Wood Products, Corncob, and Cellulose as Tablet Disintegrating Agents

By TAGHI A. FAKOUHI, NORMAN F. BILLUPS,† and ROBERT W. SAGER

A comparative study of certain powdered wood products, corncob, and cellulose has been made for their tablet disintegrating properties. A brief description for preparing the powdered disintegrating agents from the natural products is given. The various disintegrating agents were incorporated into lactose granulations, compressed, and subsequently tested for tablet disintegration time. Powdered corncob was found to be superior to starch and the wood products as a tablet disintegrating agent. The results of the disintegrating action of powdered corncob proved to be reproducible. Powdered redwood bark was as good as starch but not as effective as powdered corncob. The three physically distinctive layers of corncob—chaff, woody substance, and pith—were separated and incorporated in lactose tablets as disintegrating agents. Significant differences were seen among the disintegration times produced by the three layers of corncob. The pith showed superiority over the chaff and woody portion. A series of tests was conducted to study the separate and combination effects of cellulose and starch—the two main constituents of corncob—on tablet disintegration. Cellulose was found to be a better tablet disintegrating agent than starch. The combination of cellulose and starch indicated better results than the separate action of either agent alone. The possible mechanism of action for tablet disintegration is discussed.

THE IMPORTANCE of proper tablet disintegration cannot be overemphasized. To be effective, it is necessary for the tablet to break apart within a desirable period of time so that the medication may be absorbed. To accomplish this, a substance is added to the tablet granulation that will react when brought into contact with fluids and cause the tablet to break apart. Such a substance is termed a disintegrating agent. Disintegrating agents generally fall into three classes, according to their mechanism of action: (*a*) agents which react with moisture to constitute a foam, (*b*) effervescent substances which react with moisture to form a gas, (*c*) substances which react with moisture and swell. Those of the "absorb moisture and swell" type are by far the most commonly employed in research and industry today (1–8), and the present study is confined to this group.

Disintegration time is a function of many factors (4): (*a*) the particular characteristics of the tablet machine, (*b*) the basic formula used in preparing the granules, (*c*) the size, shape, weight, hardness, and age of the tablet, (*d*) the particle size of the medicament, and (*e*) the method of measuring tablet disintegration.

In addition to these variables Ward and Trachtenberg have included (9): (*f*) the moisture content of the granules, (*g*) the particle size of the granules, and (*h*) the particle size of the disintegrants.

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In this study each of these factors was held constant or minimized to reduce experimental error.

Billups and Cooper (2) introduced wood flour and powdered wood bark as possible tablet disintegrating agents. In an attempt to continue their work, this research was originally based on testing a large number of wood products for their tablet disintegrating effects. It was during this phase of the research that powdered corncob, one of the agents included in the preliminary study, produced significantly rapid tablet disintegration times. Because of the superior results obtained with powdered corncob, intensive study was conducted with this substance.

This paper presents the results of a comparative study of several wood products, powdered corncob, and cellulose for their potential tablet disintegrating properties. These products were compared with cornstarch, the classical and still one of the best tablet disintegrating agents known. The objectives of the study were to discover new products with superior tablet disintegrating ability and to propose a mechanism of action for the disintegrating agents tested.

EXPERIMENTAL

Selection of Disintegrating Agents.—The selection of various disintegrating agents and the reason for their selection was of primary importance.

Cornstarch was chosen because of its popularity and extensive use. Many authorities still consider this classical agent as the best tablet disintegrating agent in use today (2, 10, 11). A U.S.P. grade of cornstarch was employed in this study.

Powdered redwood bark was included as a new

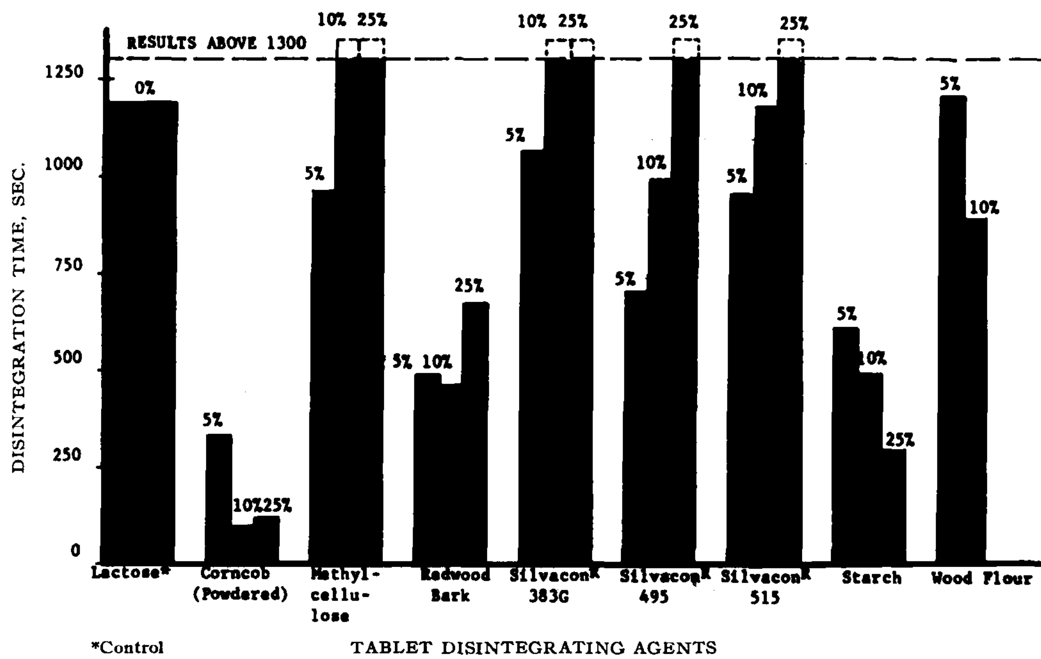

Fig. 1.—*Disintegration times of tablets containing various disintegrating agents.*

agent to be tested for tablet disintegrating properties. This agent is the powdered bark from the coniferous timber tree (*Sequoia sempervireus*) of California, found only on the Coast Range. The powdered bark was prepared by passing bark specimens, dried 2 months at 80° F., through a Wiley mill until the powder was sufficiently fine to pass through a No. 40 sieve.

Wood flour (2) was used in this study to compare with other wood products. Wood flour is the powdered inner wood from Douglas fir (*Pseudotsuga taxifolia*), a tall evergreen tree of the western United States, often known in the lumber trade as red fir or Oregon pine. The wood flour was obtained locally from the Forest Products Research Laboratories, Corvallis, Oreg.

Silvacon[1] is powdered bark from Douglas fir species. The three basic types of Silvacon are pliable, spongy flakes 383-G, tough needle-like fibers 515, and fine amorphous powders 495. Billups and Cooper used only Silvacon 383-G in their study. All three forms of Silvacon were used in this research. Silvacon products are natural plastics containing the plasticizers, cellulose, and resins found in Douglas fir bark (12).

Methylcellulose was included for comparison with the wood products. Methocel,[2] having a viscosity of 4000 cps. was used.

Powdered corncob, *Zea mays* Linné (Fam. *Gramineae*), was chosen because of its similarity to the other woody products. Corncob, considered a waste product of corn, is used only in small quantities to feed cattle, fertilize land, act as a fuel in remote farming areas, and form chemical by products. The corncob used in this study was obtained locally from the Department of Farm Crops, Oregon State University. A 50-pound randomized sample of corncob was dried for 2 months at 80° F. and powdered with a Wiley mill. Both field corncob and popcorncob were used in the preliminary tests, and since there was an indication that field corncob was slightly better as a disintegrating agent than popcorncob, the former was used throughout this study.

Lactose, a substance with no apparent tablet disintegrating property, was used as the control. Lactose is regarded as a good diluent or inert base for many tablet preparations and was used as a diluent throughout this work.

Procedure for Manufacture of Tablets.—The method of wet granulation was used to manufacture all of the tablets in this study. Tablets were prepared containing lactose as the diluent, 1% magnesium stearate as the lubricant, and syrup U.S.P. as the granulating agent. The finished granulation was separated into "fines" or particles smaller than No. 40 mesh[3] and "granules" or larger particles ranging between No. 14 and No. 40 mesh. According to the amount of disintegrating agent used, an appropriate quantity of "fines" was replaced in the granulation so that all tablets were derived from mixes containing similar proportions of "fines" and "granular" material. A ratio of 30% "fines" to 70% "granules" was used throughout this study. Since the disintegrating agents were added as "fines" to the finished granulation, they were never in contact with moisture during tablet manufacture.

The tablets were compressed on a Stokes model B-2 rotary tablet machine using $^3/_8$-in. diam. punches and dies. Each tablet batch consisted of 500 tablets. An average theoretical weight of 500 ± 10 mg. was maintained using an exact weight shadow-

[1] Marketed by Weyerhauser Timber Co.
[2] Marketed by Dow Chemical Co.
[3] All of the sieves employed in this study compiled with the standards specified in the U.S.P.

graph calibrated periodically with a torsion balance. This average tablet weight was obtained by selecting five samples from each 500-tablet batch. Each sample taken consisted of ten tablets.

Measurement of Hardness and Disintegration Time.—Tablet hardness was determined on a Strong-Cobb hardness tester for ten tablets randomly selected from each tablet batch. Preliminary studies indicated that a tablet hardness of 10 ± 1 Strong-Cobb units gave the least variation in tablet disintegration time and was used unless otherwise specified. Tablets in this hardness range were found to be more resistant to breaking and chipping when subjected to friability tests simulating the most extreme handling conditions. Finally, a hard tablet was felt to reveal better the disintegra ing ab lity of the agents selected for study.

The disintegration tests were conducted on a Gershberg-Stoll (13) type disintegration apparatus in accordance with the official U.S.P. method (14). The reported disintegration time for each batch of tablets represents an average time for 12 tablets. Distilled water was used as the disintegration medium.

RESULTS AND DISCUSSION

The research was divided into three parts: the comparative disintegration tests of wood products and other tablet disintegrating agents, the disintegrating effects of powdered corncob, and the role of cellulose in the disintegrating activity of powdered corncob.

Comparative Disintegration Tests.—The first phase of this research concerned a comparative study of the wood products and other agents for their tablet disintegrating ability. Accordingly, each of the selected agents was incorporated into a

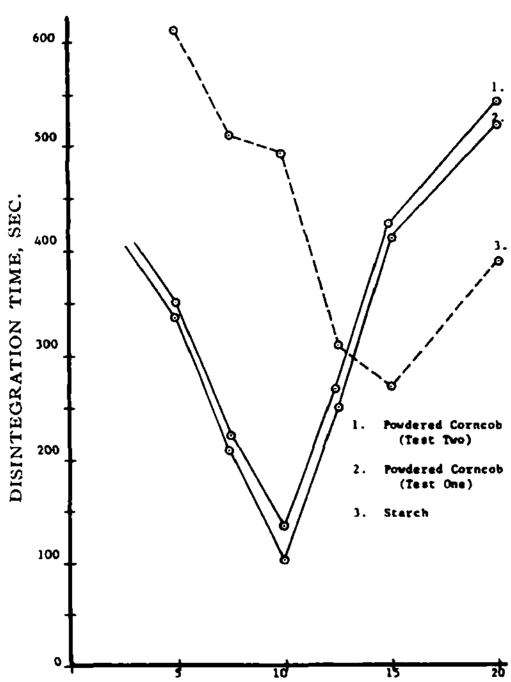

Fig. 2.—Comparison of corncob and starch as disintegrating agents in lactose tablets.

TABLE I.—EFFECT OF PARTICLE SIZE OF POWDERED CORNCOB ON TABLET DISINTEGRATION TIME

Particle Size, U.S.P. Mesh No.	Time Required to Disintegrate (Av., in sec., for 12 tablets)
No. 60	410
No. 40	95
No. 20	530
No. 14[a]	—

[a] Difficulties encountered in manufacture of tablets.

standardized lactose granulation in 5, 10, and 25% concentrations. The tablets were compressed and tested for disintegration time immediately after manufacture. The results (summarized in Fig. 1) indicate a significant variation in disintegration time among the various agents. Powdered corncob had the shortest disintegration time of all agents tested. All concentrations of corncob gave better results than starch. A 10% concentration of powdered corncob was the best disintegrating agent of the entire test series. Concentrations of 10% wood flour, 5 and 10% Silvacon and 5, 10, and 25% redwood bark gave improved disintegration times compared to the control. Methylcellulose and the Silvacon products in higher percentages gave longer disintegration times than the control. The use of these substances as disintegrating agents is questionable. Similar results for Silvacon, wood flour, and methylcellulose have been reported (2).

Normally it would be expected that the 10% concentration would produce a faster disintegration time than the 5% concentration. This was evidenced with corncob, starch, and wood flour. A reversal of this normality was observed with methylcellulose, redwood bark, and the Silvacon products. Billups and Cooper (2) have suggested that these substances possessed adhesive or binding properties which retard disintegration as the concentration is increased. They indicate that this effect may be because of the tendency of these substances to form adhesive gels when hydrated. This suggests that there may be an optimum or maximum quantity of these substances beyond which tablet disintegration will be retarded.

Disintegrating Effects of Powdered Corncob.—The second phase of this study concerned the disintegrating action of powdered corncob. A second lactose granulation was prepared to test the reproducibility of the first test series. A comparison of these results to those of earlier tests is shown in Fig. 2. From these data, no significant difference was indicated between the two tests employing powdered corncob, but significant differences were noted between powdered corncob, lactose, and starch.

Once the reproducibility of corncob had been established, a series of tests was conducted to determine the optimum particle size of powdered corncob. Tablets were made using a lactose granulation with 10% powdered corncob in No. 60, 40, 20, and 14-mesh sieves. All these tablets were readily compressed except the No. 14 mesh. The tablets in this batch were soft because of the large particle size of the powdered corncob and were easily broken before they could be subjected to the disintegration test. Results of these tests are reported in Table I. Since particles of No. 40 mesh produced the fastest

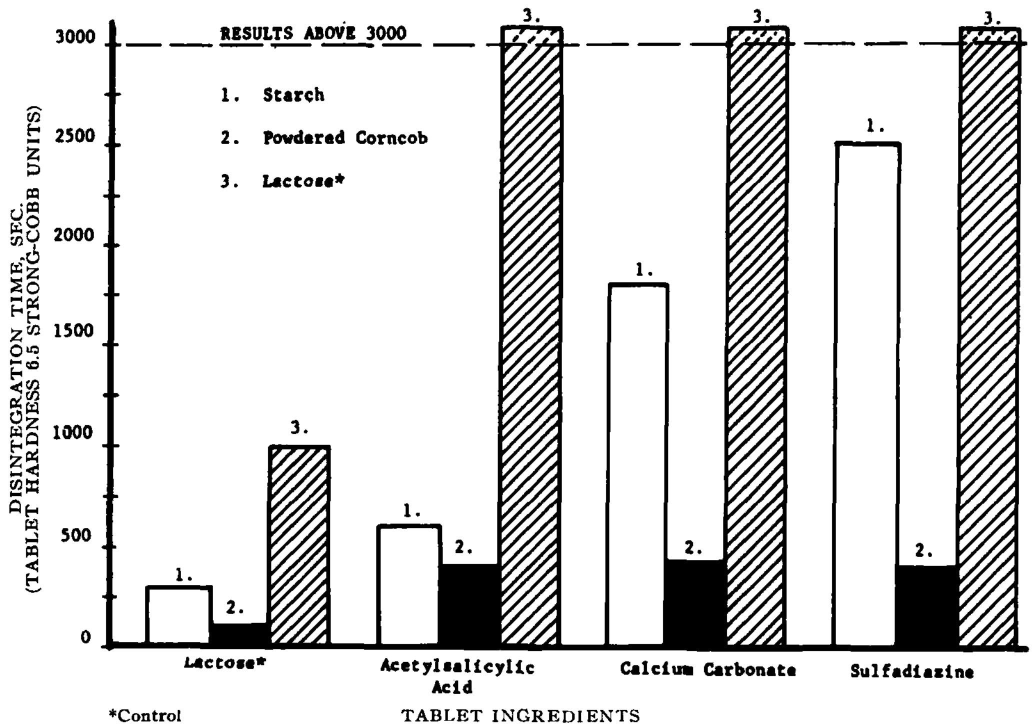

Fig. 3.—Comparison of corncob and starch as disintegrating agents in tablets containing acetylsalicylic acid, calcium carbonate, or sulfadiazine.

tablet disintegration times, this size was employed throughout the remainder of this research.

Thus far, powdered corncob had shown favorable results when used as a disintegrating agent in lactose tablets. Although these results are significant, it remained to be determined if the same results would be obtained in tablets containing active ingredients. Accordingly, powdered corncob was incorporated into granulations of acetylsalicylic acid, calcium carbonate, and sulfadiazine. Lactose was used as the control. A summary of these results is reported in Fig. 3. From these data powdered corncob appeared to be superior to starch in all tablets tested.

Disintegration Effects of Different Parts of Corncob.—The physical appearance of corncob reveals that it is composed of three distinctive parts: the inner area or pith, the middle section or woody substance, and the outer layer or chaff. Burke (15) separated the three layers of corncob and analyzed each layer both quantitatively and qualitatively. His findings, reported in Tables II and III, indicate that starch and cellulose are the two major constituents of corncob. These constituents were further found to vary among each of the three layers. Because of this variability, it was considered necessary to test each of the three parts for tablet disintegrability. The chaff was scraped off with a grater, the pith was bored out with an electric drill, and the remainder of the corncob was ground in a Wiley mill to be used as the wood substance. Each of the separated parts was ground to a fine powder and passed through a No. 40-mesh sieve. The parts were then incorporated into lactose granulations and manufactured into finished tablets. Results shown in Table IV indicate significant differences among the

Table II.—Cellulose Content of Corncob and Its Parts[a]

	As Analyzed, %	Moisture Free, %
Entire corncob[b]	25.15	26.37
Chaff	26.39	28.28
Woody part	25.89	27.30
Pith	33.45	35.85

[a] Burke, G. W., "Some Analytical Data on Corncob," (15), p. 3. [b] The entire corncob in terms of average percentages is composed of chaff 24.97, woody part 73.36, and pith 1.67.

Table III.—Starch Content of Corncob and Its Parts[a]

	Sugar as Dextrose, Gm.	Calcd. to Starch, %
Entire corncob[b]	0.3794	34.15
Chaff	0.3868	34.80
Woody part	0.3828	34.45
Pith	0.3366	30.29

[a] Burke, G. W., "Some Analytical Data on Corncob," (15), p. 3. [b] The entire corncob, in terms of average percentages, is composed of chaff 24.97, woody part 73.36, and pith 1.67.

tablet disintegration times when using different parts of corncob. The three parts of corncob in order of decreasing disintegrating action are pith, woody substance, and chaff. These results raised the question of whether the disintegrating action of powdered corncob or its parts was due solely to the activity of its starch content. It was evident that cellulose must have played an active part since the pith, with the lowest starch content and the highest

TABLE IV.—TABLET DISINTEGRATING ACTIVITY OF CORNCOB AND ITS PARTS

Part(s) Used	Disintegration Time, Av. 12 tablets, sec. Hardness 6.5 Strong-Cobb Units	Hardness 10 Strong-Cobb Units
Entire corncob	95	145
Chaff	291	577
Woody part	56	248
Pith	10	87

TABLE V.—TABLET DISINTEGRATION STUDY OF CELLULOSE *vs.* STARCH

Disintegrant	Disintegration Time, Av. 12 tablets, sec. Hardness 6.5 Strong-Cobb Units	Hardness 10 Strong-Cobb Units
Cellulose	123	245
Cornstarch	300	495
1:1 Parts of cellulose + starch	86	110

cellulose content of all parts, showed the best tablet disintegration time by a large margin.

Role of Cellulose in the Disintegrating Activity of Powdered Corncob.—The third phase of this study was conducted to find the role that cellulose played in the disintegrating activity of powdered corncob. The results from previous tests indicated that cellulose was partially or fully responsible for the disintegrating activity of corncob. To test cellulose as a tablet disintegrating agent, three batches of lactose tablets containing cellulose,[4] starch, and a combination of cellulose and starch were manufactured. Granulations containing 10% starch, 10% cellulose, and a 10% mixture of equal parts of cellulose and cornstarch were incorporated into three tablet formulations. The disintegration times for these three batches are summarized in Table V. These data indicate that cellulose has better disintegrating action than cornstarch. It further shows that a combination of equal parts of cornstarch and cellulose is superior to either of the separate agents. Thus a mutual potentiating effect is shown on the disintegrating action of starch and cellulose. In an earlier study, Crisafi and Becker (16) noticed the same potentiating effect of starch on the disintegrating action of powdered sponge. The potentiating effect of cellulose and starch could be a reasonable explanation for the improved tablet disintegrating activity of powdered corncob over either agent alone.

Mechanism of Disintegrating Action of Powdered Corncob.—The mechanism through which powdered corncob, starch, or cellulose accomplish their disintegrating action is most likely the same. These agents appear to swell when in contact with water and as a result are capable of rupturing tablets in which they are incorporated. Since moisture absorption is an important factor in this action, tests were conducted on powdered corncob, starch, cellulose, a combination of equal parts of starch and cellulose, and lactose (control) to determine the comparative rate of moisture absorption by these agents. One-gram samples of the materials were

[4] Stanocel brand of microcrystalline cellulose supplied by the Stanley Drug Co., Portland, Ore., was used in this study.

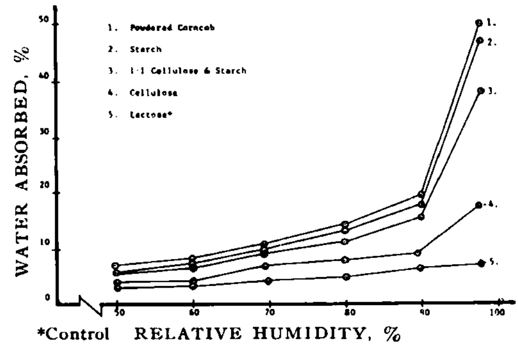

Fig. 4.—Absorptive properties of various disintegrating agents.

dried to constant weight at 120 °F. and then placed in a humidity chamber for a 24-hour period. Using a Vapor-Temp[5] humidity chamber the weight gain was calculated by reweighing each sample after the 24-hour interval. A summary of these tests is reported in Fig 4. These results indicate a slight negative correlation between water absorption and tablet disintegration time. Generally, the disintegrating agents which absorbed the most water were those which, when incorporated into tablets, required the shortest times for tablet disintegration.

It is likely that "swellability" is ultimately the most important single factor in tablet disintegration. In order to swell, however, an agent must first absorb considerable amounts of moisture (17). Figure 4 indicates that powdered corncob, starch, and cellulose each absorbed significant amounts of moisture. Visual examination of these agents indicated considerable swelling compared to the control. Accordingly, each of these agents gave superior tablet disintegration times compared to the control.

CONCLUSIONS

1. Four new substances (powdered corncob, powdered redwood bark, Silvacon 495, and Silvacon 515) have been tested as tablet disintegrating agents and compared to other agents previously reported in the literature. Powdered corncob was shown to be a superior disintegrating agent to starch and the other substances tested. In 5 and 10% concentrations powdered redwood bark was shown to be as good as starch. The Silvacon products were better than the control in 5 and 10% concentrations but not as effective as starch.
2. The disintegrating action of corncob was superior to that of starch in tablets containing soluble, partially soluble, and insoluble material.
3. Results obtained with powdered corncob were reproducible in both placebo and ingredient-containing tablets.
4. The three physically distinct layers of corncob (chaff, woody substance, and pith) were shown to produce significantly different disintegration times. Pith showed superiority over the other two parts.
5. Cellulose was found to be a better tablet disintegrating agent than cornstarch in lactose tablets.
6. Separate and combined effects of starch and cellulose as tablet disintegrating agents were studied.

[5] Marketed by Blue M Electric Co., Blue Island, Ill.

The combined action was shown to be superior to the separate action of either agent alone. This indicates a potentiation effect between these two agents.

7. The mechanism of action through which powdered corncob, starch, and cellulose accomplish their disintegrating action is most likely the same. These agents swell when in contact with water and will rupture the tablets in which they are incorporated. To swell, however, it would appear that an agent must first absorb considerable amounts of moisture. Powdered corncob, starch, and cellulose-starch combinations were shown to absorb significant amounts of moisture. Cellulose absorbed less moisture than starch and corncob but more moisture than the control.

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Notes

Rapid Visual Assay for Penicillinase Concentrates

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Enzyme activity is measured by the time required to solubilize procaine penicillin G.

THE LITERATURE abounds with assay methods for enzyme penicillinase, but most are complicated and time consuming. Among these are the microbial assay of Bowman and Holdowsky (1) and various iodometric titrations (2–4). The manometric (5) and optical rotation (6) procedures are accurate but require special equipment. Pollock (7) suggested a rapid approximate assay based on the time required to decolorize a known quantity of iodine in the presence of sufficient penicillin substrate. Ghosh and Borkar (8) recently described an assay incorporating this idea.

A new and simple assay for penicillinase activity has been developed by using a different approach. Enzyme activity is measured by the time required to solubilize completely 300 mg. crystalline procaine penicillin G in pH 7.0 buffer solution. The procaine salt of penicillin G has a solubility in buffer of about 5 mg./ml.; but as quickly as the soluble portion is converted by the enzyme to penicilloic acid, more penicillin goes into solution until finally it is all dissolved.

No requirements of potency have been established for penicillinase concentrates, but for sterility testing of preparations containing penicillin (9) a solution of the enzyme should have at least 4000 Levy units per ml. One Levy unit of penicillinase inactivates 59.3 units (35.6 mcg. or 10^{-7} moles) of penicillin G in 1 hour when the substrate is in sufficient concentration to maintain a zero-order reaction. The test to be described can measure the penicillinase potency of solutions containing approximately 4000–40,000 Levy u./ml., and within this range the solubilization time is a linear function of the dose.

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EXPERIMENTAL

Reagents.—U.S.P. procaine penicillin G, Clark and Lubs 15% buffer, pH 7.0: potassium dihydrogen phosphate, 150 Gm.; 10 *N* sodium hydroxide, 47.9 ml., *q.s.* to 1 L. with distilled water. Distilled water. Penicillinase solutions. Equilibrate all reagents at 25° before use.

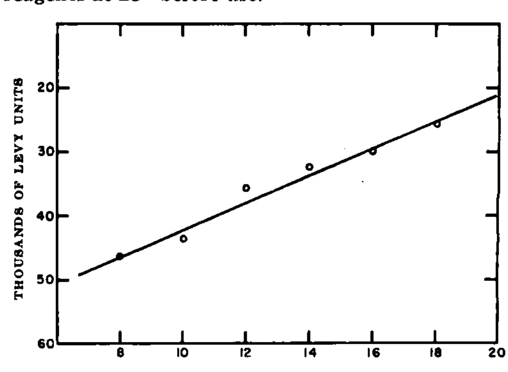

Fig. 1.—Solubilization time for 300 mg. procaine penicillin when tested with various amounts of penicillinase.