by the plunger. This results in an increasing rate of force application when Tester B is used. The air-operated testers, on the other hand, give a decreasing rate of load application as load is increased. This occurs because of the buildup of pressure within the tester air cylinder to the point where it begins to approach the pressure level supplied to the tester. Sometimes hard tablets cannot be broken by using the air-operated testers, because of the limitation of force applied by these testers. Because of the change in the rate of load application of the air-operated testers at higher load levels, the constant-speed mechanical tester would be preferred. Figure 6 also points out the fact that variable rates are obtained for different air-operated testers and that this rate is not easily adjusted or controlled.

SUMMARY AND CONCLUSIONS

A suitable method of calibrating the force response of air-operated hardness testers was developed. The results obtained from various type C testers were variable and could be traced to inconsistencies between instruments such as variable rate of load application and variable friction in the piston. The Tester A instrument load scale (kilograms) gave values about 10% higher than were obtained in Tester B.

There are distinct advantages for using a mechanical tester such as Tester A:

1. More uniform force application may be achieved.
2. Less maintenance work is required.
3. There is less need for calibration checks.

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New *In Vitro* Disintegration and Dissolution Test Method for Tablets and Capsules

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Abstract □ An *in vitro* technique for testing the disintegration and dissolution of tablets and capsules was developed and evaluated. The apparatus consists of a beaker with a cylindrical well in the bottom into which is placed a platform containing the dosage form to be tested. Shallow cylindrical depressions in the platform are used to hold capsules snugly in a vertical position for testing while variously shaped depressions are used for tablets, depending on their size and shape. Comparisons between the official and the new method indicated that the official test does not differentiate between capsule formulations containing a hydrophobic lubricant. A phenylpropanolamine hydrochloride capsule formulated with a high level of magnesium stearate was shown to release drug more slowly *in vitro* and *in vivo*. The effects of capsule formulation factors such as type and level of lubricant and disintegrant as well as the presence of a surfactant were determined. It was found that the use of magnesium stearate and hydrogenated vegetable oil as lubricants significantly prolonged the *in vitro* disintegration time of hard gelatin capsules. Hard gelatin capsules also disintegrated more rapidly in artificial gastric fluid as compared to distilled water, and machine-filled capsules generally disintegrated more slowly than hand-filled capsules. Studies on tablets containing a slightly water-soluble drug indicated that the method of preparing the granulation has an important effect on the *in vitro* release of the drug.

Keyphrases □ Dissolution—method and equipment for tablets and capsules, compared to compendial method □ Tablet dissolution—method and equipment, compared to compendial method □ Capsule dissolution—method and equipment, effect of lubricant and disintegrant characteristics, surfactants, compared to compendial method □ Surfactant effect—dissolution of capsules, method, equipment □ Phenylpropanolamine hydrochloride capsule—dissolution characteristics, effect of formulation

Progress in *in vitro* dissolution technology of solid dosage forms resulted in the adoption of a specific apparatus and methodology by NF XIII and USP XVIII for testing drug availability from tablets and capsules. In addition, the basket-rack assembly is still recognized by the official compendia as a test method for the disintegration of tablets. No test method has ever been adopted for testing the disintegration of capsules. *In*

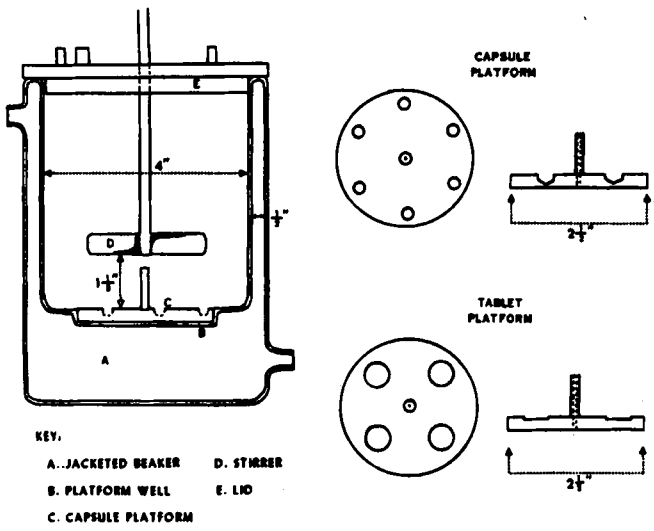

Figure 1—*Diagram of the tablet and capsule disintegration and dissolution apparatus.*

vitro test methods for gelatin capsules received little attention until Wood (1) pointed out that a standard test for this dosage form was needed. The difference in behavior between capsules and tablets in a specific dissolution apparatus has prevented the development of a standard test method suitable for both products.

Some specific faults of hard gelatin capsule formulations were pinpointed by Samyn and Jung (2). Their studies showed prolonged disintegration/dissolution times with an increase in the level of the lubricant, magnesium stearate. In these formulations, liquid penetration was increasingly retarded with increased levels of magnesium stearate and the percent of moisture in the capsule plug was inversely proportional to the amount of this lubricant. Magnesium stearate was, in effect, waterproofing the capsule contents, and it was theorized that the *in vivo* drug availability of these formulations must also be affected.

Little specific information regarding drug availability from capsules as a function of formulation is available. However, Poole (3) reported that the lubricant system in capsules significantly affected the degree of drug absorption in dogs and humans. The *in vivo* results were in rank order with *in vitro* slow dissolution results.

Samyn and Jung (2) pointed out that the official disintegration method with disks probably disguises the true disintegration time of capsules. The pharmaceutical formulator must, therefore, develop some method for testing drug availability from capsules. This is particularly necessary during early formulation when *in vivo* studies would be premature and costly. While slow dissolution methods give useful data which are readily correlatable to *in vivo* performance, a disintegration method would also be very useful for quick screening of capsule formulations.

Lin *et al.* (4) screened seven dissolution methods for release of drugs from hard gelatin capsules. They pointed out that the official method has several disadvantages. The capsule cannot be visually observed during disintegration, so a slow wetting plug cannot be seen. Also, the 40-mesh screen used in this method is prone to becoming clogged with many formulations; therefore, an 8-mesh screen was suggested by Lin *et al.* (4). Poole (3) described the difficulties of testing capsule formulations; these included the tendency of most capsules to float in the dissolution media and to become tacky and to stick to the stirrer or vessel. Also, the use of the present NF XIII and USP XVIII methods is not to be recommended since the wire mesh of the basket is easily fouled by the gelatin or other insoluble or gumming components, resulting in a nonuniform solvent flow around the capsule. Because of the seeming lack of a satisfactory disintegration testing method, one was developed in these laboratories. It allows visual observation and, hence, a quick method of screening; it is also suitable for disintegration testing of tablets as well as the dissolution testing of all solid dosage forms.

EXPERIMENTAL

Description of Apparatus—The tablet and capsule disintegration/dissolution apparatus[1] is shown in Fig. 1. It consists of a jacketed 800-ml. chamber with a centrally located well in the bottom measuring 6.35 cm. (2.5 in.) in diameter and 0.64 cm. (0.25 in.) deep. Various platforms for testing either capsules or tablets are placed into the well.

The capsule platforms are made of Plexiglas and have six shallow wells symmetrically located on the platform for the insertion of six capsules. These platforms can also be made of Teflon with Plexiglas inserts for holding the capsules. The capsule wells are drilled every 60° on a 2.54-cm. (1-in.) radius around the platform. A post, 2.54 cm. high, is placed in the center of each platform to facilitate removal of the platform from the beaker well. A small hole is drilled vertically through the post to the bottom side of the platform to allow air to escape from the underside of the platform at the beginning of a study.

The tablet platforms are similar in appearance to the capsule platforms, but they are made of Teflon. There are four shallow wells drilled on the surface of these platforms to restrain nondisintegrated tablets from changing position in the beaker. The tablet wells are drilled with an end-mill every 90° and are centered 2.54 cm. (1 in.) from the platform midpoint. Capsule platforms made solely of Teflon were impractical because of poor adhesion between the slippery Teflon surface and gelatin capsule. Platforms for capsules and tablets can be made having other configurations to hold various numbers of tablets and capsules. Well depths may be varied for tablets, depending on their size and shape.

A Plexiglas lid was made for the top of the beaker to retard evaporation of the testing fluid. The top contains holes for a stirrer, thermometer, and inlet and outlet sampling ports.

A two-bladed glass stirrer, 5.50 cm. (2.165 in.) in diameter with a 45° blade pitch, is centered and operated 2.86 cm. (1.125 in.) above the surface of the platform. The stirring speed is controlled and monitored with a constant-speed control unit[2]. The temperature of the bath was kept at 37 ± 0.5° with a constant-temperature circulating bath. An adjustable jack[3] was used to remove the stirrer and lid from the beaker after each run.

Materials—The following were used: starch USP; lactose USP hydrous, improved flow; magnesium stearate USP; microcrystalline cellulose NF[4]; tranquilizing drug powder; phenylpropanolamine hydrochloride NF (powder); sodium lauryl sulfate USP, washed and dried; stearic acid USP[5]; and hydrogenated vegetable oil[6].

[1] The apparatus was built by Mr. William Campbell with the help of Mr. Walter Lugrin, Warner-Lambert Research Institute. A forerunner apparatus was previously used in these laboratories; it consisted of a platform which was lowered into a beaker of dissolution fluid and had a centrally located well in the platform directly under the stirrer. This device, known as the "fixed geometry apparatus," was developed by Mr. Larry Kirschner, Dr. Thomas Simon, and Mr. William Campbell. Patents are pending.

[2] Standard Servodyne Controller, Cole-Parmer, Catalog No. 4420.

[3] "Quick-Action," Scientific Glass Apparatus, Catalog No. S-9014.

[4] Avicel PH 101, FMC Corp., Marcus Hook, PA 19061

[5] Groco 55-F powder, A. Gross & Co., New York, N. Y.

[6] Sterotex HM, The Capital City Products Co., Columbus, Ohio.

Table I—Disintegration Times of Capsule Formulas Tested in the New Apparatus under Various Test Conditions[a]

Disintegration Media:	No Lubricant				1.0% Magnesium Stearate			
	Distilled Water		Artificial Gastric Fluid		Distilled Water		Artificial Gastric Fluid	
Stirring Speed, r.p.m.: Formula	40	75	40	75	40	75	40	75
25% Microcrystalline cellulose	5	5	3	3	>30	>30	>30	>30
25% Microcrystalline cellulose with 0.2% sodium lauryl sulfate	5	4	3	2	>30	>30	3	5
50% Microcrystalline cellulose	5	3	3	2	>30	>30	>30	>30
50% Microcrystalline cellulose with 0.2% sodium lauryl sulfate	4	4	4	2	>30	>30	4	4
25% Starch	15	7	9	4	>30	>30	>30	>30
25% Starch with 0.2% sodium lauryl sulfate	14	9	7	4	>30	>30	>30	15
50% Starch	6	8	7	10	>30	12	15	8
50% Starch with 0.2% sodium lauryl sulfate	6	8	9	9	24	14	12	10

[a] Time in minutes.

The two-piece hard gelatin capsules[7] used were: No. 0 green opaque, No. 1 clear, No. 1 pink, No. 1 orange opaque, No. 1 two-tone blue opaque, No. 2 pink opaque, No. 3 yellow and gray opaque, and No. 4 pink.

General Procedure for Capsule Disintegration and Dissolution Studies—The proper size platform is selected for the capsule size, and the capsules are inserted into the wells, caps down, with a slight twisting action. After all capsules are in place, the platform is inverted to determine that the capsules are secured. The platform is slowly lowered into the apparatus containing 600 ml. of preheated test fluid and guided into the beaker well. The stirrer, premeasured to the proper height, is lowered and stirring is initiated. The capsule disintegration test is run until the capsule has substantially disintegrated or for a maximum of 30 min.

General Procedure for Tablet Disintegration and Dissolution Studies—The appropriate platform is fixed in the beaker well, 600 ml. of preheated test fluid is added, and the tablets are dropped into the bath and positioned, one in each well.

Preliminary Disintegration Testing in Tablet and Capsule Disintegration and Dissolution Apparatus—A formula containing 1.3% D&C Red No. 2 in lactose was hand filled into No. 1 clear gelatin capsules. Six capsules were placed in the apparatus and disintegrated in distilled water (37°) at 40 r.p.m. The medium was observed for a uniform distribution of color.

To test positional effects, a formula containing equal amounts of microcrystalline cellulose and lactose was encapsulated by hand into No. 1 red opaque capsules. The fill weight was 300 mg., and six capsules were disintegrated in distilled water (37°) using a 40-r.p.m. stirring speed.

Formulation Variables—Disintegration tests on capsules having explicit formula variations were run in the new apparatus. The factors studied were: (*a*) level of microcrystalline cellulose, 25 and 50%; (*b*) level of starch, 25 and 50%; (*c*) level of magnesium stearate, 0 and 1%; and (*d*) level of sodium lauryl sulfate, 0 and 0.2%.

In each formula, the disintegrant was dry blended with lactose. Sodium lauryl sulfate and magnesium stearate were added through No. 60 bolting cloth. The powders were mixed thoroughly in a tumbling bottle and hand filled into No. 1 red opaque capsules. Duplicate samples of each formula were randomly tested in the new apparatus.

Test Condition Variables—The capsules employed in the formula variation study were tested in the new apparatus in distilled water and artificial gastric fluid without pepsin at 40 and 75 r.p.m. These conditions, together with the formulation variables, constituted a 2^6 factorial design.

Reproducibility of Apparatus—Duplicate runs were carried out on some capsules, described under formulation variables, to demonstrate the reproducibility of the apparatus at the various test conditions. Two formulas were randomly positioned in the platform for simultaneous testing.

Comparision of New Method to USP Method—The hand-filled capsules prepared for the formula variation study were tested in the USP basket-rack assembly, with and without disks and using both distilled water and artificial gastric fluid.

Disintegration Comparison of Machine-Filled Capsules *versus* Hand-Filled Capsules—Nine formulations were filled by hand and on a semiautomatic capsule filling machine[8]. These contained stearic acid, hydrogenated vegetable oil, or magnesium stearate at three levels: 0.5, 1.0, and 2.0%. In each case, the lubricant was added to a lactose diluent through a No. 60 bolting cloth and mixed well. A No. 1 pink capsule was used, and a fill weight of 450 mg. was used for all of these experiments. The capsules were disintegrated in the new apparatus and by the USP method with and without disks.

***In Vitro* Capsule and Tablet Disintegration/Dissolution Study**—Four capsules and two tablets, each containing 10 mg. of a slightly water-soluble tranquilizer drug, were tested in the new apparatus. Variations in the capsule formulas were: (*a*) lubricant, magnesium stearate or stearic acid; (*b*) micronized *versus* unmicronized drug; and (*c*) wet process (*i.e.*, adding drug from solution) *versus* dry process. The method of preparation of the four different formulas was as follows:

Capsule A—The drug was passed through a No. 30 mesh screen and blended well with lactose. Three and one-half percent magnesium stearate was added to the formulation through a No. 60 bolting cloth and mixed well. The capsules (No. 1 orange opaque) were filled on the semiautomatic machine at 480 mg.

Capsule B—The drug was passed through a No. 30 mesh screen and blended with lactose. After sufficient mixing, the formulation was passed through a No. 40 mesh screen. An equivalent of 1.5% stearic acid was added to the blend through a No. 60 bolting cloth and mixed well. The formulation was hand filled into No. 1 two-tone blue opaque, hard gelatin capsules to 420 mg. fill weight.

Capsule C—The drug and 0.2% sodium lauryl sulfate (based on final granulation weight) were dissolved in an appropriate amount of warm isopropanol (50°) to allow for proper distribution on the lactose. The solution was added to the lactose and mixed well. The granulation was dried at 25° overnight and then passed through a No. 40 mesh screen. Two percent stearic acid was added through a No. 60 mesh bolting cloth and mixed well. The powders were hand filled into No. 1 two-tone blue opaque, hard gelatin capsules to a 400 mg. fill.

Capsule D—This formulation was prepared in the same way as Capsule B, except that micronized drug was used.

The tranquilizer tablets were randomly sampled from two different batches of the same formula. The method of tablet preparation was as follows.

Initially, the drug was milled in a Fitzpatrick comminuting machine using a 0.79-mm. round hole screen, impact forward at high speed. A color blend was prepared by micropulverizing 20% of the lactose with the starch and magnesium stearate. This blend was

[7] All manufactured by Parke-Davis, Division of Warner-Lambert Co.

[8] Parke-Davis.

Table II—Reproducibility of Capsule Disintegration Times in the New Apparatus[a]

Formula	Disintegration Time, min., in Distilled Water, 40 r.p.m. $\bar{X}$[b]	40 r.p.m. R[c]	75 r.p.m. $\bar{X}$[b]	75 r.p.m. R[c]
25% Starch	15.0	0	7.0	2
25% Starch, 0.2% sodium lauryl sulfate, 1.0% magnesium stearate	>30	—	>30	—
50% Starch, 0.2% sodium lauryl sulfate	5.5	1	8.0	2
50% Starch, 0.2% sodium lauryl sulfate, 1.0% magnesium stearate	24.5	2	16.5	2

[a] All capsules contain lactose, hydrous, improved flow. [b] $\bar{X}$, average of four capsules. [c] R, range of four capsules.

passed through a 0.99-mm. round hole screen, impact forward at high speed. The drug was then mixed with microcrystalline cellulose, the remainder of the lactose, and the color blend, and was mixed for 30 min. The final powder blend used in Tablet B was milled a second time through the same screen to obtain a better color distribution. Tablets A and B were the same weight, gauge, and hardness.

The *in vitro* test utilized only one capsule or tablet per study. The dosage form was tested in the new apparatus, using 400 ml. of artificial gastric fluid without enzymes at 37° and stirred at 75 r.p.m. During the dissolution study, samples were taken periodically, filtered, diluted, and observed spectrophotometrically at 238 nm. Placebo formulations were tested in the same way and used to correct the assay for interference caused by gelatin and excipients. The amount of drug dissolved at various times was calculated from the differential spectrophotometric values.

***In Vitro* and *In Vivo* Correlation of Phenylpropanolamine Hydrochloride Capsules**—A fast disintegrating capsule and a poor disintegrating capsule, each containing 75 mg. of phenylpropanolamine hydrochloride, were compared by testing disintegration, dissolution, and bioavailability.

In vitro testing of the two formulations was performed in the new apparatus with 600 ml. of artificial gastric fluid without enzymes at 75 r.p.m. Six capsules were used for each test. The solution was sampled periodically, filtered, and assayed by the method of Chafetz (5); the details are given below.

The preparations and an aqueous solution containing 75 mg. of phenylpropanolamine hydrochloride were administered to two healthy, fasting male subjects. These three formulations were each given, allowing 1 week between tests. The bladder was emptied approximately 1 hr. prior to taking the dosage form. The solution and capsules were taken with 120 ml. water. Immediately after administration, a urine blank was collected. Urine was collected for the 0–0.5, 0.5–1, 1–1.5, 1.5–2, 2–4, 4–6, and 6–24-hr. intervals and was refrigerated until assayed.

Assay Procedure for Phenylpropanolamine Hydrochloride—To a 60-ml. separator, add 2 ml. of urine, 1 ml. of saturated sodium carbonate solution, and 5 ml. of 5% sodium metaperiodate; mix well and let stand for 15 min. Extract the aqueous mixture with 15 ml. of hexane for 1 min. and discard the aqueous phase. Transfer the hexane to a 50-ml. stoppered centrifuge tube containing 1 g. of anhydrous sodium sulfate and shake. Determine the absorbance of the hexane phase spectrophotometrically at 241 nm. against a reagent blank.

Reagent Blank—Use 2 ml. of water to replace the 2 ml. of urine and proceed as above.

Preparation of Standard—Accurately weigh 1 g. of phenylpropanolamine hydrochloride into a 50.0-ml. volumetric flask and bring to volume with distilled water. Pipet 1 ml. of the solution to another 100-ml. volumetric flask and bring to volume with distilled water. Use 2 ml. of this solution instead of 2 ml. of urine and proceed as above.

RESULTS AND DISCUSSION

The new apparatus has been used successfully for disintegration and dissolution testing of capsules and tablets. The apparatus is

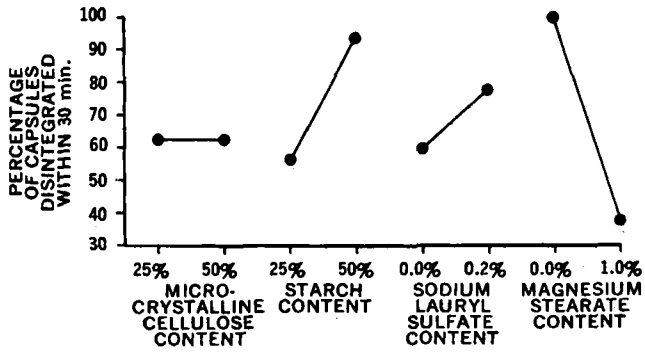

Figure 2—*Relative effects of formula variations tested in the tablet and capsule disintegration and dissolution apparatus.*

easily adapted for any size soft or hard gelatin capsule or tablet by changing the platform to accommodate the size and shape of the dosage form. The observation of either six capsules or four tablets statically positioned under mild agitation allows for disintegration comparisons to be made rapidly and accurately. Dissolution tests are run by removing fluid manually or automatically through the sampling ports.

During capsule disintegration, the top of the gelatin capsule often opens in about 2 or 3 min. and air is released from the capsule. A fast release of air bubbles is usually indicative of an immediate wetting and, consequently, is a first indication of a good disintegrating formula. If the capsule contents are wetted, the gelatin capsule itself is weakened by the test medium and the capsule will collapse. Occasionally, it is difficult to determine when the disintegration is complete. In this work, when the top half of the capsule had disintegrated, the test was judged to be complete.

Some gelatin capsule shells dissolve completely without collapse of the formulation because the capsule contents are not wetted. This capsule-shaped "plug" is often seen when testing formulas containing magnesium stearate. The disintegration test can be run for any length of time; however, in this work each study was run for a maximum of 30 min. Generally, any formula not disintegrating in 15 min. is considered unsatisfactory.

Preliminary Evaluation of Tablet and Capsule Disintegration and Dissolution Apparatus—Six capsules incorporating a dye showed a quick and uniform distribution of color in the new apparatus at a stirring speed of 40 r.p.m. This uniform flow pattern indicated that sampling can be made from any position in the beaker above the stirrer.

Capsules containing 50% microcrystalline cellulose and 50% lactose were used to test the reproducibility of all six capsule positions. All capsules disintegrated between 3 and 5 min. The wetting of the capsule formula was delayed for about 2 min. until the top of the capsule erupted. After the capsules were wetted, they collapsed within 2 min. and disintegrated to a mound within the next minute. All six positions of the sampling platform yielded similar results. The disintegration differences observed were due to individual capsule variations.

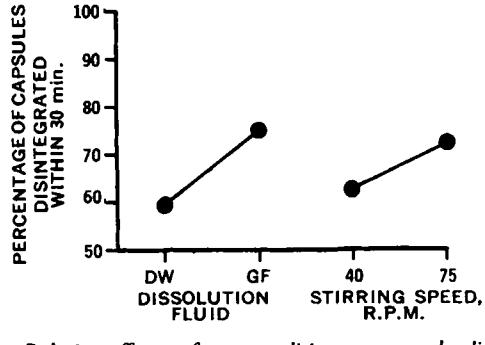

Figure 3—*Relative effects of test conditions on capsule disintegration in the tablet and capsule disintegration and dissolution apparatus. Key: DW, distilled water, and GF, artificial gastric fluid without enzymes.*

Table III—Comparative Disintegrations of Capsule Formulas Tested in the New Apparatus and the USP Basket-Rack Assembly[a,b]

Formula	Disintegration Time, min. — No Lubricant — New Apparatus	No Lubricant — USP — With Disks	No Lubricant — USP — Without Disks	1.0% Magnesium Stearate — New Apparatus	1.0% Magnesium Stearate — USP — With Disks	1.0% Magnesium Stearate — USP — Without Disks
25% Microcrystalline cellulose	5	2	2	>30	4	45
25% Microcrystalline cellulose with 0.2% sodium lauryl sulfate	4	2	2	>30	4	25
50% Microcrystalline cellulose	3	2	3	>30	4	>35
50% Microcrystalline cellulose with 0.2% sodium lauryl sulfate	4	2	3	>30	5	15
25% Starch	7	4	5	>30	8	>40
25% Starch with 0.2% sodium lauryl sulfate	9	3	4	>30	8	>40
50% Starch	8	3	7	12	5	11
50% Starch with 0.2% sodium lauryl sulfate	8	3	5	14	5	10

[a] Fluid was distilled water. [b] New apparatus stirring speed was 75 r.p.m.

Table IV—Comparative Disintegrations of Hand-Filled and Machine-Filled Capsules in the New Apparatus and USP Basket-Rack Assembly

Lubricant	Disintegration Time, min.[a] — Hand-Filled Capsules — New Apparatus	Hand-Filled Capsules — USP — With Disks	Hand-Filled Capsules — USP — Without Disks	Machine-Filled Capsules — New Apparatus	Machine-Filled Capsules — USP — With Disks	Machine-Filled Capsules — USP — Without Disks
0.5% Stearic acid	4	2	3	4	2	3
1.0% Stearic acid	4	2	3	4	2	3
2.0% Stearic acid	4	2	3	4	3	4
0.5% Hydrogenated vegetable oil[b]	3	2	3	4	2	3
1.0% Hydrogenated vegetable oil[b]	3	2	3	4	2	4
2.0% Hydrogenated vegetable oil[b]	3	2	3	>30	3	16
0.5% Magnesium stearate	>30	3	18	>30	7	16
1.0% Magnesium stearate	>30	5	>30	>30	11	19
2.0% Magnesium stearate	>30	6	>30	>30	22	25

[a] Average of four determinations. [b] Sterotex HM.

Duplicate runs were made on selected capsules of the formulation variables study shown in Table I. The disintegration times of the capsules retested were observed throughout the 30-min. test period. The average disintegration times and the range of four observations are shown in Table II. The disintegration times were rounded off to the nearest minute. The results can vary ±0.5 min. from the average for any observation. In Table II the largest range for any average disintegration time is 2 min. Factors such as the condition of the gelatin capsules, the composition of the capsule formula, the compaction forces during filling, or the testing conditions can affect the reproducibility of the test.

Formulation Variables—The effects of these factors are illustrated in Table I and Fig. 2. The formulation effects illustrated in Fig. 2 indicate that the major factor affecting capsule disintegration is the absence or presence of magnesium stearate. All formulations without 1% magnesium stearate disintegrated within 16 min., while only 38% of those with the lubricant disintegrated within 30 min. Capsule studies by Samyn and Jung (2) in the USP apparatus without disks also showed retarded disintegration and dissolution rates in formulations containing magnesium stearate. This finding was attributed to poor wetting of the formulation due to the hydrophobic lubricant. The addition of a wetting agent, namely sodium lauryl sulfate, improved the disintegration of the capsules when tested in artificial gastric fluid without enzymes. There was an overall increase from 59 to 78% in the capsule disintegrations due to the presence of sodium lauryl sulfate. It is notable that this surfactant allowed disintegration in gastric fluid of magnesium stearate-containing formulas, but disintegration in water was still slow.

The disintegrants used in this study, that is, starch and microcrystalline cellulose, provide fast disintegration of formulations containing no lubricant. The capsules containing microcrystalline cellulose disintegrated, on the average, in 4 min., while those containing starch disintegrated in 8 min.

A further effect of each disintegrant can be seen when capsules containing magnesium stearate are considered. Sixty-two percent of all the capsules containing 25% microcrystalline cellulose disintegrated within 30 min. The same percentage disintegration was obtained for capsules containing 50% microcrystalline cellulose. An increase in the level of starch from 25 to 50% provided better disintegration; the percentage of disintegrations increased from 56 to 93%. In formulas containing 1% magnesium stearate, starch has been shown to be a better disintegrant than microcrystalline cellulose.

Test Condition Variables—The comparison of distilled water *versus* artificial gastric fluid without enzymes and 40 r.p.m. *versus* 75 r.p.m. is shown in Table I and Fig. 3. Seventy-five percent of the capsule formulations disintegrated in artificial gastric fluid, with only 59% disintegrating in distilled water. Seventy-two percent of the capsules disintegrated at 75 r.p.m., whereas only 63% disintegrated at 40 r.p.m. There is a mound formation following the capsule disintegration at 40 r.p.m. that is not recommended for dissolution studies. However, at 75 r.p.m. the capsule disintegration test is satisfactory and the agitation is sufficient to disperse the disintegrated portion of the capsule in the bath.

Comparison of New Method to USP Method—According to the data reported in Table III, the USP method with disks yielded disintegration times that were much faster and less discriminating than those obtained by the new method or the USP method without disks. This was especially true for formulas containing magnesium stearate. Dissolution studies by Withey and Mainville (6) on chloramphenicol capsules in a modified USP apparatus were too rapid for proper differentiation between the various formulations. Using the USP method with disks, all capsule formulas without magnesium stearate disintegrated within 4 min., while those with magnesium stearate disintegrated between 4 and 8 min. The USP method without disks provides the longer disintegration times

Table V—Disintegration and Dissolution of Capsules and Tablets Containing a Water-Insoluble Tranquilizer Drug[a]

Formula	Method of Preparation	Disintegration Time, min.	50% Dissolution, min.
Capsule A	Dry blend, 2.5% magnesium stearate	>180	>180
Capsule B	Dry blend, 1.5% stearic acid	3	103
Capsule C	Drug added from alcoholic solution, 1.5% stearic acid	3	29
Capsule D	Dry blend of micronized drug, 1.5% stearic acid	3	20
Tablet A	Drug milled once	1	29
Tablet B	Drug milled twice	20	12

[a] Data obtained using the tablet and capsule disintegration and dissolution apparatus.

that differentiate between the fast and slow disintegrating formulations. However, a larger variation in disintegration times was obtained in testing some capsule formulas using this method.

Hand-Filled Capsules *versus* Machine-Filled Capsules—Three methods of disintegration testing showed major differences between uniformly hand-filled and machine-filled capsules (Table IV and Fig. 4). The results were expressed as the percentage of formulations that disintegrated within 30 min. The new apparatus was the most sensitive to the difference in filling method, while the USP method with disks was the least sensitive. Use of the USP method without disks gave results more closely aligned to the new apparatus. The shift toward longer disintegration for machine-filled capsules cannot be explained by bulk density differences since all capsules were prepared at a fill weight of 450 mg. If the new method or the USP method without disks is used as a criterion for the disintegration of machine-filled capsules, it can be noted in Table IV that 2% stearic acid and 1% hydrogenated vegetable oil are satisfactory lubricant levels. These formulations disintegrate in 4 min., while those containing 2% hydrogenated vegetable oil or magnesium stearate all exceed 30 min.

***In Vitro* Capsule and Tablet Disintegration/Dissolution Study**—The disintegration and dissolution comparison of capsule and tablet formulations tested in the tablet and capsule disintegration and dissolution apparatus is shown in Table V. The presence of 3.5% magnesium stearate in Capsule A retarded both the disintegration and dissolution of the water-insoluble tranquilizer from the formulation. Magnesium stearate, being a strong hydrophobic lubricant, does not allow the formulation to become wetted. After 3 hr. of testing, only 6% of the dose was released from the non-disintegrated capsule plug. The 3.5% magnesium stearate used in Capsule A was replaced with 1.5% stearic acid in Capsule B. The dry-blend Capsule B disintegrates quickly (3 min.) and has a dissolution half-life of 103 min.

Efforts to improve the dissolution of the tranquilizer capsules resulted in the formulation of Capsules C and D. In Capsule C, both the drug and sodium lauryl sulfate were added to the lactose diluent from alcoholic solution. This method of formulation allows the drug to be finely distributed onto the surface of the water-soluble lactose particles. Capsule C had a dissolution half-life of 29 min. This value is 3.5 times faster than the dissolution of Capsule B. The improved dissolution rate is probably due to the presence of a smaller drug particle size and the improved wetting of the drug by the addition of 0.2% sodium lauryl sulfate.

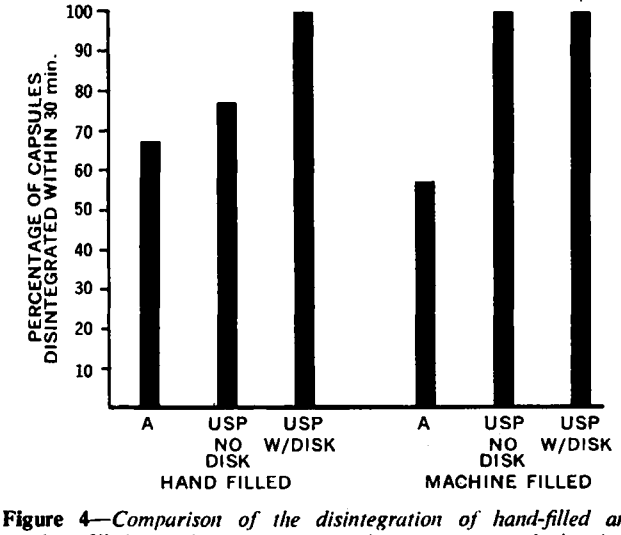

Figure 4—*Comparison of the disintegration of hand-filled and machine-filled capsules using various disintegration methods. A = new apparatus.*

Because of the low solubility of the drug in water (0.14 mg./ml.), the drug was micronized to increase the drug surface area available for dissolution. The micronized powder was then dry blended with lactose and stearic acid as in Capsule B. The only difference between Capsules B and D is that Capsule D contained finer drug particles. Capsule D showed a dissolution half-life of 20 min., which was five times faster than that of Capsule B but only slightly faster than that of Capsule C.

The tablet disintegrations are not in rank order with the 50% dissolution results. Tablet A showed an immediate disintegration with a dissolution half-life of 29 min. Tablet B was the same formula as Tablet A, but in the preparation of Tablet B the powder blend was milled a second time to obtain better color distribution. Tablet B disintegrated much slower than Tablet A but, nevertheless, dissolved much faster. Tablet B had a 50% dissolution of 12 min., which was 2.5 times faster than that of Tablet A. The improved dissolution rate in Tablet B is again attributed to the smaller drug particle size. The unexpectedly long disintegration time of Tablet B can only be explained by an improvement in the binding capacity of smaller and more homogeneously mixed excipients. The lack of a rank order correlation between the disintegration and dissolution data contradicts the general assumption that fast disintegration is necessary for fast dissolution. Since disintegration is easy to test, the formulator usually makes this the first objective and runs dissolution studies afterward. It is logical to assume that fast disintegrations can improve dissolutions by making the drug available for dissolution quickly, but this is not always true. Satisfactory dissolution rates can be obtained from dosage forms with slow disintegrations and, furthermore, improved disintegrations may or may not improve dissolution.

***In Vitro* and *In Vivo* Correlation of Phenylpropanolamine Hydrochloride Capsules**—The disintegration and dissolution data shown in Table VI demonstrate the *in vitro* differences obtained with the new apparatus for the two capsules. Capsule B disintegrated in 3 min., and 94% of the phenylpropanolamine hydrochloride was dissolved in 30 min. Capsule A, containing 5% magnesium stearate,

Table VI—Dissolution of Phenylpropanolamine Hydrochloride Capsules in the New Apparatus[a,b]

Time, min.	Cumulative Percentages of Drug Release Capsule A	Capsule B
3	4.6	11.3
5	8.7	27.0
10	21.1	67.6
15	28.2	84.5
30	44.9	94.0
60	66.6	—
90	80.9	—
120	87.9	—

[a] Dissolution fluid was 600 ml. of artificial gastric fluid without enzymes, and stirring speed was 75 r.p.m. [b] Disintegration times were: Capsule A, >2 hr.; and Capsule B, 3 min.

Table VII—Comparison of Cumulative Percentages of Phenylpropanolamine Hydrochloride Excreted in the Urine[a]

Dosage Form	Subject	Time, hr. 0.5	1	1.5	2	4	6	24
Solution	1	1.6	7.7	—	17.8	38.0	52.0	93.9
Solution	2	0.5	8.7	—	20.0	38.3	49.9	93.4
Solution	Average	1.1	8.2	—	18.9	38.2	51.0	93.6
Capsule A	1	0.0	1.3	4.4	11.4	35.9	50.5	90.5
Capsule A	2	0.0	2.6	5.5	12.5	30.7	46.4	89.4
Capsule A	Average	0.0	2.0	5.0	12.0	33.3	48.4	90.0
Capsule B	1	0.2	6.3	15.2	22.4	43.3	58.7	94.8
Capsule B	2	0.0	4.1	8.4	20.5	36.5	49.1	86.1
Capsule B	Average	0.1	5.2	11.8	21.4	39.9	53.9	90.4

[a] All dosages contained 75 mg. of drug.

did not disintegrate but released 88% of the drug in 2 hr. Capsule B had a dissolution half-life about 4.5 times faster than Capsule A. This illustrates the large difference between the capsule dissolution rates, even for a highly water-soluble drug.

Bioavailability data are shown in Table VII as the cumulative percent of phenylpropanolamine hydrochloride excreted in the urine *versus* time. A solution containing the same dose was used as a standard. The urine data showed a lag time in the excretion from both capsules in the 30-min. sampling. However, after the first interval, significant differences in the amounts of phenylpropanolamine hydrochloride excreted were apparent. There was a delay in the urinary excretion of Capsule A through the first 6 hr. of the study. The largest difference in the excretion data of the two capsules occurred in the 1.5–2-hr. interval, where 21.4% was excreted from Capsule B and only 12.0% from Capsule A. After 24 hr., the average cumulative percent of drug excreted from both Capsules A and B was similar, that is about 90% of the dose was excreted.

The rank order correlation between the *in vitro* and *in vivo* data demonstrates how the new apparatus can be used effectively in the evaluation of capsule formulations. In this situation with phenylpropanolamine hydrochloride capsules, the extent of the *in vitro* dissolution differences was evaluated through *in vivo* testing and was found to be significant.

CONCLUSION

The tablet and capsule disintegration and dissolution apparatus has been shown to be a useful tool for characterizing the disintegration and dissolution properties of capsule and tablet formulations. Although the explicit formula variation gave noticeable *in vitro* differences, biological testing is necessary to determine the extent of these differences. The phenylpropanolamine hydrochloride *in vivo* studies clearly demonstrate that careless capsule formulation can result in retarded *in vivo* drug availability, and the new apparatus can provide data that will lead the researcher to improving the formulation for better *in vivo* performance.

Wagner (7) proposed three requirements for an apparatus that qualifies it for both research and quality control purposes. The tablet and capsule disintegration and dissolution apparatus satisfies these requirements in that it is inexpensive, scientifically realistic, versatile, and has good precision. Wagner (8) also pointed out that a universal dissolution test is desirable but largely impractical, since each drug must be handled on an individual basis. However, the new apparatus offers flexibility which enables the formulator to alter the test conditions for any drug in a solid dosage form. After the *in vitro* test conditions are correlated with *in vivo* data, the new apparatus with its established testing specifications can be subsequently used in quality control laboratories for testing batches of either tablets or capsules.

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