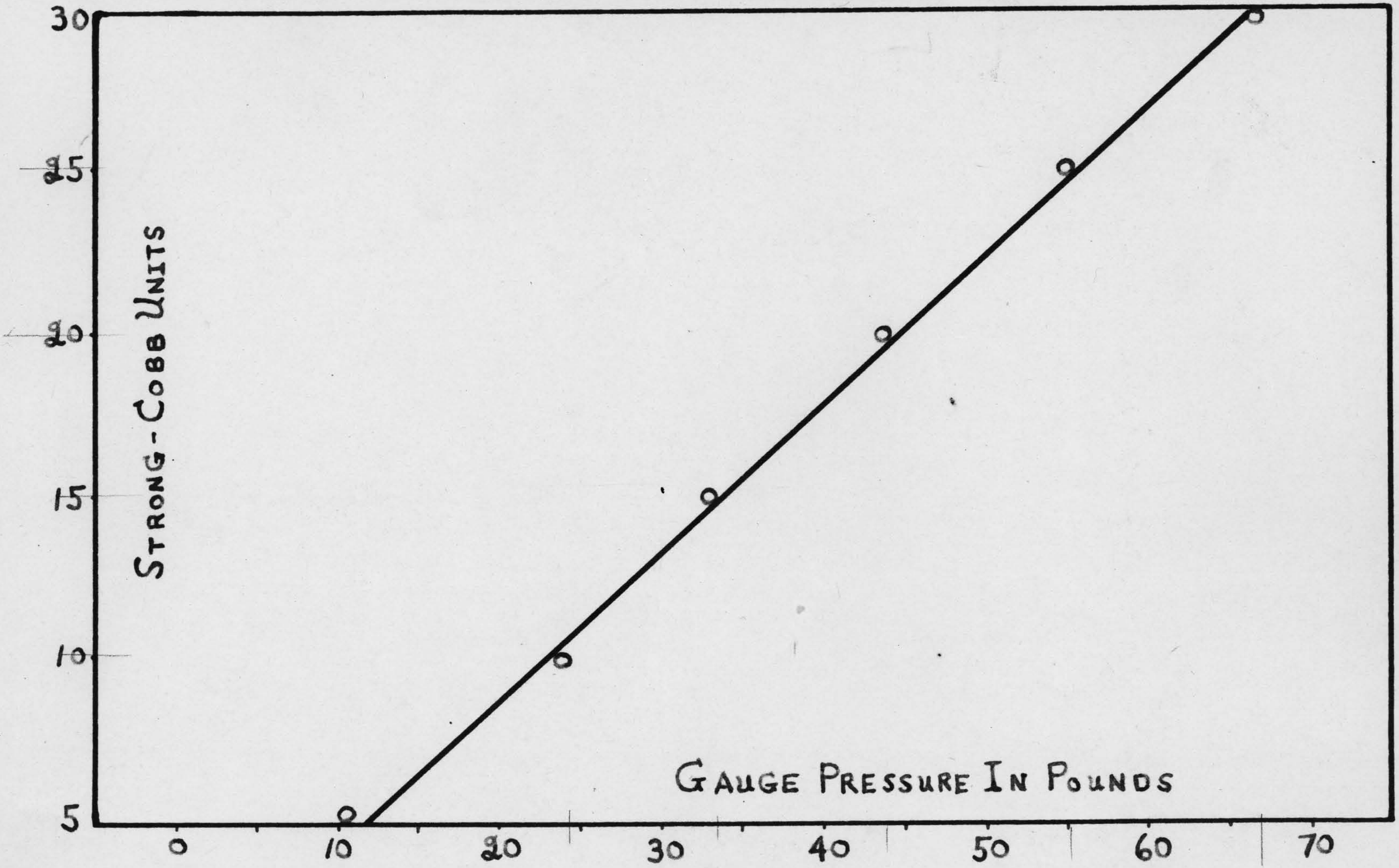


Figure 45

Graph shows relationship of the units of the Strong. Cobb Hardness

Tester to gauge pressure.

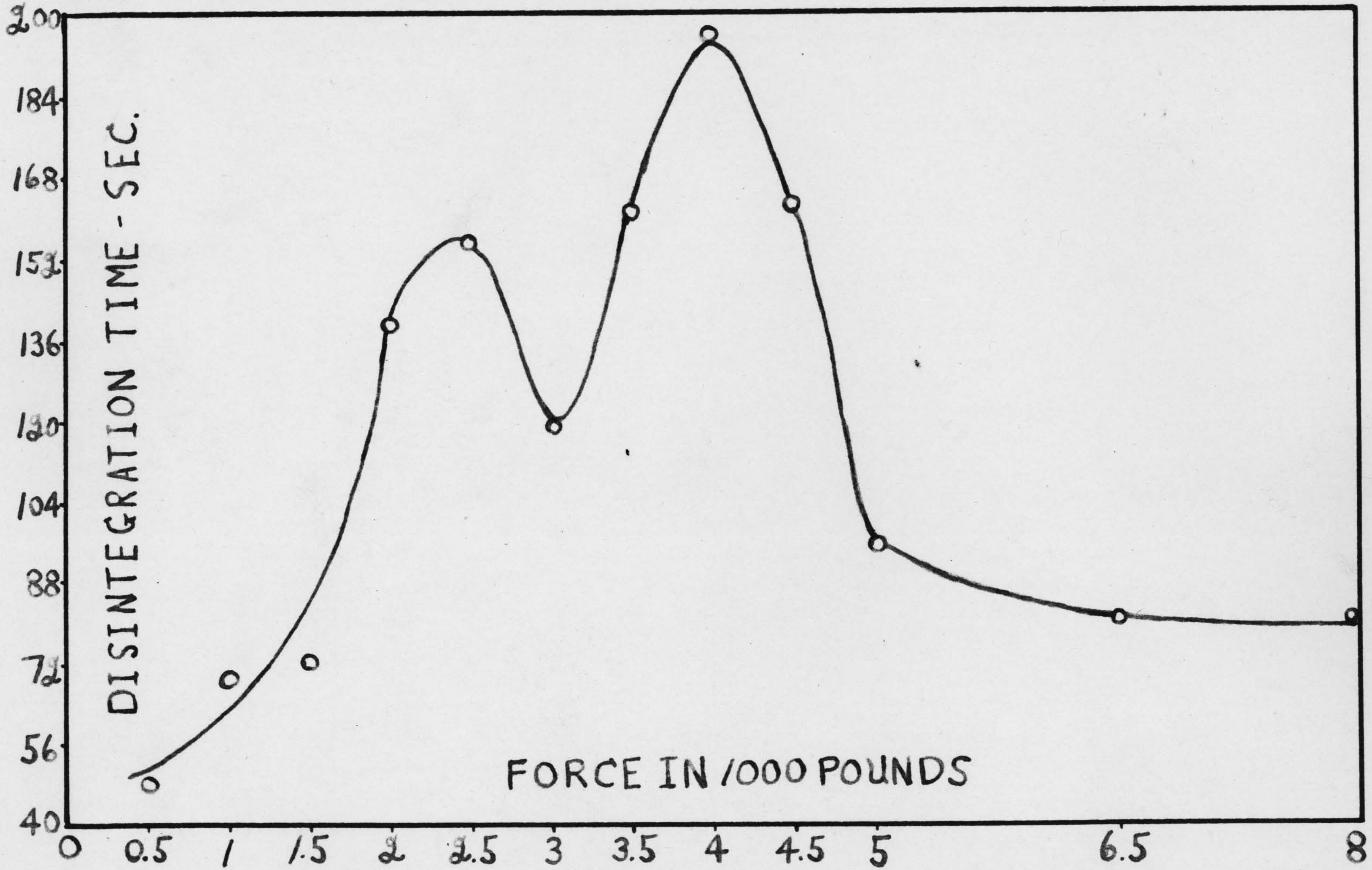


Figure 46. Disintegration time vs. compressional force graph of sulfathiazole tablets containing 4% CMCA as disintegrant.

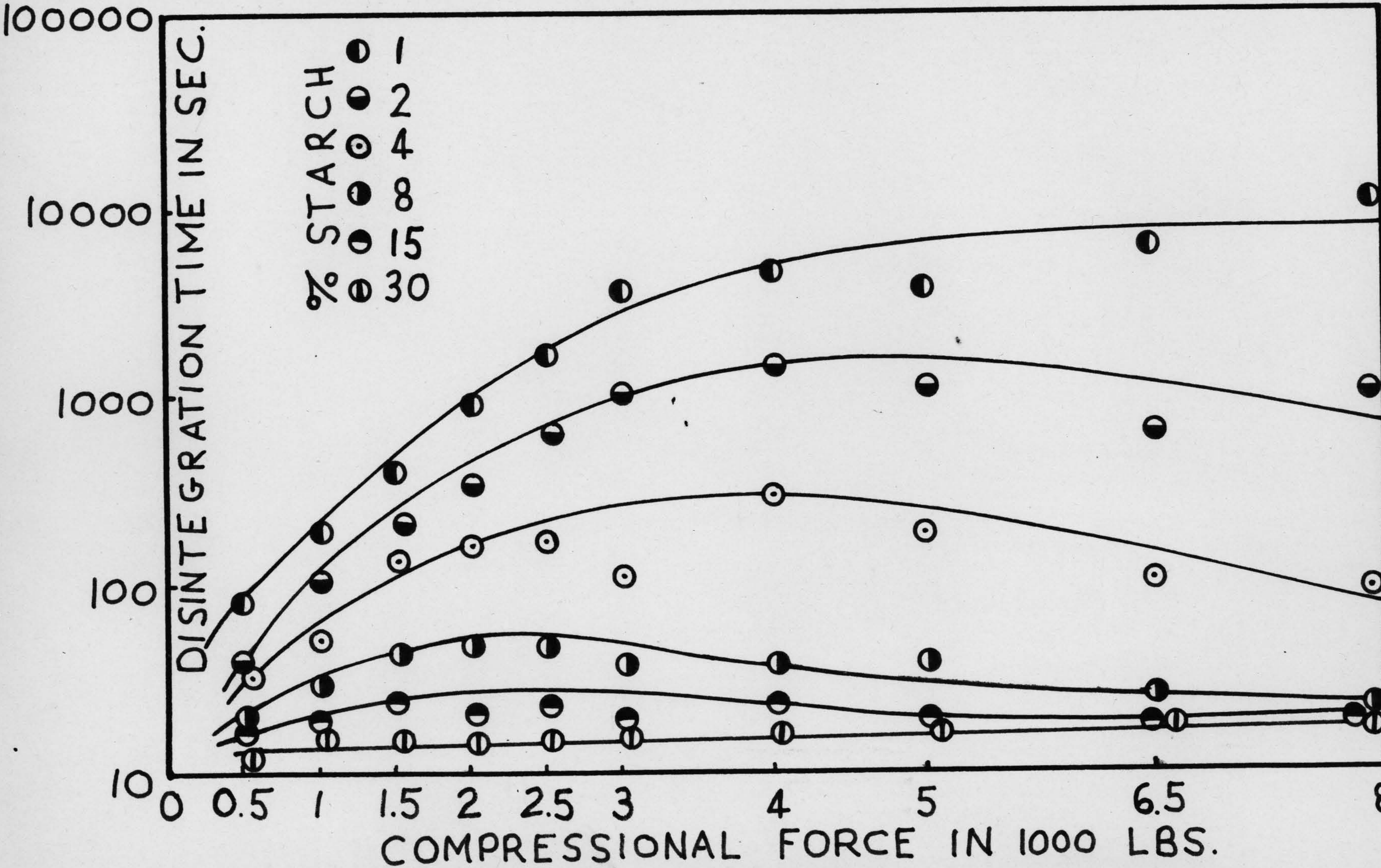


Figure 47. The effect of compressional force on disintegration time of sulfathiazole tablets containing various amounts of starch as disintegrant.

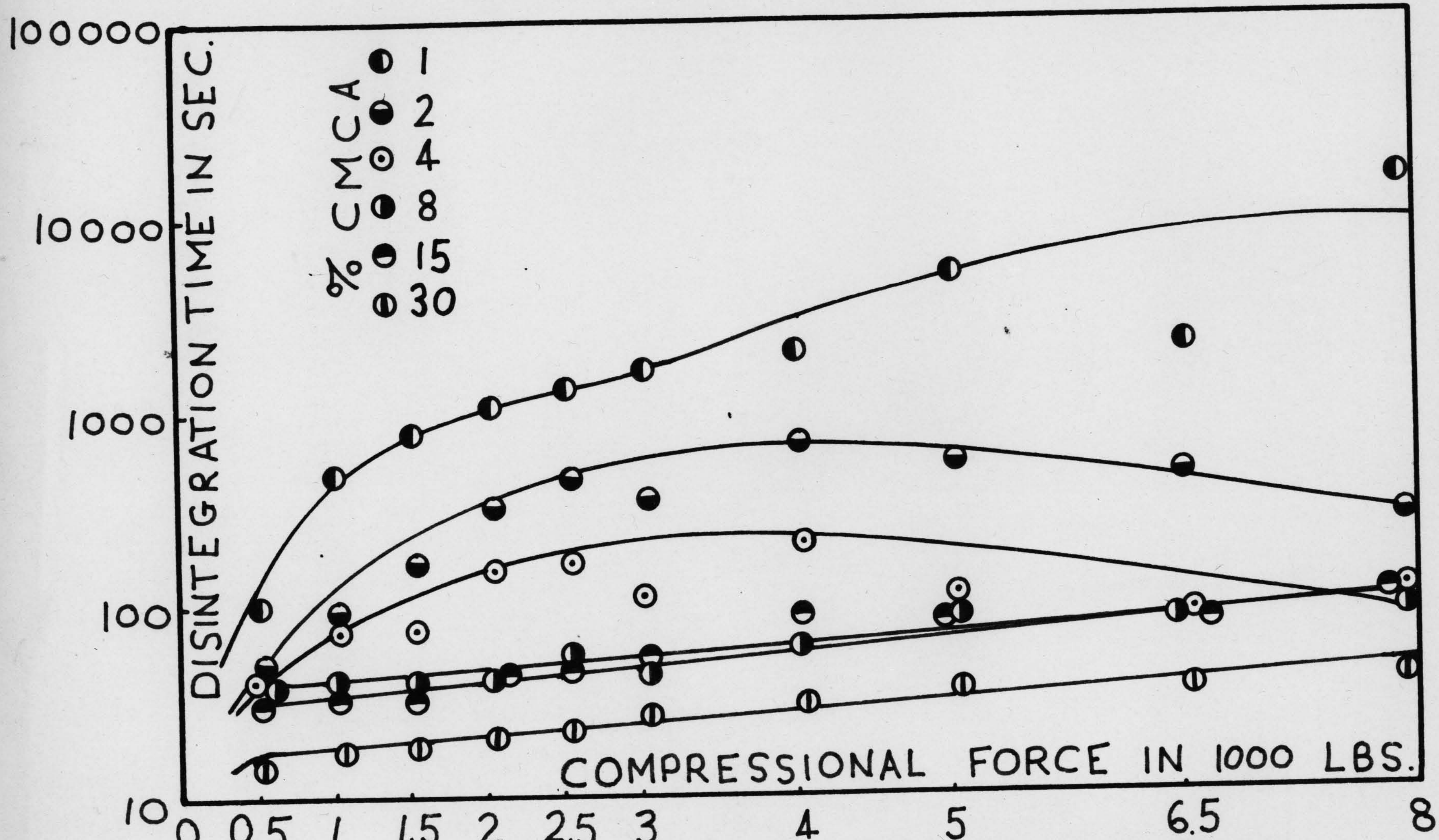


Figure 48. The effect of compressional force on disintegration time of sulfathiazole tablets containing various amounts of CMCA as disintegrant.

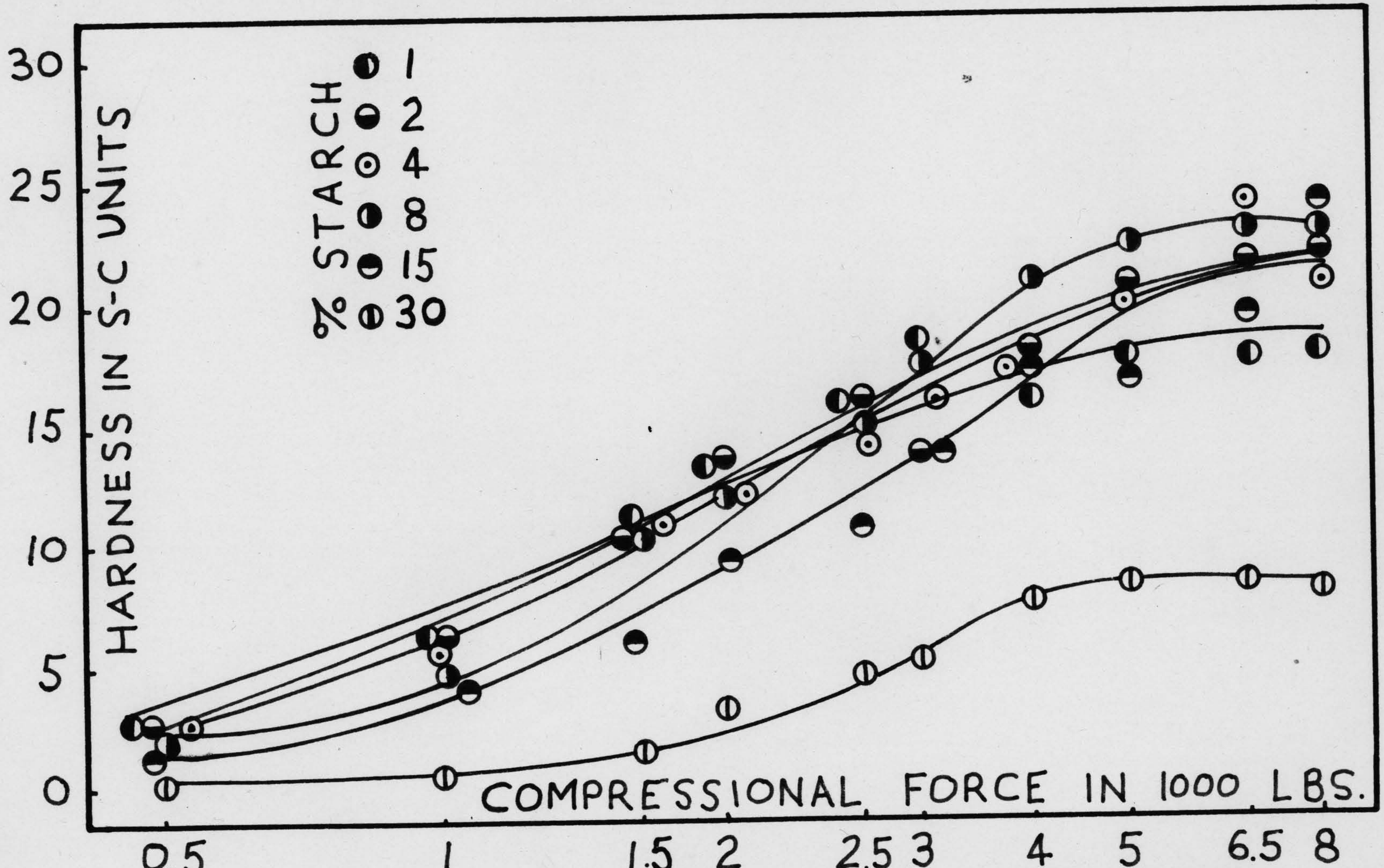


Figure 49. The effect of compressional force on hardness of sulfathiazole tablets containing various amounts of starch as disintegrant.

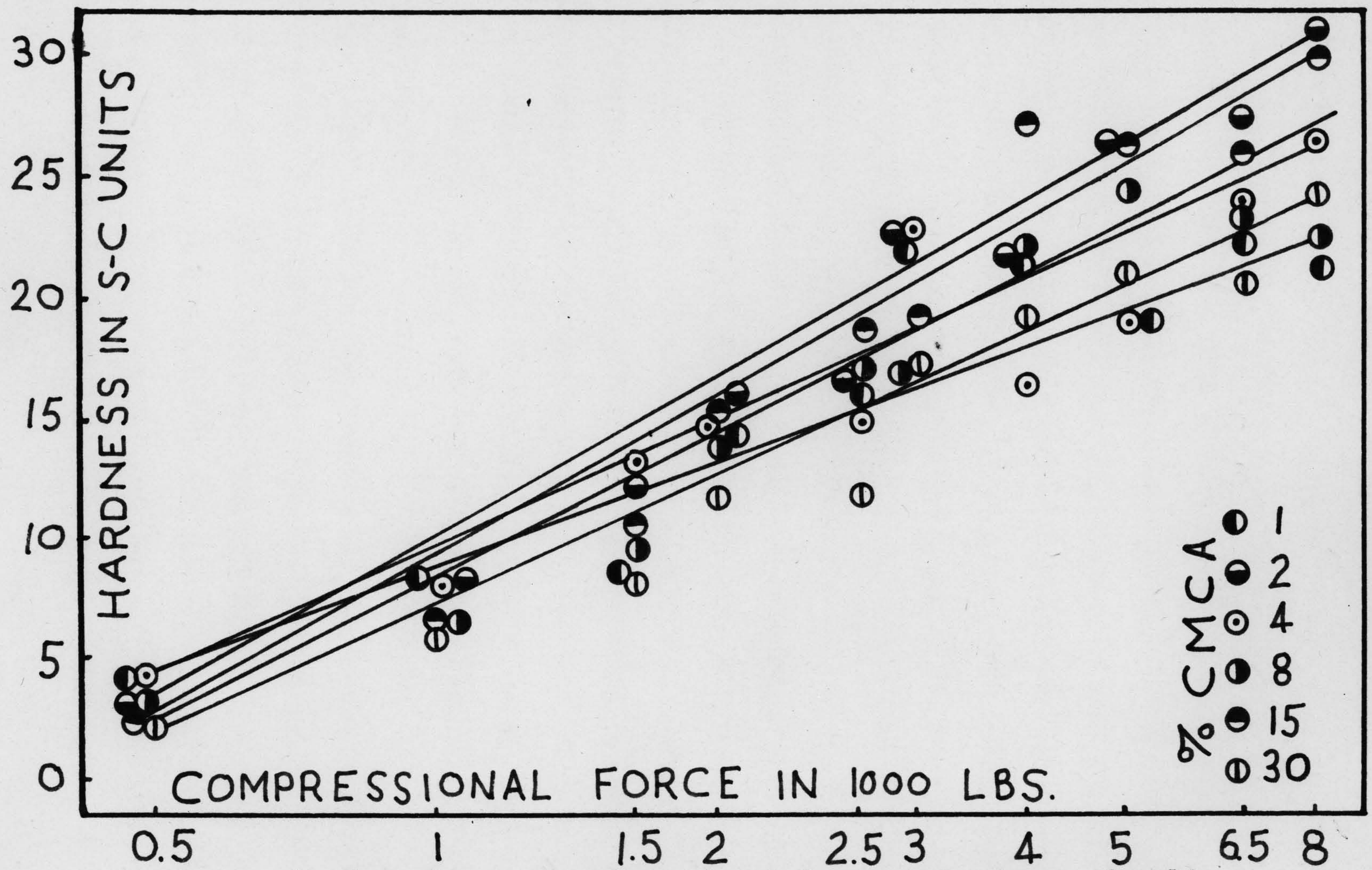


Figure 50. The effect of compressional force on hardness of sulfathiazole tablets containing various amounts of CMCA as disintegrant.

DISCUSSION OF RESULTS

The graphs may be conveniently grouped as follows for purposes of discussion:

1. Figures 1-12: Observation of the log disintegration time vs. compressional force graphs indicates increased disintegration time as the compressional force used to make the tablets is increased. In some cases, especially with 8% starch (Figure 4) and 4% CMCA (Figure 9), the curves descend after rising showing that the disintegration times at 8000 pounds force were approximately equal to those at 500 pounds; maxima are seen to lie between 1500 and 4000 pounds force. For 30% starch the times are so short that a straight line with only a very slight upward slope can be drawn.

2. Figures 13-22: Observation of the log disintegration time vs. log percent starch graphs indicates strictly linear relationships of these coordinates in the lower compressional force range, the disintegration times decreasing greatly as the percentage of starch is increased. The relationships as the compressional forces are increased from 3000 toward 8000 pounds are still nearly linear, and the curves rise steeply as did the straight lines.

3. Figures 23-32: The lines relating the log percent of CMCA to the log disintegration time are not nearly as straight as with the starch group just mentioned above. The time of disintegration decreases greatly as the percentage of CMCA increases, yet here there is a tapering or leveling off as the CMCA concentration in the tablets reaches 8, 15, and 30%. Figures 24-29 illustrate this well. As the compressional forces are increased

to the 5000-8000 range, there is little difference between the disintegration times of the tablets containing 4, 8, 15, and 30% CMCA. Figures 30-32 bear this out.

4. Figures 33-38: The relationships found between hardness and the log of compressional force are the following: Hardness increases linearly and quite rapidly with an increase in force with starch concentrations of 1-4%. As the concentration of starch reaches 8% and 15%, leveling off is noted. This is best exemplified by Figure 38 (30% starch) where hardness increases very little with an increase in compressional force. This is to be expected since the large proportion of dry starch powder causes the poor compressibility.

5. Figures 39-44: These curves are similar to those mentioned above except that the leveling off is not noted. All the curves are linear or nearly so. Since CMCA was granulated with the sulfathiazole powder and was not added as a powder after granulation, compressibility and hence hardness was maintained throughout, even at the 30% concentration.

6. Figures 47-50: Figures 47 and 48 combine Figures 1-6 and 7-12, respectively. As the amount of disintegrant increases, disintegration times become shorter through the whole range of compressional forces. The graphs also illustrate this effect at any particular compressional force if read vertically. At a concentration of 30% disintegrant it is observed that disintegration time is essentially unaffected by compressional force, all the tablets having the same time of disintegration. Figures 49 and 50 combine Figures 33-38 and 39-44, respectively. As compressional force increases, hardness increases at each

disintegrant concentration. With the exception of the very soft tablets containing 30% starch, it is observed that hardness increases independently of the amount of disintegrant present and is a function only of the compressional force.

7. Figure 46: The graph of disintegration time vs. compressional force of sulfathiazole tablets containing 4% CMCA is shown only to call attention to the fact that a regular pattern was formed as the series of disintegration time vs. force graphs were plotted nonlogarithmically. For this graph two additional points at 3500 and 4500 pounds were determined. The other graphs in the series (not shown here) varied from essentially straight lines to curves with one or two maxima; the graph shown exemplifies the latter. Further investigation and analysis is needed before any postulations or conclusions are warranted here.

The granulation containing 60% dry starch was not found amenable to compression into tablets even with high compressional forces.

CONCLUSIONS

This study indicates that CMCA compares favorably to starch as a disintegrating agent; the one causing faster tablet disintegration than the other in some instances and vice versa, as may be noted by comparing the data of Tables II and III.

CMCA also has three distinct advantages over starch:

1. CMCA-sulfathiazole granulation drying times are much shorter. The CMCA granulations were dry in two hours whereas the starch-sulfathiazole granulation was not found to be dry after this period of time.

2. CMCA can be mixed with other powders in the tablet formulation before the binding paste is added. Since the disintegrant does not have to be added after the granulation process, an extra weighing and mixing step in the tablet manufacturing procedure is eliminated.

3. Sulfathiazole tablets employing CMCA as disintegrant and prepared at a given compressional force are harder than the corresponding tablets employing starch as disintegrant. Much of this increased hardness is no doubt due to the fact that no extra "fines" are added since CMCA is granulated with the other ingredients.

The long-standing empirical observations that tablets become harder as the compressional forces used to make them are increased and that disintegration times become shorter as the amount of disintegrant is increased, have been abundantly verified.

As the concentration of disintegrant approaches 30%, it is observed that disintegration time is essentially unaffected by compressional force, all the tablets having the same disintegration time.

The data here presented may also have value as a basis for predicting at least qualitative effects to be expected when the variables of compressional force and amount of disintegrant are changed. Other compounds may be studied similarly to determine if the conclusions drawn from this investigation are generally applicable.

Eventually exact knowledge of all static and dynamic factors concerning and affecting tablets may be found. Then tableting will cease to be an art and will become a science.

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