establish the kinetics of the absorption phenomena in this biologic model.

Although major abdominal surgery is required, the chronicity of the fistula dog permits each animal to serve as its own control. The same animal can be used repeatedly to compare the absorption characteristics of the same drug at different dosage levels, as well as different drugs at the same and alternate dosage levels. It may also be possible to evaluate absorption from various dosage formulations such as solutions, suspensions, single dose, and sustained-release solid dosage forms. Investigations of the interactions of drug combinations with regard to intestinal absorption are also feasible because the animal is serving as its own control. This is in contrast to other techniques, such as the ligated rat intestine, where the viability of the isolated segment is in question after a relatively short period of time.

Furthermore, the animal and *in situ* loop may be considered essentially identical for each experiment. The uniformity of the absorbing surface (*i.e.*, the loop) does not vary in a given animal as contrasted with the use of different animals. The mucosal epithelium, the blood, lymph, and nerve supplies remain essentially constant from one experiment to another.

The absorbing surface of the intestinal mucosa of the dog is closely related to that of man. Thus, preliminary investigations using Thiry-Vella dogs can provide data from which at least semi-quantitative predictions may be made of the absorption of a compound in man.

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Keyphrases

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Jejunal loop—Thiry-Vella fistula
N-Acetyl-*p*-aminophenol—absorption
Plasma-*N*-acetyl-*p*-aminophenol—analysis

Factors Affecting the Dissolution Rate of Medicaments from Tablets I

In Vitro Dissolution Rate of Commercial Phenobarbital Tablets

By JAMES T. JACOB* and ELMER M. PLEIN

An *in vitro* dissolution test method is described and 42 lots of commercial phenobarbital tablets produced by 24 manufacturers were evaluated by means of the test. Thirteen lots of tablets showed incomplete dissolution within 30 min., six of which failed to release 100 percent of the drug in 1 hr. The dissolution rate data are compared with those obtained by the USP XVII tablet disintegration procedure. No correlation existed between the two tests.

THE IMPORTANCE of determining physiological availability of medicaments from tablets was recognized only recently. Even though the USP tablet disintegration test is not designed to show a measure of physiological availability of medicament, this test is used by manufacturers, as well as drug control agencies, as one of the criteria in determining the quality of tablets. There is evidence in the literature that this test leaves much to be desired as a control test in the production of tablets (1–3).

Nelson (4) reported that dissolution rate was the rate-determining factor in absorption of

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* Present address: Product Development and Services Laboratories, Merck and Co., Inc., Rahway, N. J.

tetracycline, provided that the dosage form restricted the initial surface area. He reported also that absorption of benzylpenicillin and of acetylsalicylic acid was proportional to the dissolution rate of the drugs in the gastrointestinal tract (5). Levy (6) has pointed out that the dissolution rate of a drug in particulate form is determined by a number of factors including intrinsic dissolution rate, particle size distribution, speed and type of agitation, anisotropism, and presence of other solids.

A variety of techniques is used to determine *in vitro* dissolution rates of medicaments from tablets. Levy and Hayes (7) used a beaker method to determine the dissolution rates of nationally advertised brands of aspirin. Later Levy devised the oscillating tube method and the rotating disk method (8). A revolving plastic dialysis cell containing a paper membrane was used by Marlowe and Shangraw (9) to determine dissolution rate of sodium salicylate from tablets. Schroeter and Wagner (10) used an automatic dissolution apparatus consisting of a USP tablet disintegration apparatus connected through a flow cell to a spectrophotometer, with attachments for filtration and dilution of solution. Several solid dosage forms were studied by this procedure.

A survey of recent literature shows several instances of clinical ineffectiveness of commercial tablets which met USP requirements including disintegration tests. These reports include prednisone tablets evaluated by Campagna *et al.* (3), studies by Carter (11), by Levy (12), and Brudney *et al.* (13) of tolbutamide tablets, and a study by Lozinski (14) of bishydroxycoumarin tablets. In each case the *in vitro* dissolution rate of the drug was found to be poor.

An *in vivo* dissolution and absorption test would likely give a more complete evaluation of a tablet formulation than could an *in vitro* test; however since an *in vivo* test would involve such factors as individual and species variation in absorption as well as tablet dissolution, interpretation of the results of such tests is very complex. Whereas *in vitro* dissolution tests do not register physiological availability of a drug *per se*, yet carefully designed *in vitro* dissolution tests can be used as an index of the physiological availability of active constituents from tablets. Different formulation and manufacturing procedures are known to influence the disintegration rate and the dissolution rate of tablets. The objectives of this study were (*a*) to determine the USP disintegration rate and the *in vitro* dissolution rate of a generic name product, namely phenobarbital tablets manufactured by several companies and (*b*) to study how some variable factors in manufacture and storage affect the availability of phenobarbital from the uncoated tablet. This portion of the report is concerned with commercially available tablets.

Phenobarbital is supplied in tablets of various strengths by a number of different pharmaceutical companies. Phenobarbital is a weak acid with a pKa of 7.5. It is readily absorbed from stomach, small intestine, rectum, and intramuscular sites. The mechanism of absorption from gastrointestinal sites is by nonionic diffusion (15).

EXPERIMENTAL

Commercial Phenobarbital Tablets—Forty-two lots of uncoated phenobarbital tablets of various strengths (1/4 gr., 1/2 gr., and 1 1/2 gr.) manufactured by 24 different pharmaceutical concerns within the United States were purchased either directly from the manufacturer or from wholesale drug suppliers. The dissolution rate of each lot of tablets was determined. The USP disintegration test was carried out on those lots of tablets which showed poor dissolution rate in the acid medium.

In Vitro Dissolution Test—A modified oscillating tube method originally designed by Levy (8) was used. The modified apparatus consisted of an oscillating tube which was a Plexiglas cylinder (19 cm. in length and 1.9 cm. in diameter) with a 40-mesh stainless steel screen fused to one end and a wire hook attached to the other end. The cylinder was attached to the basic unit of USP tablet disintegration apparatus by means of the wire hook (oscillating tube replacing basket-rack assembly). The cylinder was inserted through the opening of a plastic lid into a 400-ml. beaker containing 300 ml. of 0.1 *N* HCl of pH 1.2 (acid medium) or a buffer solution[1] (alkaline medium) of pH 9.5 maintained at 37° ± 0.5°. A 2-blade stirring shaft was introduced into the beaker through another opening in the plastic lid. The shaft was attached to a variable speed external stirrer.[2] The apparatus was set in motion, and a weighed tablet was dropped into the cylinder. At the end of 5 min. the apparatus was stopped, the cylinder was detached and gently raised above the level of the medium. The solution was then stirred at 600 r.p.m. for 30 sec. and 5 ml. was pipeted for analysis. The oscillating tube was then slowly immersed into the medium and the apparatus was set in motion once again. Five milliliters of medium was added to the solution in the beaker to replace that amount withdrawn. Samples were taken similarly at 10-, 20-, 30-, and 60-min. intervals and analyzed. Three runs were made on each lot of tablets and their average was recorded. If readings were not within 2% of average, then the experiment was repeated three more times and the average of the six readings was recorded.

Analytical Method—Phenobarbital was determined spectrophotometrically with a Beckman

[1] The buffer solution (boric acid–potassium chloride–sodium hydroxide) was prepared according to the method described by Mattson (16).

[2] Manufactured by Gerald K. Heller Co., Las Vegas, Nev.

TABLE I—DISSOLUTION RATES AND DISINTEGRATION TIMES[a] OF SOME COMMERCIAL PHENOBARBITAL TABLETS

Manufacturer	Strength, gr.[b]	% Phenobarbital Dissolved in Acid, 30 Min.	% Phenobarbital Dissolved in Acid, 60 Min.	% Phenobarbital Dissolved in Alkali, 30 Min.	Disintegration Time, Min., with Disks	Disintegration Time, Min., without Disks	Hardness[c]
A	1/2	69.9	100	74.2	12 (11–13.5)	48 (40–60)	4.5
B	1/4	25.0	32.0	100	12 (11–13)	134 (100–168)	2.5
C	1/2	43.0	100	100	8 (7–12)	23 (16–28)	3.5
D	1/4	80.0	100	86.6	6 (6–7)	34 (28–40)	5.5
E	1/2	18.4	29.8	22.2	20 (18–21)	65 (55–90)	9.0
F	1/2	42.0	82.5	50.0	16 (13–18)	48 (46–49)	5.5
G	1 1/2	11.2	18.3	20.4	45 (38–51)	...[d]	11.0
H	1 1/2	80.6	100	88.1	20 (19–20)	50 (39–64)	10.5
I	1 1/2	43.6	67.2	84.8	7 (6–8)	...[d]	7.0
J	1/2	89.3	100	46.9	19 (15–20)	...[e]	7.0
K	1 1/2	60.9	74.0	53.7	4 (3–5)	202 (150–270)	5.5
L	1/2	84.7	100	35.6	7 (7–8)	33 (30–35)	2.5
M	1 1/2	51.7	78.6	49.6	24 (20–25)	...[d]	6.5

[a] Determined by USP XVII procedure. [b] The approximate metric equivalents of 1/4 gr., 1/2 gr., and 1 1/2 gr. are 15 mg., 30 mg., and 100 mg., respectively. [c] As Strong-Cobb units. [d] All 6 tablets remained on the screen at the end of 120 min. [e] Three tablets disintegrated in 100–115 min.; 3 remained on the screen at the end of 120 min.

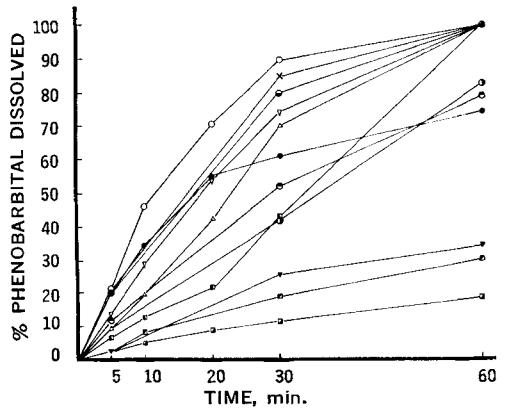

Fig. 1—Dissolution rates in 0.1 N HCl, of some commercial phenobarbital tablets. Key: ○, J 1/2 gr.; ×, L 1/2 gr.; ◒, D 1/4 gr.; ▽, H 1 1/2 gr.; △, A 1/2 gr.; ●, K 1 1/2 gr.; ◓, M 1 1/2 gr.; ◧, C 1/2 gr.; ◑, F 1/2 gr.; ▼, B 1/4 gr.; ◩, E 1/2 gr.; ◪, G 1 1/2 gr.

model DU spectrophotometer. Solutions were filtered through Whatman No. 41 filter paper and were diluted appropriately with buffer solution of pH 9.5 and the absorbance was measured at 240 mμ.

Disintegration Test—The USP XVII tablet disintegration test with and without disks was carried out on 13 lots of tablets which showed poor dissolution rates in acid medium. Actual disintegration times were recorded.

RESULTS AND DISCUSSION

Dissolution—Twenty lots of tablets out of 42 lots studied released 100% phenobarbital within 5 min., 4 lots within 5–10 min., 3 lots within 10–20 min., and 2 lots within 20–30 min. when a 0.1 *N* HCl bath was used. Thirteen lots of tablets failed to release 100% phenobarbital into the acid medium within 30 min. (Table I). At the end of 60 min. of test, 3 out of the 13 lots of tablets did not release at least 50% of the drug. A comparison of dissolution pattern of 12 out of these 13 lots of tablets is illustrated in Fig. 1. One lot (manufacturer I, 1 1/2 gr.) showed considerable tablet-to-tablet variation in dissolution rate. In order to get an approximation of the dissolution rate of the tablets in the intestinal tract, the 13 lots of tablets were subjected to dissolution test in an alkaline medium consisting of a buffer solution of pH 9.5. Despite the fact that phenobarbital is highly soluble in buffer solution of pH 9.5, 11 out of the 13 lots of tablets did not release 100% phenobarbital in 30 min. In some cases the dissolution rate in alkaline medium was slower than in acid medium (manufacturers J, K, L, and M). In most cases the tablets broke apart into fairly large pieces, but failed to disintegrate any further, thereby failing to release phenobarbital into the medium. The failure of medium to penetrate the granules may be attributed to formulation factors such as types and concentrations of binder, disintegrant, filler, and lubricant, and hardness of compression.

Another interesting finding from the dissolution study in the acid medium was the great difference in dissolution rate of phenobarbital from tablets of various strengths manufactured by the same company (Table II). The difference in dissolution rates of these tablets was thought possibly to be due to several factors such as size, hardness, shape, whether scored or unscored, quantity of excipients, *etc.*, but Table II seems to indicate that these properties were not responsible for the variable rates. Since the two lots of tablets were formulated separately, it has to be presumed that some of the formulation factors have influenced the dissolution rate of these tablets.

Disintegration—The USP XVII tablet disintegration test with and without disks showed remarkable difference in results. From Table I it can be seen that all lots of tablets except one passed the test with disks, whereas 12 lots of tablets failed the test without disks. There was absolutely no correlation between disintegration times (with disks) and dissolution rates. The tablet that disintegrated within 4 min. (manufacturer K, 1 1/2 gr.) had released only 61% of the drug into acid medium in 30 min., whereas the same lot of tablets took 202 min. to disintegrate completely when disks were not used in the test. The disks exerted a slight pounding action on tablets and resulted in fast and fairly uniform disintegration times. Although it can be generalized that tablets which took a long time to disintegrate (without disks) had relatively poor dissolution rates, no quantitative correlation can be made between the two tests. Tablets which dis-

TABLE II—VARIATIONS IN THE DISSOLUTION RATES OF PHENOBARBITAL TABLETS OF DIFFERENT STRENGTHS PRODUCED BY THE SAME MANUFACTURERS

Manufacturer	Strength, gr.[a]	% Phenobarbital Dissolved in 30 min.	% Excipient in the Tablet	Hardness[c]	Shape
A	1 1/2	100 (3)[b]	42.3	7.0	S.C.;[d] scored
A	1/2	70	73.4	4.5	S.C.; unscored
I	1/2	100 (4)[b]	69.8	10.0	Scored pellet[e]
I	1 1/2	44	50.0	6.5	S.C.; scored
J	1/4	100 (10)[b]	92.9	6.5	Large scored pellet
J	1/2	89	70.1	7.0	S.C.; unscored
K	1/4	100 (30)[b]	84.1	3.5	Unscored pellet
K	1 1/2	57	47.4	5.5	S.C.; scored

[a] The approximate metric equivalents of 1/4 gr., 1/2 gr., and 1 1/2 gr. are 15 mg., 30 mg., and 100 mg., respectively [b] Actual time in minutes for complete dissolution. [c] As Strong-Cobb units. [d] S.C. = Standard concave. [e] Flat-faced tablet.

integrate into particles small enough to pass through 10-mesh screen may still contain drug within the cores which may not be released into the medium.

Experimental data indicated usefulness of test apparatus for determining *in vitro* availability of active ingredients from tablet bases. It was found that stirring the solution using an external stirrer (not by movement of oscillating tube alone) was essential to get accurate and reproducible results. Since the solution was maintained at 37°, covering the beaker during the experiment also helped to obtain more reproducible results.

SUMMARY AND CONCLUSIONS

A modification was made in the dissolution, apparatus described by Levy, and this apparatus was used to determine the *in vitro* dissolution rate of phenobarbital from tablets. Forty-two lots of commercial phenobarbital tablets from 24 companies were tested. Thirteen out of the 42 lots of tablets failed to release 100% phenobarbital in 30 min. when 0.1 *N* HCl was used as the medium. Out of these 13 lots 11 lots failed to release 100% of the drug in 30 min. when the acid medium was replaced by an alkaline medium. The dissolution rate in the two media differed markedly and this fact has to be taken into consideration in evaluating the physiological availability of the drug. Since the dissolution rates of tablets of different strengths made by the same manufacturers showed considerable variation, factors such as types and concentrations of diluent, binder, disintegrant, and lubricant, as well as hardness of compression, should be considered in the formulation of tablets.

There was absolutely no correlation between the dissolution rate and the disintegration time (with and without disks). The USP disintegration test should be replaced by a dissolution test and the limits of dissolution rate should be based on *in vitro* determination or *in vitro-in vivo* correlations (wherever possible to determine) specific for the drug in question and the type of the tablet.

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Keyphrases

Dissolution rates, phenobarbital tablets—factors affecting
In vitro dissolution test—method
Disintegration—dissolution rates compared
UV spectrophotometry—analysis