Factors Affecting Dissolution Rate of Medicaments from Tablets II

Effect of Binder Concentration, Tablet Hardness, and Storage Conditions on the Dissolution Rate of Phenobarbital from Tablets

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A series of formulations is described in which several binders are used in varying proportions and the tablets are compressed at different pressures. Results show the effects of these variables on dissolution rates of phenobarbital tablets in an acid medium of pH 1.2. Some data on the effects of storage of tablets under controlled conditions are presented.

IN ORDER that a clinical response be elicited by administration of a tablet, not only should the tablet contain the labeled amount of medicament, but also the medicament should be fully available to the body. When drugs are administered in dosage forms other than solutions, the rate at which the dosage form releases the medicament into gastrointestinal fluid may be more important than the effective surface area of the absorbing agent. For this reason with solid dosage forms (tablets, capsules, powder, *etc.*) the absorption of medicament may depend upon the dissolution rate of the formulation and/or the medicament (1).

Several workers have studied the effects of various formulation factors on dissolution rates of medicaments from compressed tablets. Sunkes (2) found an inverse relationship between the amount of salicylamide dissolved from granules and the percent of granulating agent used in preparing these granules. He found also that tablets released salicylamide at a faster rate than did granules from which tablets were made. An opposite observation was reported by Harris (3) who found that granules released medicament faster than did tablets made from the same granules. Henderson's (4) studies indicated that the effect of particle size upon either tablet hardness or dissolution time is characteristic of a particular compound and that no general prediction could be made as to quantitative correlation among these factors for all drugs. Levy *et al.* (5) studied effects of granule size, starch concentration, and compression pressures on the dissolution rate of salicylic acid from granules prepared by double compression. They found that the dissolution rate increased with decreasing granule size, with increasing starch content, and with increasing precompression pressures. Levy and Gumtow (6) in a study of the effect of lubricants on the dissolution rate of salicylic acid from tablets reported that a hydrophobic lubricant (magnesium stearate) retards dissolution rate, whereas a water-soluble surface-active agent (sodium lauryl sulfate) increases dissolution rate. Yen (7) conducted an extensive study on various factors affecting the dissolution rate of triamterene tablets and concluded that besides studying individual factors affecting the dissolution rate the combination of various factors should be considered for a true evaluation. Parrot *et al.* (8) reported that when neutral, ionic, and nonionic organic compounds were employed as additives, the dissolution rate of benzoic acid was linearly dependent upon its solubility in the particular solvent system.

In a study of commercial phenobarbital tablets it was found that several lots of tablets showed poor dissolution rates in an acid medium and also in an alkaline medium (9). Since one or more various formulation factors could contribute to the slow dissolution rate of these commercial tablets, this investigation was undertaken to study two factors, in particular—namely, binder concentration and compression hardness. Effects of certain storage conditions on dissolution rate also were studied. Fumed silicon dioxide[1] which is used chiefly as a free flowing agent and arabinogalactan[2] which is a natural gum exudate were evaluated for their tablet-binding properties.

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[1] Marketed as Cab-O-Sil by Cabot Corp., Boston, Mass.

[2] Marketed as Stractan by Stein, Hall and Co., Inc., New York, N. Y.

TABLE I—COMPOSITION, HARDNESS, AND DISSOLUTION RATES OF PHENOBARBITAL TABLETS[a]

Batch No.	Lactose %	Fumed SiO_2 %	Arabinogalactan %	Hardness[b]	Time for 100% Dissolution, sec.
1	36	1	2	6.0	30
2	36	0	3	6.5	55
3	33	1	5	5.0	600
4	36	1	2[c]	5.0	40
5	33	1	5[c]	6.5	3600[d]
6	34	5	0	7.0	40
7	37	2[c]	0	6.0	60
8	34	5[c]	0	6.5	20

[a] Each tablet contained 50% phenobarbital, 10% starch, and 1% magnesium stearate in addition to the ingredients listed in table. [b] As Strong-Cobb units. [c] As solution or gel in water. [d] 94% released in 30 min.

TABLE II—EFFECT OF HARDNESS ON DISSOLUTION RATES OF PHENOBARBITAL TABLETS PREPARED WITH 5% ARABINOGALACTAN

Batch No.	Hardness[a]	% Phenobarbital Dissolved per Time Interval, min. 5	10	20	30	60
3A	5.0	92.6	100.0	...	...	...
3B	6.0	44.2	95.9	100.0	...	...
5A[b]	5.0	100.0	...	...	...	...
5B[b]	6.5	20.0	34.3	84.4	94.3	100.0
5C[b]	9.5	13.4	[c]	37.2	76.3	98.4

[a] As Strong-Cobb units. [b] Binder added as solution. [c] Did not determine.

EXPERIMENTAL

Formulation of Tablets—A number of batches of phenobarbital tablets was manufactured by wet granulation (approximately 250 tablets to a batch). Each tablet was made to contain 100 mg. of phenobarbital and 100 mg. of excipients composed of varying quantities of binders. Besides fumed silicon dioxide and arabinogalactan, a few commonly used binders also were used (acacia, gelatin, ethyl cellulose,[3] and hydroxyethyl cellulose[4]). Various concentrations of fumed silicon dioxide and arabinogalactan were used either as powders or as solutions or gels in water to make the tablets. Tablets were compressed from 20/40-mesh granules on a Stokes single-punch machine model 511-5 using $^1/_{16}$-in. (~0.8 cm.) die and standard concave punches.

Hardness—Tablets were compressed at various pressures maintaining a minimum hardness of 5 Strong-Cobb units.

Dissolution Test—Rate of release into 0.1 *N* HCl (pH 1.2) was determined by the use of the test method previously described (9).

USP XVII tablet disintegration test with and without disks was carried out only on those batches of tablets which did not release 100% phenobarbital in 30 min.

Aging—Six tablets from each batch were kept in an open 2-dram (~10 ml.) vial in an oven set at 55° for 16 days and then were tested for hardness and dissolution rate at the end of the storage period.

Humidity Studies—Six tablets from each batch containing fumed silicon dioxide or arabinogalactan were stored at 98% relative humidity in a desiccator containing a saturated solution of potassium dichromate kept at 25° (10), for 30 days, and the following tests were carried out: amount of absorbed moisture (tablets were weighed before and after storage in the desiccator), hardness, and dissolution rate. The dissolution rates were determined immediately after removing the tablets from the desiccator and also after exposing them to room temperature for 24 hr. during which time they lost moisture and attained constant weight.

[3] Marketed as Ethocel by Dow Chemical Co., Midland, Mich.

[4] Marketed as Natrosol by Hercules Powder Co., Glens Falls, N. Y.

RESULTS AND DISCUSSION

Table I gives the dissolution rates of phenobarbital from tablets manufactured using fumed silicon dioxide or arabinogalactan as a binder. Granules made with fumed silicon dioxide in concentrations of 2% and 5% as a gel in water and 5% as powder possessed good binding qualities and produced smooth, shiny tablets of satisfactory hardness and fast dissolution rates (maximum dissolution time 60 sec.). Arabinogalactan was found to be a good binder when used in concentrations of 2–5%. An increase in concentration of arabinogalactan, however, resulted in a decrease in dissolution rate, especially when the binder was used in the form of a gel in water (dissolution time 3600 sec.).

Table II shows effect of hardness on dissolution rates of phenobarbital tablets prepared with 5% arabinogalactan added as a powder and granulated with water or used as a solution in water to granulate the powder mixture.

Tests on tablets formulated with acacia, gelatin, ethyl cellulose, and hydroxyethyl cellulose used as binders in various concentrations clearly indicate how dissolution rates can be affected by altering the concentration of binder as well as hardness of the tablet (Table III). Satisfactory tablets were obtained with acacia or gelatin as a binding agent, although differences in hardness of the tablets affected their dissolution rates. An increase in hardness by 2 Strong-Cobb units was responsible for about 50% reduction in dissolution rate of tablets prepared with acacia (Batch No. 9A and 9B). Hardness of tablets is also a factor in dissolution rates of tablets prepared with 2% gelatin (Batch No. 10A and 10B), with 4% gelatin (Batch No. 11A and 11B), and perhaps with 5% ethyl cellulose. The effects of concentration of gelatin and hardness of compression

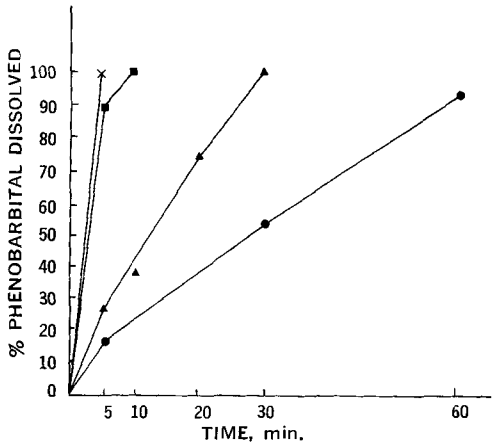

Fig. 1—Dissolution rates in 0.1 N HCl, of phenobarbital tablets made with gelatin as a binder. Key: ×, 2% gelatin (No. 10A) compressed at a hardness of 6.5 Strong-Cobb units; ■, 2% gelatin (No. 10B) compressed at a hardness of 10.0 Strong-Cobb units; ▲, 4% gelatin (No. 11A) compressed at a hardness of 6.5 Strong-Cobb units; ●, 4% gelatin (No. 11B) compressed at a hardness of 13.0 Strong-Cobb units.

on dissolution rates of tablets are illustrated in Fig. 1. Ethyl cellulose and hydroxyethyl cellulose possess good binding properties and produced tablets with good physical appearance; however, the poor dissolution rates shown in Table III indicate they are unsatisfactory binding agents in these formulations.

The USP tablet disintegration test with and without disks was carried out on tablets with slow dissolution rates in 0.1 *N* HCl and the results are shown in Table III. A comparison of dissolution rates and disintegration times (with and without disks) showed no correlation between the two tests. Tablets formulated with 1% ethyl cellulose took 60 min. to release 98% of the drug into acid medium, but the disintegration time in water was only 30 sec. (No. 12, Table III). This great disparity can be attributed to the fact that tablets swelled on contact with water and broke apart into small particles, whereas in the acid medium no such swelling was observed.

The results of aging tablets at 55° for 16 days, which storage time is approximately equivalent to a storage time at room temperature for 2 yr. (11), showed slight increase in tablet hardness (Table IV). This observation substantiates earlier reports found in the literature (12, 13). There was no decrease in dissolution rates as a result of increased hardness due to aging.

Considerable quantities of moisture were absorbed by tablets when they were exposed to 98% relative humidity for 30 days as a result of which the dissolution rates of these tablets were markedly decreased. A comparison of data in Tables I and V shows the differences in the dissolution rates. The quantity of moisture absorbed and retained depended upon the type and concentration of binder used. Tablets made with arabinogalactan absorbed more moisture than did those made with fumed silicon dioxide (Table V). The quantity of absorbed moisture was directly proportional to the concentration of binder used. There were remarkable differences in dissolution rates of tablets determined immediately after removal from the humidity chamber and after they had lost most of the absorbed moisture. Tablets made with fumed silicon dioxide clearly indicated this variation (Batch No. 6, 7, and 8, Table V). The absorbed moisture retarded the dissolution rates of drug by preventing the acid solution from penetrating into the tablets. After losing most of the absorbed moisture (by evaporation at

TABLE IV—EFFECT OF ACCELERATED AGING OF PHENOBARBITAL TABLETS AT ELEVATED TEMPERATURE ON HARDNESS AND DISSOLUTION TIME

Batch No.	Hardness[a] A[b]	Hardness[a] B[c]	Time for 100% Dissolution in 0.1 *N* HCl (sec.) A[b]	Time for 100% Dissolution in 0.1 *N* HCl (sec.) B[b]
1	6.0	7.0	30	40
2	6.5	7.0	55	60
3	5.0	5.0	600	300
4	5.0	6.0	40	50
5	6.5	7.0	3600[d]	600
6	7.0	9.0	40	35
7	6.0	6.0	60	60
8	6.5	7.3	20	30

[a] As Strong-Cobb units. [b] Immediately after manufacture. [c] After storing for 16 days at 55°. [d] 94% release in 30 min.

TABLE III—EFFECT OF HARDNESS ON DISSOLUTION RATES AND DISINTEGRATION TIMES OF PHENOBARBITAL TABLETS PREPARED WITH SOME COMMON BINDERS

Batch No.	Binder	Concentration of Binder %	Hardness[a]	% Phenobarbital Dissolved per Time — Interval, min. 5	10	20	30	60	Disintegration Time, min. with Disks	Disintegration Time, min. without Disks
9A	Acacia	4	6.5	71.8	100	...	...	...	...	...
9B	Acacia	4	8.5	36.8	52.2	89.3	100	...	...	...
10A	Gelatin	2	6.5	100	...	...	...	...	...	...
10B	Gelatin	2	10.0	89.1	100	...	...	...	...	...
11A	Gelatin	4	6.5	26.1	38.9	73.8	100	...	...	...
11B	Gelatin	4	13.0	16.4	[b]	[b]	52.3	92.1	15.0	35.0
12	Ethyl cellulose	1	6.5	70.1	[b]	[b]	93.3	98.3	0.5	10.0
13A	Ethyl cellulose	5	6.5	5.0	[b]	[b]	11.6	15.6	57.0	[c]
13B	Ethyl cellulose	5	9.0	4.1	[b]	[b]	8.0	14.0	[d]	[e]
14	Hydroxyethyl cellulose	2	5.0	19.2	30.9	43.7	59.5	83.2	16.0	20.5
15	Hydroxyethyl cellulose	4	6.5	4.3	11.0	18.8	22.3	36.8	[f]	82.0

[a] As Strong Cobb units. [b] Did not determine. [c] Over 120 min. [d] Approximately 75% of the tablet remained on the screen after 120 min. [e] Approximately 90% of the tablet remained on the screen after 120 min. [f] Could not determine accurately since the tablets remained glued to the disks from the beginning of the test.

TABLE V—EFFECT OF MOISTURE ON THE DISSOLUTION RATES OF PHENOBARBITAL TABLETS EXPOSED TO 98% RELATIVE HUMIDITY FOR 30 DAYS

Batch No.	% Moisture Absorbed	% Moisture Retained	% Phenobarbital Dissolved in 30 min. A[a]	% Phenobarbital Dissolved in 30 min. B[b]	% Phenobarbital Dissolved in 60 min. A[a]	% Phenobarbital Dissolved in 60 min. B[b]
1	4.69	0.36	17.0	21.9	30.6	34.7
2	5.64	0.29	17.9	19.4	31.1	42.5
3	7.81	0.37	21.2	24.6	33.1	37.6
4	4.82	0.33	18.0	22.0	31.5	33.9
5	7.73	0.35	16.0	17.1	30.0	31.8
6	6.54	0.23	24.9	77.1	30.5	90.7
7	4.57	0.07	15.1	33.5	21.4	61.4
8	6.78	0.36	20.0	72.2	37.1	93.7

[a] Dissolution rate determined immediately after removal from the humidity chamber. [b] Dissolution rate determined following storage in the humidity chamber and after the tablet had been exposed to room temperature to a constant weight.

room temperature) the tablets were more vulnerable to penetration of 0.1 *N* HCl resulting in an increased dissolution rate. However, the increased dissolution rates were considerably lower than the dissolution rates of the same tablets prior to their storage in the humidity chamber.

SUMMARY AND CONCLUSIONS

1. Fumed silicon dioxide and arabinogalactan in concentrations of 2–5% possess good tablet-binding qualities.

2. Increase in binder concentration and hardness of compression resulted in a decrease in the dissolution rates of phenobarbital tablets. Selection of binder, its concentration, and hardness at which tablets are compressed are important factors which should be properly controlled so that the medicament will be completely released for quick physiological availability.

3. No apparent change in dissolution rate was observed when phenobarbital tablets were aged at 55° for 16 days.

4. Depending upon type and concentration of binder, phenobarbital tablets absorbed varying quantities of moisture when exposed to 98% relative humidity for 30 days. As a result of moisture absorption, dissolution rates of phenobarbital from those tablets were considerably decreased. An increased dissolution rate was observed when the moist tablets were tested after exposure to room temperature for 24 hr. during which time they lost most of the absorbed moisture. However, this increased dissolution rate was much lower than the original dissolution rate of the tablet.

5. No correlation was found between dissolution rate and USP tablet disintegration test with and without disks.

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Keyphrases

Tablets—compressed
Dissolution rates, phenobarbital tablets—factors affecting
Binders—tablet dissolution rate
Hardness—tablet dissolution rate
Aging—tablet dissolution rate
Moisture—tablet dissolution rate