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New *In Vitro* Dissolution Test Apparatus

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Abstract □ A new *in vitro* dissolution test apparatus was designed and evaluated. Compressed tablets of drugs representing different solubility characteristics were tested at various air pressures and compared to dissolution patterns of similar tablets by the Levy beaker and USP methods. Air pressure of 46 mm generally was suitable for determining the dissolution rates of tablets. This new dissolution tester possibly can be useful in determining drug release from solid dosage forms and correlating it with *in vivo* bioavailability because dissolution rate can be controlled easily with the adjustment of air pressure without complicated changes in the apparatus, there is no excessive settling of particles, and complete drug dissolution can be achieved with no clogging of the screen.

Keyphrases □ Dissolution test apparatus—designed, evaluated with various drugs at various air pressures, compared to other methods □ Apparatus, dissolution test—designed, evaluated with various drugs at various air pressures, compared to other methods

Determination of *in vitro* dissolution rates is important in the design, evaluation, and quality control of solid dosage forms. The USP and NF dissolution tests suffer from a number of technical problems (1, 2).

Various other methods generally involve induced agitation. The Levy beaker method (3) is the most commonly used method and is generally recommended as a standard. Other reported methods (4–7) have the commonly encountered problem of mound formation of particles at the bottom of the container due to poor particle dispersion. Mound formation may affect apparent dissolution characteristics (8). In this study, a better correlation was observed with a rotating flask that allowed good dispersion at low agitation. Another problem is the degree of agitation, which is usually greater than what the dosage form will encounter in the GI tract.

The USP and NF methods also are subject to poor dispersion. In these methods, the screen acts as an interfacial barrier at moderate stirring rates. In addition, the fine mesh screen is clogged by undissolved particles (9).

An apparatus will be most suitable for *in vitro* testing of solid dosage forms if it achieves a thorough dispersion of particles with minimum agitation, similar to the agitation in the GI tract. With these factors under consideration, an *in vitro* dissolution tester was designed and evaluated.

EXPERIMENTAL

Description of Apparatus—The apparatus (Figs. 1 and 2) consists of two cylindrical glass tubes: tube A, 28.4 cm long × 3.4 cm i.d.; and tube B, 29.4 cm high × 2.8 cm i.d. Tube B is connected to tube A at the base and at a length of 17.3 cm by tubes with an identical diameter of 1.0 cm and a length of 4.7 cm.

A stainless steel basket and an air tube are suspended in tube A. The bottom of the basket is approximately 15.7 cm from the bottom of tube A, and the air tube just protrudes from the stopper.

The basket consists of a solid metal top with a small vent and is fitted

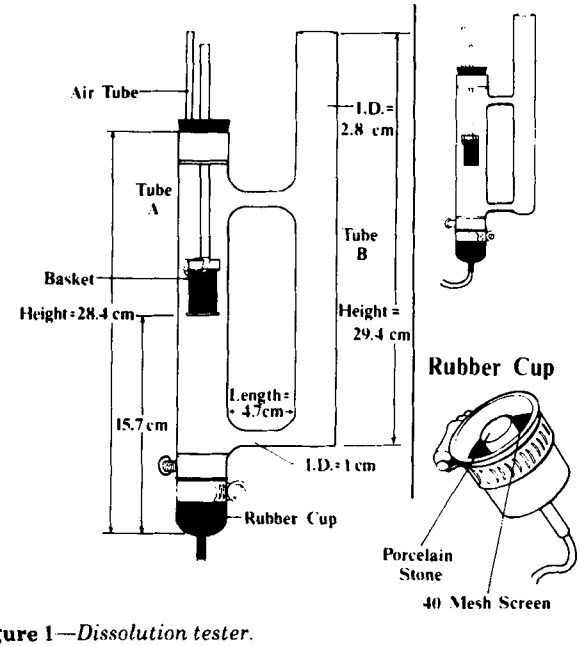

Figure 1—*Dissolution tester.*

Table I—Levels of Significance (t Values) of Dissolution Rates of Piperazine Citrate and Isoniazid Tablets at Various Times with the New Tester at Various Air Pressures, the Levy Tester, and the USP Dissolution Tester at $p = 0.05$

	Piperazine Citrate Tablets				Isoniazid Tablets				
	5 min	10 min	20 min	30 min	5 min	10 min	20 min	30 min	40 min
Levy *versus* new tester at various air pressures									
40 mm Hg	2.8982	2.6963	2.2218[a]	2.58888[a]	5.2981	4.2100	3.8107	3.4330	4.5120
43 mm Hg	2.0600[a]	1.5716[a]	1.4132[a]	1.4258[a]	3.5750	3.8300	3.7600[a]	2.7791	3.7850
46 mm Hg	0.5891[a]	0.4715[a]	0.4761[a]	0.3158[a]	1.4100[a]	0.8455[a]	1.8530[a]	1.0100[a]	0.6740[a]
50 mm Hg	3.3870	3.4576	—	—	6.2040	4.2700	4.4131	5.6340	1.6752[a]
55 mm Hg	4.7290	4.9785	—	—	7.8131	5.976	4.738	5.988	2.000[a]
USP *versus* new tester at various air pressures									
40 mm Hg	4.9138	3.5336	3.3733	1.7978	2.6000	9.5890	10.7170	14.2012	14.0258
43 mm Hg	5.7963	4.3974	4.1262	2.5678	4.3340	10.5890	12.1508	15.3370	15.4827
46 mm Hg	8.6940	6.7307	6.0306	4.6922	13.5800	17.7680	21.1520	21.8700	23.8440
50 mm Hg	11.5979	9.5923	—	—	23.8791	23.4086	29.5544	28.0192	25.5271
55 mm Hg	12.4310	10.6009	—	—	29.2345	28.2037	29.7330	28.8143	26.1031
USP *versus* Levy tester					8.7450	16.3810	17.4100	19.1720	22.1480

[a] Statistically not significant.

to the basket with three spring clips. The basket is cylindrical and is made of stainless steel 40-mesh wire cloth, 3.66 cm high and 2.50 cm in diameter.

A cylindrical porcelain stone protruding through a central circular hole in a circular piece of 40-mesh stainless steel screen inside a rubber cup is fixed at the bottom, supported by a stainless steel sleeve. An opening at the bottom of the rubber cup adjacent to the bottom of the porcelain stone is connected by 5.5-mm polyethylene tubing to an air pump through a mercury manometer.

Dissolution Test Procedure—A 350-ml volume of 0.1 N HCl was the dissolution medium. One tablet was added to the basket, and the basket base was adjusted to a distance of 15.7 cm from the tester bottom. The dissolution tester was then immersed in a constant-temperature water bath maintained at 37°.

The dissolution tester was connected to an air pump. The air flow was controlled with a mercury manometer. Tests were conducted at air pressures of 40, 43, 46, 50, and 55 mm. The air pressure created circulation of liquid in the two tubes.

Samples of 5 ml were withdrawn from tube B at specified intervals, and an equal volume of 0.1 N HCl was added after each withdrawal. Each sample was then filtered and assayed by a procedure specified for each drug.

Twenty tablets each of commercial piperazine citrate and isoniazid and six tablets each of aspirin, phenobarbital, and sulfadiazine from various batches were tested. Aspirin (3) and phenobarbital (10) were assayed by the procedures reported previously. Isoniazid (11), piperazine citrate (12), and sulfadiazine (13) were assayed by the USP XVIII procedures.

For comparison, 20 representative tablets of isoniazid and piperazine citrate from the same batches were tested in the USP dissolution test apparatus. Similarly, isoniazid, piperazine citrate, aspirin, phenobarbital, and sulfadiazine were also tested by the Levy method (3), modified by using 350 ml of 0.1 N HCl as the dissolution medium instead of 250 ml. Samples of 5 ml were withdrawn at specified intervals, and equal volumes of 0.1 N HCl were added after each withdrawal. These samples were then assayed for drug concentration.

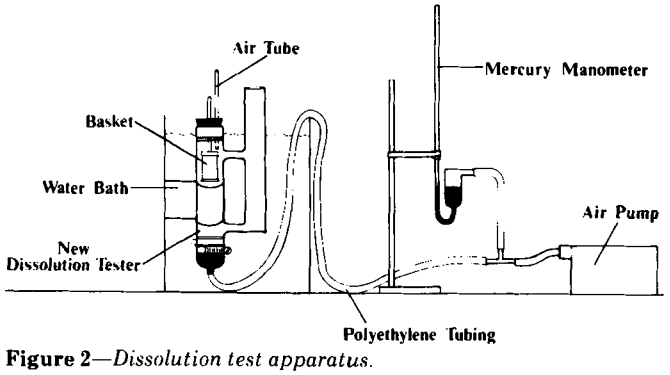

Figure 2—*Dissolution test apparatus.*

RESULTS AND DISCUSSION

The Levy beaker method has been recommended as a standard to compare other dissolution testers (14). This method also showed excellent *in vitro-in vivo* correlation (15, 16) and was used for comparison purposes previously (17, 18).

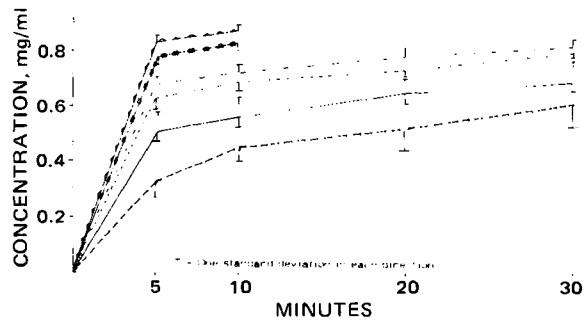

Figure 3—*Comparative dissolution rates of piperazine citrate tablets with the new dissolution tester at various air pressures, the Levy tester, and the USP dissolution tester. Key: HH, USP tester; —, 40 mm Hg; ···, 43 mm Hg; - - -, Levy tester; ·····, 46 mm Hg; □, 50 mm Hg; and △, 55 mm Hg.*

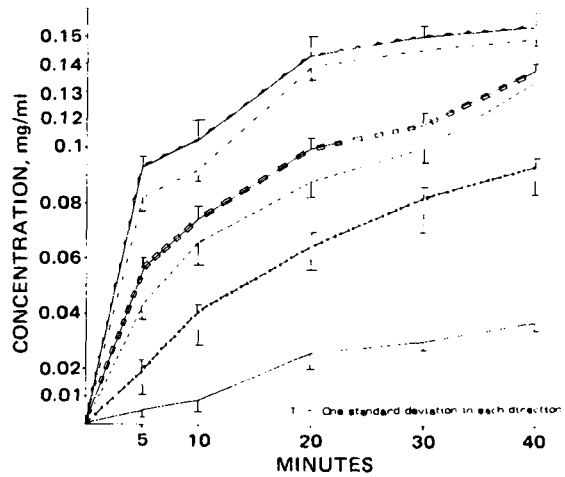

Figure 4—*Comparative dissolution rates of isoniazid tablets with the new dissolution tester at various air pressures, the Levy tester, and the USP dissolution tester. Key: —, USP tester; ····, 40 mm Hg; ●—●, 43 mm Hg; - - -, Levy tester; □, 46 mm Hg; ·····, 50 mm Hg; and △, 55 mm Hg.*

Table II—Levels of Significance (t Values) of Dissolution Rates of Aspirin, Sulfadiazine, and Phenobarbital Tablets at Various Times with the New Tester at Various Air Pressures and the Levy Dissolution Tester at $p = 0.05$

Product	Air Pressure, mm Hg (New Tester)	5 min	10 min	20 min	30 min	55 min	75 min
Aspirin							
Brand I, Batch A	40	1.1050[a]	1.5785[a]	3.6305	4.8932	—	—
Brand I, Batch A	43	0.9866[a]	0.9471[a]	2.5256[a]	4.1040	—	—
Brand I, Batch A	46	0.7893[a]	1.1050[a]	1.2628[a]	2.0677[a]	—	—
Brand I, Batch A	50	4.1438	4.2621	7.8925	7.4187	—	—
Brand I, Batch A	55	7.1037	7.2614	7.4189	7.8923	—	—
Brand I, Batch B	46	1.9930[a]	2.5573[a]	2.5700[a]	0.0159[a]	—	—
Brand II, Batch A	46	0.959[a]	0.732[a]	1.079[a]	0.825[a]	—	—
Brand II, Batch B	46	2.4850[a]	0.6485[a]	2.5600[a]	0.7279[a]	—	—
Sulfadiazine							
Batch A	40	—	30.000	15.930	13.892	16.734	4.908
Batch A	43	—	4.349	5.693	0.999	12.939	5.317
Batch A	46	—	5.480	3.424	6.410	5.899	5.310
Batch A	50	—	0.813[a]	4.962	2.010[a]	2.617	1.694[a]
Batch A	55	—	9.180	24.325	12.808	45.027	12.815
Batch B	46	—	1.602[a]	6.788	4.737	2.292[a]	2.509[a]
Phenobarbital							
Batch A	40	8.776	8.667	4.840	4.840	—	—
Batch A	43	3.112	2.360	4.469	4.469	—	—
Batch A	46	0.846[a]	1.681[a]	0.110[a]	0.110[a]	—	—
Batch B	46	0.533[a]	2.434[a]	2.432[a]	2.432[a]	—	—

[a] Statistically not significant.

Isoniazid, piperazine citrate, aspirin, phenobarbital, and sulfadiazine tablets consisted of 50, 315, 324, 30, and 500 mg of active ingredients/tablet, respectively. The dissolution rate studies with the new apparatus were conducted at 40, 43, 46, 50, and 55 mm of air pressure. All air pressures were sufficient to induce uniform circulation of the liquid in the apparatus. The use of an air tube prevented air bubbles from collecting at the bottom of the stainless steel basket. Any air bubbles at the bottom of the tube immediately combined into a larger bubble and broke off without hindering the movement of solid particles.

Although the circulation of fluid was not violent, it was sufficient at all speeds not to allow settlement of any solid particles at the bottom of the two tubes of the dissolution tester, probably because of the continuous movement of particles and the pattern and path of flow of fluid. There was no clogging of the screen during the test, probably because of the circulation of the dissolution medium through the screen.

Dissolution rates of 20 tablets from the same batch of isoniazid and piperazine citrate were determined. The dissolution rates of these tablets increased with the increase in air pressure. The results (Table I and Figs. 3 and 4) indicate that, for both types of tablets, there was less significant difference in the dissolution rates in the new tester at 46 mm and the Levy tester as compared to 40, 43, 50, and 55 mm of air pressure. Significant differences were observed between dissolution rates in the USP dissolution tester and the new tester at all air pressures. Similar results were obtained for the dissolution in the Levy tester and the USP dissolution tester (Figs. 3 and 4 and Table I).

The dissolution rates of Brand I, Batch A aspirin tablets were determined in the new dissolution tester at air pressures of 40, 43, 46, 50, and 55 mm. The dissolution rate increased with the increase in the air pressure (Fig. 5). The results (Table II and Fig. 5) again indicate less significant difference in the dissolution rate of these aspirin tablets in the new tester at 46 mm and the Levy tester as compared to 40, 43, 50, and 55 mm of air pressure. Therefore, it seemed to be the most appropriate pressure and was used in further investigations of aspirin tablets.

Batch B of Brand I aspirin tablets and Batches A and B of Brand II aspirin tablets also were tested by the Levy tester and the new dissolution tester at 46 mm of air pressure (Figs. 6 and 7, respectively).

Similar studies were conducted on two batches each of one brand of sulfadiazine and phenobarbital tablets at various air pressures (Figs. 8 and 9). Batch A sulfadiazine tablets were tested for dissolution with the

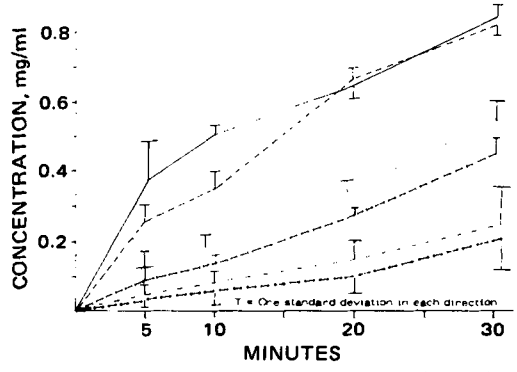

Figure 5—*Comparative dissolution rates of Brand I, Batch A aspirin tablets with the new dissolution rate tester. Key: ·····, 40 mm Hg; -·-·-, 43 mm Hg; ⊢⊣⊢, Levy tester; ····, 46 mm Hg; – – –, 50 mm Hg; and —, 55 mm Hg.*

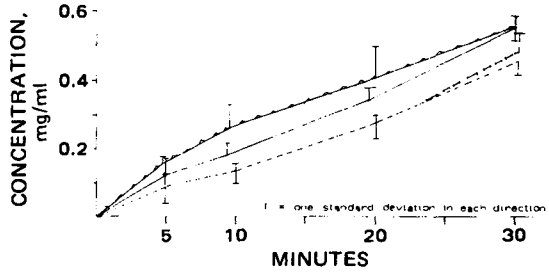

Figure 6—*Comparative dissolution rates of Brand I, Batch B aspirin tablets with the Levy tester and the new dissolution rate tester. Key: Δ, Brand I, Batch B with new tester; —, Brand I, Batch A with new tester; ⊢⊣⊢, Brand I. Batch A with the Levy tester; and - - - -, Brand I, Batch B with the Levy tester.*

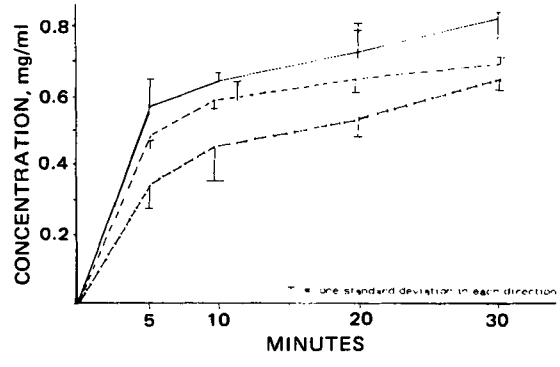

Figure 7—*Comparative dissolution rates of Brand II, Batches A and B aspirin tablets with the Levy tester and the new dissolution rate tester. Key: —, Brand II, Batch A with new tester; ····, Brand II, Batch B with new tester; - - -, Brand II, Batch A with Levy tester; and ⊢⊣⊢, Brand II, Batch B with the Levy tester.*

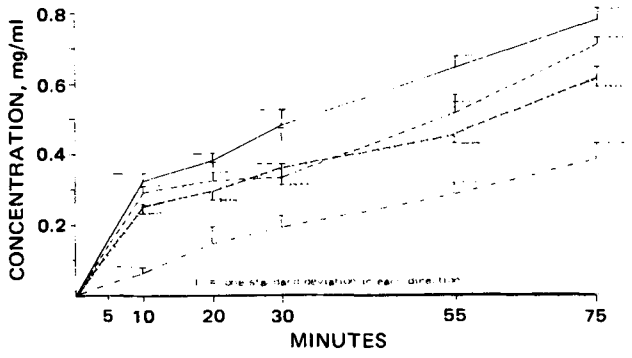

Figure 8—*Comparative dissolution rates of Batch A sulfadiazine tablets with the new dissolution rate tester. Key: ·····, 40 mm Hg; ⊢⊣, 43 mm Hg; ····, 46 mm Hg; - - -, 50 mm Hg; and —, 55 mm Hg.*

new tester at air pressures of 40, 43, 46, 50, and 55 mm. Batch A phenobarbital tablets were not tested at 50 and 55 mm because preliminary studies showed that the tablets went into solution within 5 min, which was less than their disintegration time. The dissolution rate increased with the increase in air pressure. Batch B sulfadiazine tablets were tested at 46 mm of air pressure.

Similar tablets of sulfadiazine and phenobarbital were also tested with the Levy dissolution tester, and the results were compared statistically with the results obtained at various air pressures with the new dissolution tester. There was less significant difference between dissolution rates of sulfadiazine tablets with the Levy tester and the new dissolution tester at 50 mm of pressure as compared to other speeds (Table II). On the other hand, there was a nonsignificant difference between the dissolution rates of phenobarbital tablets with the Levy tester and the new dissolution tester operated at 46 mm of air pressure (Table II).

The results of the dissolution rates of Batches A and B sulfadiazine and phenobarbital tablets with the Levy tester and the new dissolution tester at 46 mm are shown in Figs. 10–13.

Table III—Levels of Significance (t Values) of Dissolution Rates of Various Batches of Tablets at Various Times with the New Tester at 46 mm of Air Pressure at $p = 0.05$

Product	5 min	10 min	20 min	30 min	55 min	75 min
Aspirin Brand I, Batch A *versus* Brand I, Batch B	0.572[a]	1.1087[a]	0.8869[a]	0.1108[a]	—	—
Aspirin Brand II, Batch A *versus* Brand II, Batch B	1.465[a]	0.800[a]	0.526[a]	0.395[a]	—	—
Sulfadiazine Batch A *versus* Batch B	—	0.316[a]	1.517[a]	1.257[a]	0.765[a]	0.607[a]
Phenobarbital Batch A *versus* Batch B	0.667[a]	0.892[a]	0.892[a]	0.892[a]	—	—

[a] Statistically not significant.

Further evaluation of the results by statistically comparing the dissolution rates of two batches of the same brand, each with the Levy tester and with the new dissolution tester at 46 mm of air pressure (Tables III and IV), indicates a nonsignificant difference in the dissolution rates of the two different batches of the same brand when tested with the new tester and the Levy tester, except for sulfadiazine Batches A and B, where the difference was significant with the Levy tester.

Groups of tablets of each product from the same batch were tested individually in the new tester, and the deviations (Figs. 3–13) indicate reproducibility of results within a batch. These results also indicate that this method appears to be as reproducible as the USP or Levy method. In addition, a batch-to-batch nonsignificant difference in the dissolution rates was observed. As shown in Table V, these batches had well-controlled physical properties such as hardness and disintegration time.

An overall reevaluation of the results show that an air pressure of 46 mm generally was suitable in correlating the dissolution rates of various tablets studied with the new tester with the results obtained with the Levy

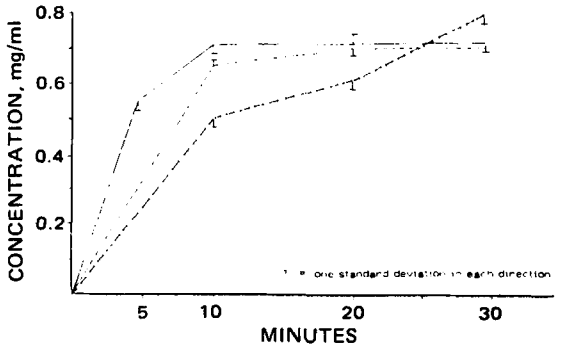

Figure 9—*Comparative dissolution rates of Batch A phenobarbital tablets with the new dissolution rate tester. Key: ⊢⊣, 40 mm Hg; - - -, 43 mm Hg; and —, 46 mm Hg.*

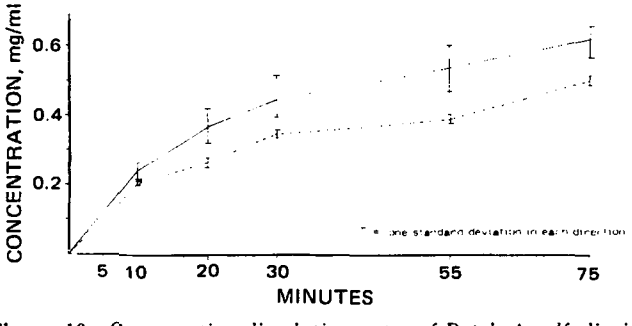

Figure 10—*Comparative dissolution rates of Batch A sulfadiazine tablets with the Levy tester (- - -) and the new dissolution rate tester (—).*

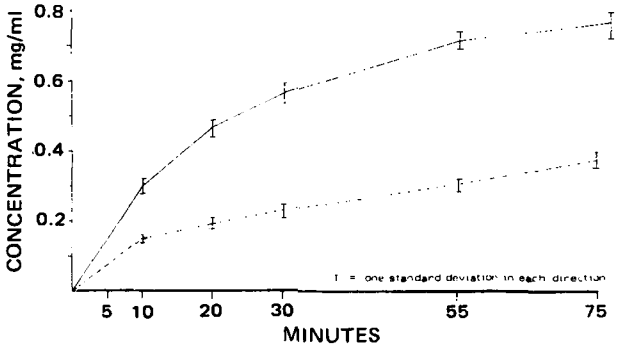

Figure 11—*Comparative dissolution rates of Batch B sulfadiazine tablets with the Levy tester (- - -) and the new dissolution rate tester (—).*

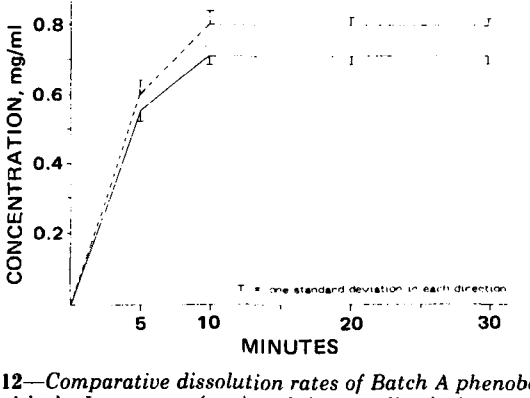

Figure 12—*Comparative dissolution rates of Batch A phenobarbital tablets with the Levy tester (- - -) and the new dissolution rate tester (—).*

Table IV—Levels of Significance (t Values) of Dissolution Rates of Various Batches of Tablets at Various Times with the Levy Tester at $p = 0.05$

Product	5 min	10 min	20 min	30 min	55 min	75 min
Aspirin Brand I, Batch A *versus* Brand I, Batch B	0.000[a]	0.000[a]	0.000[a]	0.2300[a]	—	—
Aspirin Brand II, Batch A *versus* Brand II, Batch B	1.2928[a]	1.3181[a]	1.593[a]	0.4486[a]	—	—
Sulfadiazine Batch A *versus* Batch B	—	4.903	3.531	10.804	61.118	4.302
Phenobarbital Batch A *versus* Batch B	1.123[a]	1.189[a]	0.310[a]	0.310[a]	—	—

[a] Statistically not significant.

tester. On the other hand, less significant differences in the dissolution rate of sulfadiazine tablets with the Levy tester and the new dissolution tester at 50 mm of pressure as compared to other pressures also indicate that other air pressures may be more suitable for some products with considerably different solubility characteristics.

Poor agreement was observed in the dissolution rates of piperazine citrate and isoniazid tablets in the USP dissolution rate tester as compared to the new tester at all pressures and the Levy tester. For better correlation of dissolution rates in the new tester and the USP dissolution tester, other pressures and speeds may be suitable. A detailed study is being conducted.

This new dissolution tester possibly can be useful in determining and correlating *in vitro* drug release from solid dosage forms with *in vivo* bioavailability, because dissolution can be controlled easily with the adjustment of air pressure without complicated changes in the apparatus. Other advantages of this dissolution tester are that, in all systems studied, no excessive settling of solid particles was observed and a complete dissolution of the drugs was achieved with no clogging of the screen. The possibility exists, however, that tablets with significantly different properties may produce contrary results.

Detailed studies also are being conducted to compare *in vitro* dissolution of tablets in the new dissolution tester with *in vivo* availability of various drugs.

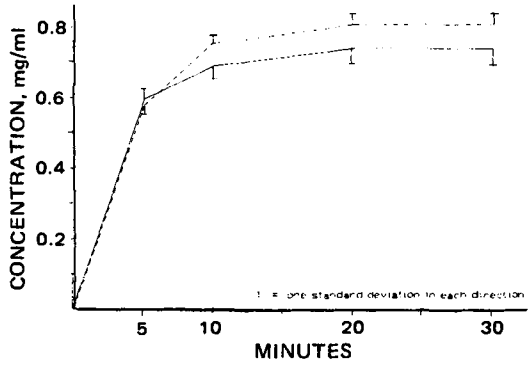

Figure 13—*Comparative dissolution rates of Batch B phenobarbital tablets with the Levy tester (- - -) and the new dissolution rate tester (—).*

Table V—Physical Properties of Various Commercial Tablets Used in the Dissolution Studies

Product	Hardness, kg stokes ± SD	Disintegration Time, sec ± SD
Piperazine citrate	5.5 ± 0.029	55.00 ± 0.030
Isoniazid	4.1 ± 0.004	31.90 ± 0.008
Aspirin Brand I, Batch A	11.333 ± 0.6054	10.833 ± 0.983
Aspirin Brand I, Batch B	11.416 ± 0.4915	11.00 ± 0.8944
Aspirin Brand II, Batch A	5.00 ± 0.5477	9.000 ± 0.8944
Aspirin Brand II, Batch B	5.50 ± 0.6324	9.833 ± 0.7527
Sulfadiazine Batch A	5.333 ± 0.408	283.000 ± 25.976
Sulfadiazine Batch B	8.166 ± 0.605	280.66 ± 25.64
Phenobarbital Batch A	4.083 ± 0.204	387.50 ± 27.522
Phenobarbital Batch B	4.10 ± 0.252	396.00 ± 24.23

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