plasma (Table III) than in urine. A ratio of one-half to two-thirds was maintained in the urine for the first 6 hours after intramuscular injection while the drop in plasma bioassay accompanied a change in the ratio from one-third to zero.

When bile and urine were collected after intramuscular administration of nafcillin in a separate experiment, bile and urine maintained fairly high bioassay/radioassay ratios for the first 6 hours (the bioassay ranging from 32 to 100% of the radioassay) but plasma samples bioassayed 20% or less for the first 4 hours and *nil* at the sixth hour. By comparing the amounts of the drug excreted in bile (Table IV) with those finally appearing in feces (Fig. 3), a fair degree of reabsorption of nafcillin from gut is apparent.

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# Physics of Tablet Compression XIII

## Development of Die-Wall Pressure During Compression of Various Materials

By JOHN J. WINDHEUSER†, JAGDISH MISRA, STUART P. ERIKSEN, and TAKERU HIGUCHI

**A method for determining the pressure transmitted to the die wall during tablet compression is described. Basically, the method involves strain-gauge measurement of die expansion and the relation of this to the transmitted pressure. The pressure transmitting behavior of a number of compounds, both organic and inorganic, have been studied; some correlations between observed response and physical properties are suggested. Limited studies on the effect of the addition of a lubricant to the crystals are also reported. It was noted that change in the magnitude of transmission to the die wall was not a simple linear function of lubricant concentration.**

Earlier reports (1–6) of measurements of several variables involved during compression of pharmaceutical tablets did not attempt to determine the relative magnitude of the lateral forces developed during formation of compressed tablets on the die wall by various types of materials. Nelson (7), reporting earlier from these laboratories, proposed and tested a method for possible measurement of these forces but did not study the comparative behavior of different materials. Results of direct measurements carried out on a number of organic and inorganic substances by a relatively simple technique are presented in this communication.

The perpendicular force developed in a die cavity during tablet formation obviously is related to the flow characteristics of the compressed material. If the confined substance acted simply as a hydraulic fluid, the lateral pressure should be essentially equal to the compressional pressure. Compaction of any common granular solid, on the other hand, would lead to development of much lower sideward pressure—the extent of lowering being (in a sense) a measure of ease of lateral distortion or flow of the compressed material. This property would be reflected in the relative ease of ejection of the formed tablet and the moldability of the compacted mass. All this may depend on such

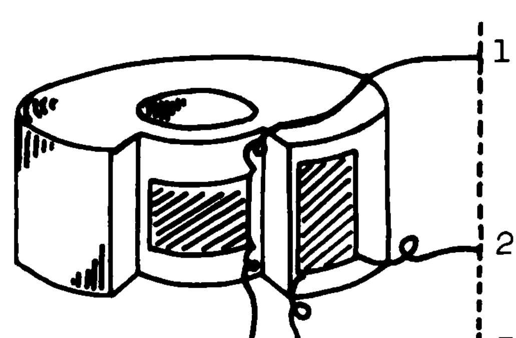


Fig. 1.—Standard steel die modified to accept strain gauges. Numbers refer to connections in circuit diagram in Fig. 2.

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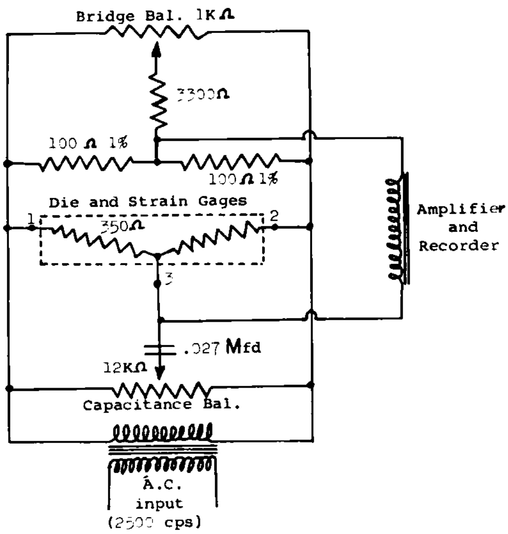


Fig. 2.—Wheatstone bridge arrangement of strain gauges for measurement of die response.

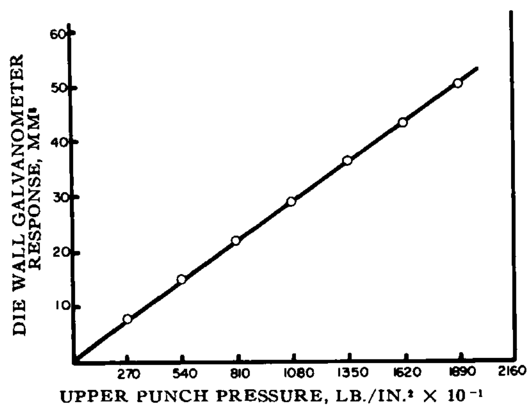


Fig. 3.—Typical calibration curve obtained for die-wall response as a function of applied pressure when using a rubber plug as the transmitting media.

factors as the hardness, shape, and/or the frictional properties of the crystals involved.

Data are presented for a number of halide salts, certain antacids, and a number of organic compounds. Of particular interest are results obtained on phenacetin, acetanilide, and stearic acids—all substances having leaf-like crystalline structure.

## EXPERIMENTAL

**Instrumentation.**—The apparatus used for compression of the tablets was a high force hydraulic press as previously described by Nelson (7). The force exerted by the press was measured with an electrical load cell. In these studies the force applied was measured on the moving upper punch operating against a fixed lower punch. The electrical response of the transducer was followed by a strain-gauge resistance bridge and recorded on one channel of a Sandborn dual-track magnetic oscillograph in the manner previously described (8). The force transmitted to the die wall was recorded simultaneously on the second channel of the recorder as described below. Punches used were $^3/_8$-inch flat faced; the die was adapted from a standard steel $^3/_8$-inch die for the Stokes model A-3 tablet machine.

The die was modified as shown in Fig. 1. A segment of the wall was ground out to increase the sensitivity of the system and to render the stress forces more parallel in the sensed area. Two strain gauges were mounted on the die wall, one normal and the other parallel to the die bore. The strain gauges formed a part of a Wheatstone bridge circuit as shown in Fig. 2. The gauge placed parallel to the die bore was introduced into the circuit to compensate for temperature changes during the compression cycle. The response of the strain gauges was measured and recorded on the Sanborn magnetic oscillograph as noted earlier for the upper punch response. This system offered the advantages of not altering the internal die bore and not having the measurements depend on extrusion characteristics (which have been shown to vary widely for different substances) (9).

**Instrument Calibration.**—The upper punch response was calibrated by applying known forces

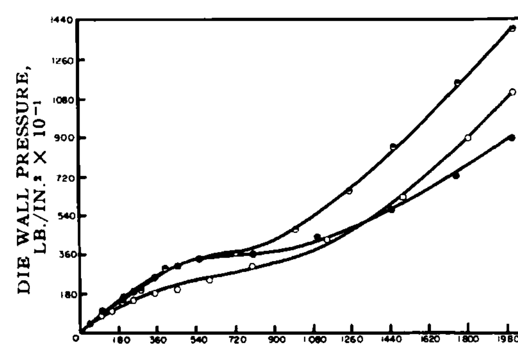


Fig. 4.—Die wall pressure response curve as a function of applied punch pressure for the chloride salts of lithium, sodium, and potassium. ●, LiCl; ○, NaCl; ◒, KCl.

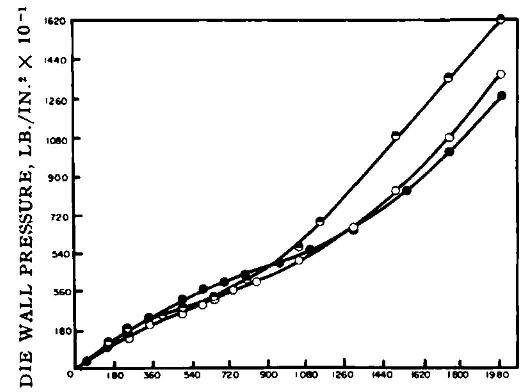


Fig. 5.—Die wall pressure response curve as a function of applied punch pressure for the bromide salts of lithium, sodium, and potassium. ●, LiBr; ○, NaBr; ◒, KBr.

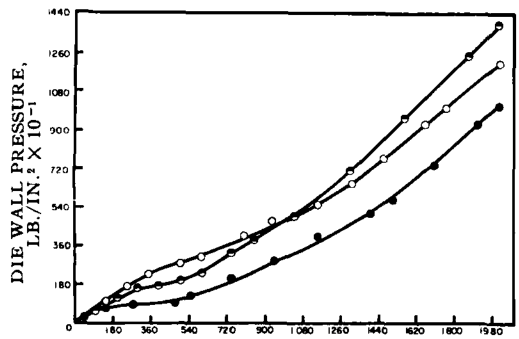


Fig. 6.—Die wall pressure response curve as a function of applied punch pressure for the iodide salts of lithium, sodium, and potassium. ●, LiI; O, NaI; ◓ KI.

with a lever arm, the applied force-response curve being essentially linear over the force range employed. The exact response of the die wall to known lateral pressure was determined by inserting a rubber plug into the die bore and measuring the response of the strain gauges to varying forces applied to the upper punch.

According to Adams and Gibson (10), rubber behaves under compression essentially as a liquid, so it was chosen for the calibration. Because of this apparent hydraulic behavior of rubber, the pressure applied by the upper punch can be assumed to be same as that transmitted directly to the die wall. Figure 3 shows a typical calibration curve for the electrical die wall response as a function of applied pressure. These determinations were repeated throughout the study to compensate for strain gauge drift. The response of the die wall strain gauges to a given normal compressional force obviously is a function of the rubber plug or tablet thickness. To eliminate this variable, a constant final thickness of 5 mm. was adopted for all experiments. Although some volume contraction occurs during compression, it was found that this change was not sufficient to alter seriously the results observed for rubber. In the case of tablets, only a 5% reduction in height was noted from the point of initial pressure response to the final thickness of 5 mm. This change appeared to be negligible based on experiments with tablets of varying final thickness.

**Compression.**—Compression of the material under test was carried out in a manner generally similar to that described previously (7) but with certain modifications. Since the observed response was dependent on final tablet thickness, preliminary trials were necessary for each compound to determine the weight which would yield a 5-mm. tablet. Also all dies were surface lubricated prior to use. In preliminary investigations apparent increases in die-wall forces were observed when unlubricated material was compressed in an unlubricated die as compared to a die with walls coated with a hydrocarbon lubricant.[1] It was felt that the increased response was a function of particle–die wall friction and may be due to the torque exerted on the die by the granulation during compression. As the purpose of the research was to study the effects of particle-particle interaction on the transmission of the forces to the die wall, all investigations were conducted using a die which was lubricated prior to each compression.

**Compounds Tested.**—All substances tested were of highest chemical purity commonly obtainable. They were dried at suitable temperatures and stored in vacuum dessicators prior to use. Storage was found necessary since variation in moisture content appeared to alter the compression characteristics.

## RESULTS AND DISCUSSION

### Effect of Particle Size

Changes in the particle size of the material subjected to compression appear to have only a minor (if any) effect on the side wall pressure transmission. A sample of sodium chloride crystals was fractionated by using standard screens in three general size ranges: larger than 20-mesh, through a 20-mesh and caught on a 40-mesh screen, through a 40-mesh and retained on a 60-mesh screen. Within experimental variation, the curves were identical with that for an unsegregated sample indicating no significant difference arising from particle-size variation over the range studied. For this reason no serious effort was made in the succeeding determinations to control particle sizes.

### Compression of Inorganic Compounds

**Alkali Metal Halides.**—The compressional characteristics of the chloride, bromide, and iodide salts of lithium, sodium, and potassium were studied in some detail since these compounds were available in pure states and because of the availability of precise effective radii of the ionic components. Since the internal crystal attractions (and consequently crystal hardness) appear to depend on inter-ionic distances, some correlation was expected between these values and the efficiency of pressure transmission.

Figures 4–6 show the typical relationships found between applied pressure and the pressure transmitted to the die wall during several runs carried out on the halide salts. In all cases the general shapes of the curves were similar, they had an initial linear segment, then passed through an area having reduced transmittance characteristics, and then a subsequent linear portion which in most cases appeared to approach a slope of one. Although duplicate runs on a given material showed some variation, these variations were small relative to the dif-

Table I.—Initial Slope $\left(\frac{\Delta dw}{\Delta up}\right)$

| | $Cl^-$ | $Br^-$ | $I^-$ |
|---|---|---|---|
| $Li^+$ | 0.80 | 0.70 | 0.54 |
| $Na^+$ | 0.75 | 0.60 | 0.65 |
| $K^+$ | 0.71 | 0.70 | 0.56 |

Table II.—Apparent Yield Value[a] in lb./in.²

| | $Cl^-$ | $Br^-$ | $I^-$ |
|---|---|---|---|
| $Li^+$ | >12,000 | 9,000 | 9,100 |
| $Na^+$ | 9,100 | 8,600 | 7,500 |
| $K^+$ | 6,300 | 5,400 | 5,700 |

[a] Final slope extrapolated to zero-die response.

[1] Lubriseal—Arthur H. Thomas Co., Philadelphia, Pa.

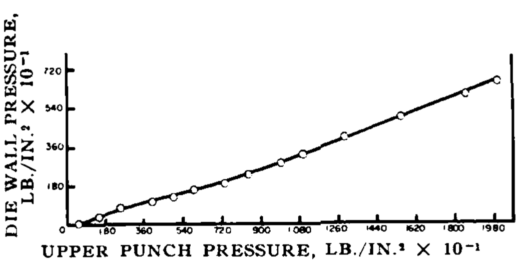


Fig. 7.—Die wall pressure response curve of DASC as a function of applied upper punch pressure.

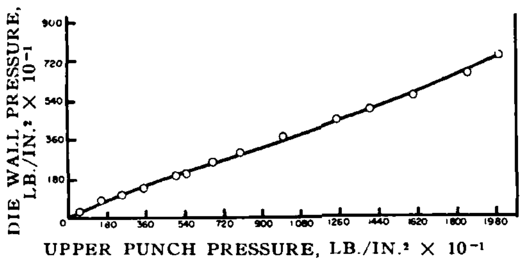


Fig. 8.—Die wall pressure response curve of potassium carbonate as a function of applied upper punch pressure.

ferences observed between materials. Usually replicate sidewall pressure determinations agreed within ±5% for a given substance at a particular compressional pressure.

Although the present state of knowledge cannot totally explain the observed results, some rationalization is possible. For example, the die-punch response curve may depend on crystal hardness, particle-particle friction, and/or shape of the crystal. Table I shows that the initial slopes of the curves plotted in Figs. 4–6 appear to follow the pattern of the hardest crystals (LiCl) having the highest initial slopes, and the softest (KI) having the lowest initial slopes, although exceptions appear to exist. The slopes seem to be somewhat more dependent on the nature of the anionic than on the cationic part.

The subsequent decrease in slopes occur in the compressional range associated with the fracturing of crystals and the assumption of increasingly closer packing. That the fraction of the pressure transmitted to die wall is reduced in this region is certainly not unexpected. The final slope, approaching a direct transmission condition, may represent a void-free, solid-state compression and flow. Table II represents a tabulation of the apparent "yield values" for the salts investigated. These values, which are the extrapolations of the final slopes back to zero die wall response, may be expected to increase with crystal hardness if the previous assumptions have some validity. This seems to be generally the case.

**Some Antacids.**—Figures 7 and 8 show the data obtained when dihydroxy aluminum sodium carbonate[2] and potassium carbonate were compressed. Both exhibited a rather low degree of transmission of the punch force to the die wall, indicating relatively poor flow tendency. During the compression and ejection of the tablets, the machine emitted sounds which indicated marked binding between tablet and die wall. The low initial slope shown by the DASC curve was also reflected by stratification within the finished tablet (inidicative of layer formation).

[2] DASC-Chatanooga Chemical Brand of dihydroxy aluminum sodium carbonate.

## Compression of Organic Substances

Lateral pressure transmission characteristics of some organic compounds of pharmaceutical importance were studied. The results of these investigations are shown in Figs. 9 and 10. Although the shapes of the curves are similar to those observed with the alkali metal halides, the curves for benzocaine, aspirin, and phenobarbital do not exhibit the pronounced leveling that was previously found. This might be attributed to the crushing of the crystals even at low pressure and the assumption of a state of closest packing, followed by essentially void-free compression. In the case of the carbohydrates, the plateau is more extended as might be expected from the relative hardness of the sugars (in comparison to the other compounds tested). From Figs. 9 and 10 the "yield values" of aspirin and lactose were found to be 5800 lb./in.² and 12,700 lb./in.², respectively. Higuchi, *et al.* (3), had found earlier that lactose appeared to be three to four times as hard as aspirin. This investigation agreed qualitatively with the apparent "yield values" found in this study.

It is a well known fact that certain compounds are relatively difficult to compress into acceptable tablets. Phenacetin is an outstanding example of a

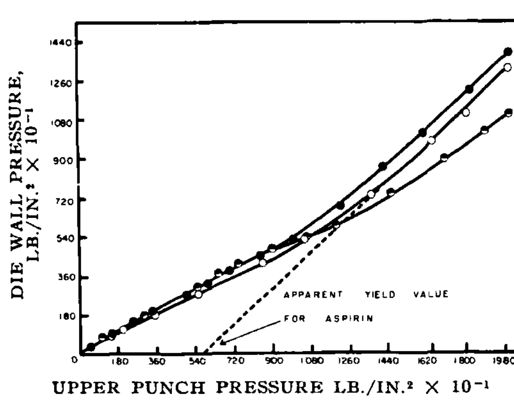


Fig. 9.—Die wall pressure response curve of benzocaine, aspirin, and phenobarbital as a function of applied upper punch pressure. ●, Benzocaine; ○, aspirin; ◒, phenobarbital.

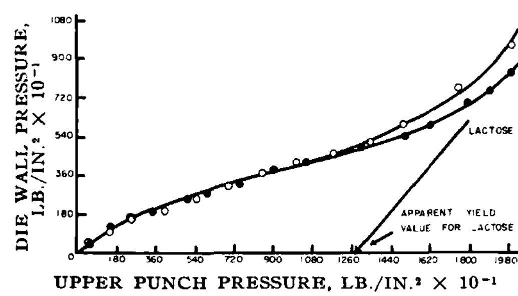


Fig. 10.—Die wall pressure response curve of sucrose and lactose as a function of applied upper punch pressure. ○, Sucrose; ●, lactose.

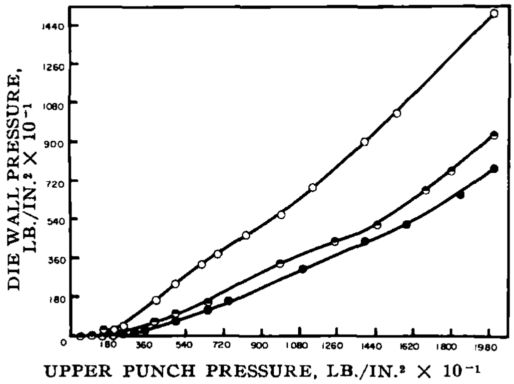


Fig. 11.—Die wall pressure response curve of stearic acid, acetanilid, and phenacetin as a function of applied upper punch pressure. O, Stearic acid, m.p. 69–70°; ◒, acetanilid, m.p. 113–115°; ●, phenacetin, m.p. 134–135°.

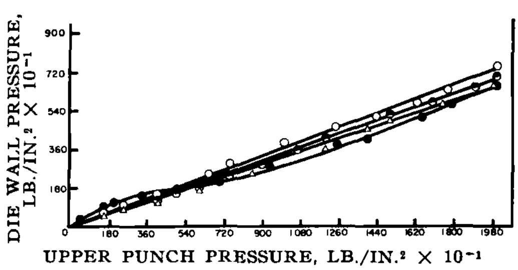


Fig. 12.—The effect of lubrication with magnesium stearate on the die wall–punch pressure response curve of sulfathiazole. Key: ●, unlubricated sulfathiazole; O, sulfathiazole plus 0.25% magnesium stearate; ◒, sulfathiazole plus 0.50% magnesium stearate; Δ, sulfathiazole plus 1.00% magnesium stearate.

substance yielding tablets which are prone to capping. Such tablets when cleaved show indications of lamination. It was felt that this behavior may be reflected in the die wall–punch response curve.

Figure 11 shows the results obtained during compression of crystalline stearic acid, acetanilid, and phenacetin. The essentially zero initial slope in the plots is common to all three compounds, indicating almost no lateral force transmission during the initial phase of compression. After this stage the shape of the curve is similar to that observed with the alkali halides, except that the plateau region is less pronounced than that previously observed.

This behavior may be related to the shape factor mentioned earlier. Each of these three compounds exists in plate-like crystals which might tend to form layers under compression. This layering effect would reduce the lateral forces observed and possibly contribute to the tendency to cap. Although "yield values" were not determined since the final slopes did not appear linear at the higher pressures, it is apparent that qualitatively they would be in the expected order of the softest crystal—stearic acid having the lowest value and the hardest phenacetin having the highest.

## Effect of Lubricants

In the previous work by Nelson (7), it appeared that the addition of to 1.6% magnesium stearate to a sulfathiazole granulation increased the force transmitted to the die wall by approximately 25%. Observations made as a part of this study with sulfathiazole and potassium chloride crystals lubricated by addition of 0.25, 0.5, and 1% magnesium stearate differed to some extent. The lubricant was incorporated into the system by trituration. The results are depicted in Figs. 12 and 13. In sulfathiazole, the unlubricated material exhibited the typical sigmoid curve but with lower transmittance than other organic compounds tested.

The lubricated samples, contrary to expectations, showed lower transmission characteristics at low punch pressures than the unlubricated materials, but higher ratios of the die-wall response at high pressures. It was surprising that transmission decreased with an increased addition of lubricant after an initial rise. A maximum increase of 10% transmission was found at higher pressures when 0.25% magnesium stearate was added, but only a 5–7% increase was recorded at 1% lubricant concentration. Similar results were found in the compression of potassium chloride, except that the increase with 0.25% magnesium stearate was more pronounced

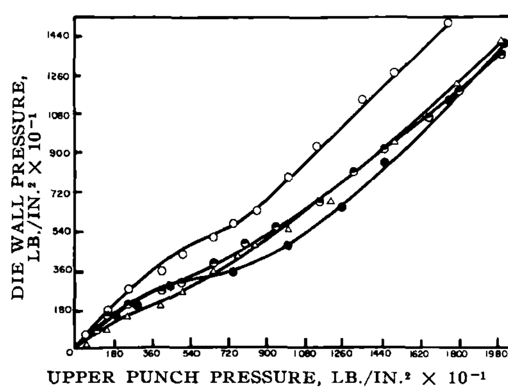


Fig. 13.—The effect of lubrication with magnesium stearate on the die wall–punch pressure response curve of potassium chloride. ●, Unlubricated KCl; O, KCl plus 0.25% magnesium stearate; ◒, KCl plus 0.50% magnesium stearate; Δ, KCl plus 1.00% magnesium stearate.

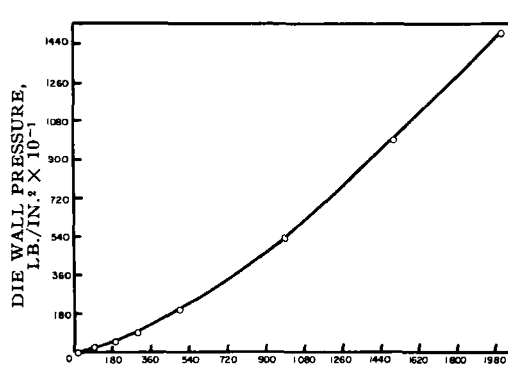


Fig. 14.—Die wall pressure response curve of magnesium stearate as a function of applied upper punch pressure. O, Magnesium stearate.

than with sulfathiazole; however, it presented the same trend at higher lubricant concentration that had been found with the sulfonamide.

The reason for the observed behavior may be found in the compressional characteristics of magnesium stearate. Figure 14 shows the curve obtained for the compression of pure magnesium stearate which is qualitatively similar to the curve shown for stearic acid in Fig. 11. The poor transmission behavior under lower pressure might give rise to the effect seen above, but this is not clearly established.

## CONCLUSION

Although these studies have been largely preliminary, the results suggest that measurements of lateral pressure developed during formation of pharmaceutical tablets may provide a useful indication of compressional characteristics of various materials. As a broad and possibly too sweeping conclusion, it appears that materials which permit rather good conversion of normal pressure to lateral pressure tend to form good tablets. Substances expected to exhibit poor flow properties under pressure, such as those composed of thin, flat, leaf-like crystals, appear to be shown by this technique to behave in this manner.

The general method of study seems to be adaptable to pilot plant and commercial tablet machines with appropriate modifications. It is relatively simple and rapid. The rubber plug technique seems to provide a ready and quick means of calibration.

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# Sabadilla Alkaloids VIII

## Isolation of Sabadillines I, II, and III

By GLENN R. SVOBODA†, HYMAN MITCHNER‡, and LLOYD M. PARKS§

**The techniques of partition and adsorption chromatography as well as countercurrent distribution have been applied to alkaloidal concentrates from both sabadilla and veratrine. Whereas sabadilline previously was considered to consist of a single alkaloidal constituent, the present work has resulted in the isolation of three different materials which possess the characteristic ultraviolet absorption maximum at 238 mμ. These materials have been named sabadilline I, II, and III. Only sabadilline II was obtained in crystalline form. Attempts to establish a relationship between the three compounds were unsuccessful. Only sabadilline II yielded an alkaline isomerization product and this was not similar to either sabadillines I or III.**

THE PRESENCE of an alkaloidal constituent of *Schoenocaulen officinale* (sabadilla) which exhibited an ultraviolet maximum at 238 mμ was first noted by Poetsch (1). This material was obtained from a commercial concentrate sold under the name "sabadilline." This was the name applied to the crystalline material, isolated by Hennig (2), which exhibited a similar ultraviolet spectrum. The work of Stuart (3) and Mitchner (4) confirmed the presence of a sabadilline-like material in both sabadilla and the commercial concentrate, veratrine, an alkaloidal extract of sabadilla.

A material which appeared to be similar to sabadilline was isolated by Auterhoff (5) and partially characterized by Vejdelek, Macek, and Kakac (6). To this material, which was named veragenine, was attributed an αβ-unsaturated ketone structure, unknown for any isolated sabadilla constituent other than sabadilline, for which an αβ-unsaturated ketone structure previously had been postulated by Stuart (3). The possibility of a similarity between the two compounds indicated the necessity of further investigation of the substance which exhibited

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