Effect of Tablet Processing and Formulation Factors on Dissolution Rate of the Active Ingredient in Human Gastric Juice

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Abstract □ *The effect of the granulation and tableting processes* on the dissolution rate of phenobarbital, sodium phenobarbital, phenacetin, and prednisone in human gastric juice has been investigated. A study has also been made on the influence of the particle size of the active ingredient and the effect of different binders on the dissolution rate of phenobarbital.

Keyphrases □ Tablet dissolution rates—human gastric juice □ Gastric juice, human—phenobarbital, phenacetin, prednisone tablets, dissolution □ Formulation, processing effects—dissolution rates □ Particle size effect—phenobarbital dissolution □ Binders effect—tablet dissolution

The effect of formulation and processing factors on the dissolution rate of the active ingredients of compressed tablets has been the subject of a number of reports (1–14). Various dissolution media such as water, hydrochloric acid, buffer solutions, simulated gastric juice, and simulated intestinal fluid, have been used, but, surprisingly enough, not that solvent, in which the dissolution process takes place *in vivo*—that is, human gastric juice.

The scope of the present investigation was to study *the effect of the granulation and tableting processes* and the influence of certain formulation factors on the dissolution rate of the active ingredient in human gastric juice.

EXPERIMENTAL

Materials—All drugs were of Pharmacopoea Nordica grade. The phenobarbital and phenacetin powders were separated into the desired size fractions by sieving. The prednisone used was a micronized product, having a particle size between 1 and 8 μ determined with a Celloscope, an apparatus that works on the Coulter counter principle.

The gastric juice was obtained as described in an earlier paper (15). A mixture of equal parts of gastric juice and water was used as dissolution medium. This mixture is named "diluted gastric juice" in the present paper.

Preparation of Granules and Tablets—The desired size fraction of the drug powder was mixed with potato starch (or potato starch + lactose) and gently moistened with the granulating solution. The moistened mass was sieved and dried. The dry granules were separated into different size fractions by sieving. The 0.71–1.00 mm. size fraction of the granules[1] was mixed with a lubricant and compressed into tablets on a single punch tablet machine. Specifications for the experimental granules and tablets are given in Table I.

Determination of Hardness—The hardness of the tablets was determined with a Pfizer tablet hardness tester.

Determination of Disintegration Time—The disintegration time of the tablets was determined according to *The Nordic Pharmacopeia:* three tablets were placed in a conical flask, mixed with 30 ml. of water at a temperature between 36 and 40° and kept at this temperature with frequent swinging of the flask.

Determination of Dissolution Rate—The dissolution rate was determined by the beaker method of Levy (16) with minor changes (15). For each test the drugs, granules, and tablets were—if not otherwise stated—used in amounts that were more than sufficient for saturation of the dissolution medium with the drug. The drug powders and the granules were gently spread over the surface of the fluid, and settled down through the fluid during the test. The tablets were dropped into the dissolution medium. At appropriate intervals samples of the dissolution medium were withdrawn, filtered and analyzed.

Analytical Methods—*Determination of Prednisone*—The samples withdrawn were diluted with 0.1 *N* HCl and absorbances were

[1] Granules passing through standard sieve U. S. No. 18 (sieve opening 1.00 mm.), but not through sieve No. 25 (sieve opening 0.71 mm.).

Table I—Specifications for Experimental Granules and Tablets

	Phenobarbital Granules and Tablets[a] I	II	III
Phenobarbital[b]	100 g.	100 g.	100 g.
Potato starch	70 g.	70 g.	70 g.
Gelatin[c]	A sufficient quantity		
Carboxymethylcellulose[d]		A sufficient quantity	
Polyethylene glycol 6000[e]			A sufficient quantity
Magnesium stearate and talc (1+9)	10 g.	10 g.	10 g.
Tablet hardness	4.4 kg.cm.$^{-2}$	2.1 kg.cm.$^{-2}$	0.9 kg.cm.$^{-2}$
Disintegration time	30 sec.	5 min.	20 sec.

Sodium Phenobarbital Granules and Tablets I[f]	
Sodium phenobarbital[g]	125 g.
Potato starch	70 g.
Gelatin[h]	A sufficient quantity
Magnesium stearate and talc (1+9)	10 g.
Tablet hardness: 6.4 kg.cm.$^{-2}$	
Disintegration time: 3 min.	

Phenacetin Granules and Tablets[i]	
Phenacetin (0.21–0.30 mm.)	500 g.
Potato starch	115 g.
Gelatin[c]	A sufficient quantity
Magnesium stearate and talc (1+9)	30 g.
Tablet hardness: 4.5 kg.cm.$^{-2}$	
Disintegration time: 1 min.	

Prednisone Granules and Tablets[j]	
Prednisone (<8 μ)	5 g.
Lactose	80 g.
Potato starch	85 g.
Gelatin[c]	A sufficient quantity
Magnesium stearate and talc (1+9)	10 g.
Tablet hardness: 6.6 kg.cm.$^{-2}$	
Disintegration time: 1.5 min.	

[a] 1000 tablets, diameter 8 mm. [b] Particle size: 0.21–0.30 mm., if not otherwise stated. [c] 4% solution of gelatin in water as granulating agent. [d] 2% solution of sodium carboxymethylcellulose in water as granulating agent. [e] 50% solution of Carbowax 6000 in alcohol (95%) as granulating agent. [f] 1000 tablets, diameter 8 mm. [g] A crystalline powder with most particles within the 0.11–0.30 mm. range was used. [h] 10% solution of gelatin in alcohol as granulating agent. [i] 1000 tablets, diameter 13.5 mm. [j] 1000 tablets, diameter 8 mm.

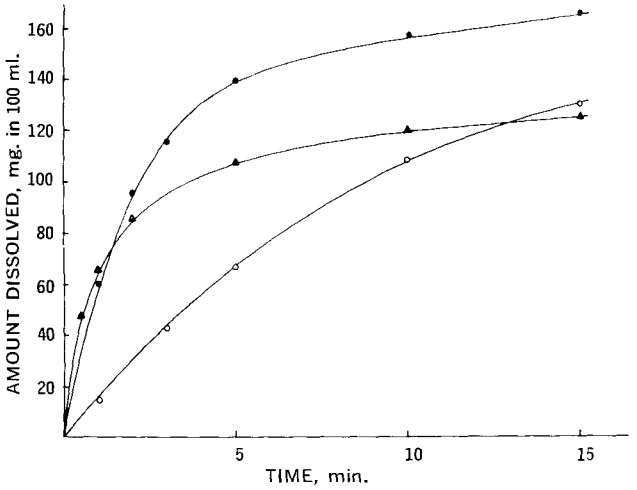

Figure 1—*Rate of dissolution of phenobarbital from powder, granules I, and tablets I in diluted gastric juice (surface tension 42.5 dynes cm.$^{-1}$, pH 1.70). Key: ○, phenobarbital powder; ▲, phenobarbital granules I; ●, phenobarbital tablets I.*

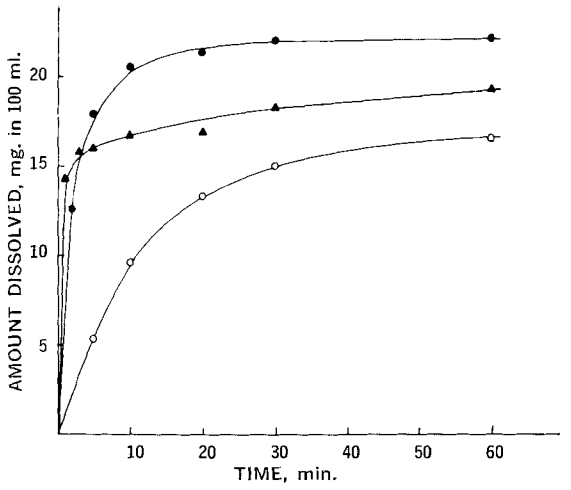

Figure 3—*Rate of dissolution of prednisone from powder, granules, and tablets in diluted gastric juice (surface tension 41.1 dynes cm.$^{-1}$, pH 1.50). Key: ○, prednisone powder; ▲, prednisone granules; ●, prednisone tablets.*

measured at 243 mμ with a Beckman DK 2A spectrophotometer.

Phenobarbital and phenacetin were determined as described earlier (15).

RESULTS AND DISCUSSION

Effect of the Granulation and Tableting Processes—The rate of dissolution of phenobarbital, phenacetin, and prednisone was determined before and after granulation and compression into tablets.

It will be seen from Figs. 1–3 that the rate of release of all three drugs from the granules is higher than the rate of dissolution of the pure drugs. The granulation process has increased the dissolution rate, probably by making the originally hydrophobic drug particles hydrophilic.

Figs. 1 and 3 show that phenobarbital and prednisone are released at a higher speed from the tablets than from the granules. The reason for this is probably that the drugs—during the dissolution test—are more rapidly wetted when contained in tablets, because the tablets are dropped into the dissolution medium and disintegrate completely within 1–2 min., whereas the granules are spread over the surface of the fluid and settle more slowly down through the fluid. It is also possible that the compression process leads to deformation or crushing of the granule particles, thus increasing the specific surface area of the granules and their rate of dissolution. In this connection it may be noted that Higuchi *et al.* (17) have shown that the specific surface area of tablet granules becomes greater with increasing compression pressure. These authors assumed that this was due to the crushing of the granule particles. In a later paper Higuchi *et al.* (18) have shown that with normal tableting pressures, deformation of the granules takes place but without the particles breaking up. The particles are changed from being almost spherical to being nearly disk-shaped and hence their surface area is increased.

The experiments, the results of which are given in Figs. 1–3, were so scaled that there would always be undissolved drug remaining at the end of each test. Figure 4 shows the results of an experiment where such amounts of phenobarbital powder, granules and tablets were used for each test that a complete dissolution might occur (one 100-mg. tablet or an equivalent amount of granules or drug powder). It will be seen that this procedure leads in principle to the same result as the other procedure, *i.e.*, the tablets showing a faster dissolution rate than the granules and the drug powder.

Effect of Particle Size of the Active Ingredient—Phenobarbital tablets were prepared according to Formula I. Different size fractions of the drug powder were used. Figure 5 shows that the rate of dissolution of phenobarbital from the tablets increases with decreasing particle size of the drug. This result was expected since the granulation process has made the surface of the drug particles hy-

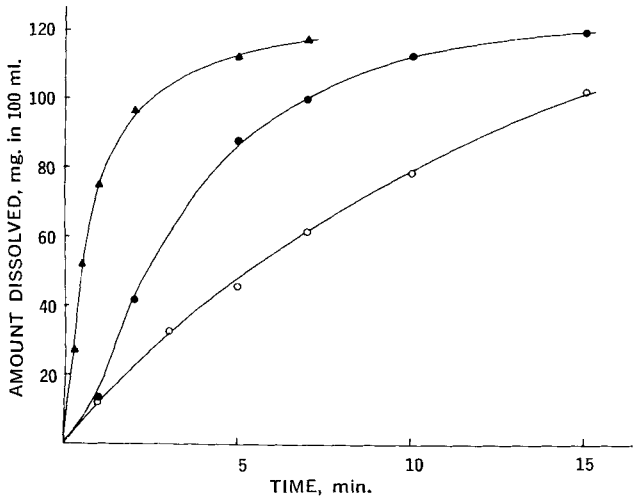

Figure 2—*Rate of dissolution of phenacetin from powder, granules, and tablets in diluted gastric juice (surface tension 42.7 dynes cm.$^{-1}$, pH 1.85). Key: ○, phenacetin powder; ▲, phenacetin granules; ●, phenacetin tablets.*

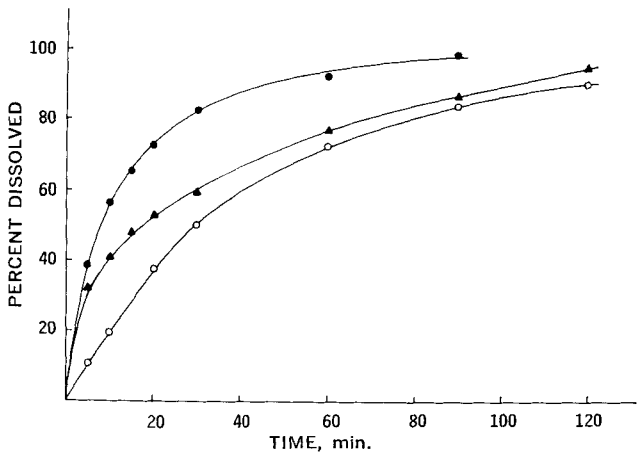

Figure 4—*Rate of dissolution of phenobarbital from powder, granules I, and tablets I in diluted gastric juice (surface tension 46.4 dynes cm.$^{-1}$, pH 1.95). Key: ○, phenobarbital powder; ▲, phenobarbital granules; ●, phenobarbital tablets.*

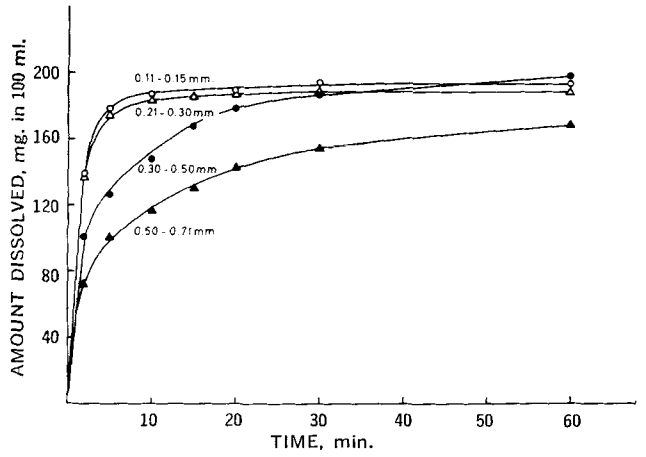

Figure 5—*Effect of particle size of phenobarbital on dissolution rate of the drug from tablets I in diluted gastric juice (surface tension 40.5 dynes cm.$^{-1}$, pH 1.50).*

drophilic. In addition the dissolution medium has a low surface tension.

Effect of Different Binders—Phenobarbital tablets were prepared according to Formulas I, II, and III. The same pressure was, as far as possible, used for the compression of the three batches of tablets.

Figure 6 shows that there are great differences in dissolution rates. These differences could not be attributed to differences in disintegration times during the dissolution test. Tablets I disintegrated within 45 sec., tablets II within 6 min., and tablets III within 20 sec. This means—as an example—that even though tablets III had a slightly shorter disintegration time in diluted gastric juice than tablets I, the rate of dissolution was much lower.

It will be seen from Fig. 6 that the tablets prepared with gelatin as granulating agent have a much higher dissolution rate than the tablets prepared with CMC or polyethylene glycol 6000 as binders. This result is in accordance with earlier findings (8) from this laboratory that the use of gelatin as binder leads to granules and tablets with a very high dissolution rate in 0.1 *N* HCl. The high dissolution rate of these granules and tablets is believed to be due to the ability of gelatin to make originally hydrophobic surfaces of drug particles hydrophilic. This theory is supported by earlier experiments with phenacetin as model substance, showing that this hydrophobic drug after mixing with potato starch and granulation with gelatin dissolved at the same high rate in 0.1 *N* HCl as the ungranulated drug did in 0.1 *N* HCl containing 0.2% polysorbate 80 as wetting agent (8).

The reason why phenobarbital dissolves so slowly from tablets II is probably that the binder, sodium carboxymethylcellulose, at

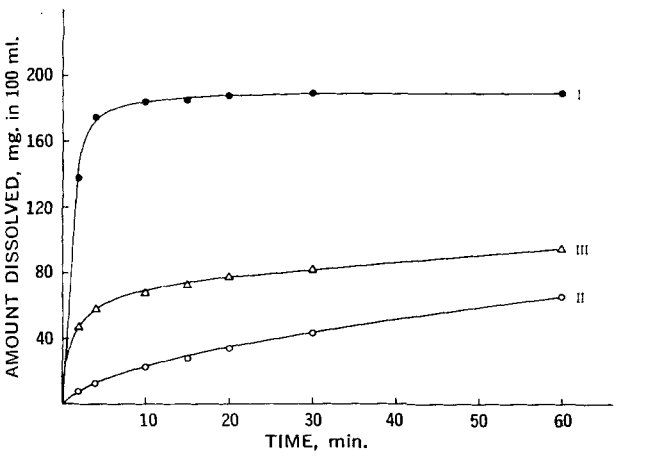

Figure 6—*Rate of dissolution of phenobarbital from tablets I, II, and III in diluted gastric juice (surface tension 39.4 dynes cm.$^{-1}$, pH 1.50).*

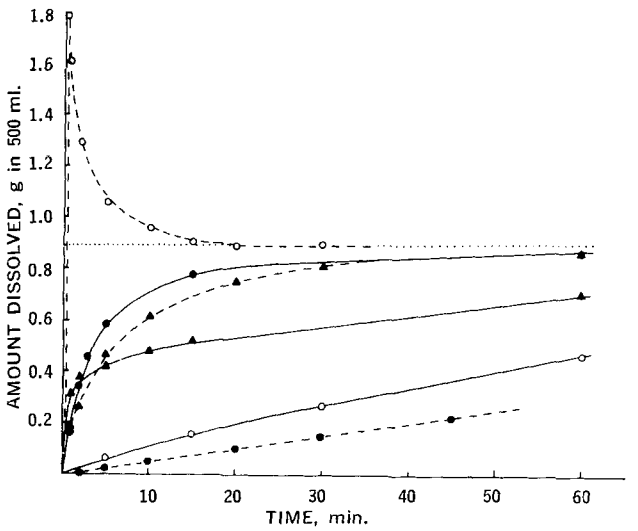

Figure 7—*Rate of dissolution of phenobarbital and sodium phenobarbital from powder, granules I, and tablets I in 0.1 N HCl. The dotted line parallel with the x-axis indicates the concentration of a saturated solution of phenobarbital in 0.1 N HCl at 37°. Key: ——, phenobarbital; - - -, phenobarbital sodium; ○, powder; ▲, granules I; ●, tablets I.*

the pH of the dissolution medium (pH 1.5) is converted into the less hydrophilic free acid.

As far as tablets III is concerned the slow dissolution is assumed to be due to a complex formation between the drug and the granulating agent. Each tablet III contained 100 mg. of phenobarbital and about 35 mg. of polyethylene glycol 6000. Higuchi and Lach (19) and later Singh *et al.* (20) have shown that phenobarbital forms stable compounds of reduced solubility with polyethylene glycols. Singh *et al.* found the ratio to be 45.5 mg. of polyethylene glycol 4000 per 100 mg. of phenobarbital at 37° and pH 5.3. The following experiment seems to indicate that a complex of reduced solubility is formed between the drug and the granulating agent of tablets III.

Two tablets were placed in 40 ml. of hydrochloric acid solution pH 1.5 (the pH of the diluted gastric juice) and the mixture was equilibrated at 37° for 30 hr. A phenobarbital concentration of only 65 mg.% was found, whereas tablets I and II gave a phenobarbital concentration of 180 mg.% under the same experimental conditions. The complex between the drug and the granulating agent of tablets III is probably formed during the dissolution test and not

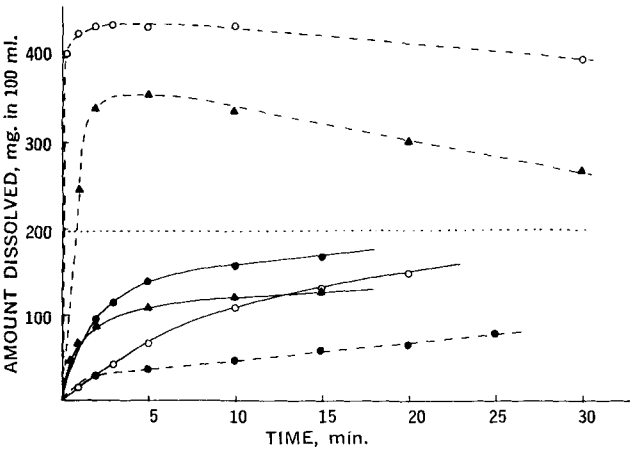

Figure 8—*Rate of dissolution of phenobarbital and sodium phenobarbital from powder, granules I, and tablets I in diluted gastric juice (surface tension 40.5 dynes cm.$^{-1}$, pH 1.70). The dotted line parallel with the x-axis indicates the concentration of a saturated solution of phenobarbital in diluted gastric juice at 37°. Key: —, phenobarbital; - - -, phenobarbital sodium; ○, powder; ▲, granules I; ●, tablets I.*

during the preparation of the tablets, since the amount of alcohol used for granulation (about 35 g. per 100 g. of phenobarbital) can not dissolve more than 4% of the total amount of drug present.

It may be mentioned that complexation in some cases may *increase* dissolution rates. Wurster and Kildsig (21) found that addition of creatinine, tartaric acid, malic acid, or succinic acid to the dissolution medium increased the solubility and the dissolution rate of *m*-aminobenzoic acid.

Comparative Studies of Release Rate of a Drug and Its Sodium Salt from Granules and Tablets—In a previous study (15) the rate of dissolution of sodium phenobarbital in diluted gastric juice was determined and compared with the rate of dissolution of the salt in a hydrochloric acid solution having the same pH as the diluted gastric juice. It was found that initially nearly the same high drug concentration was obtained in both dissolution media. However, the precipitation of the free acid in excess of solubility took place at a much slower rate in gastric juice than in hydrochloric acid.

In the present study the rate of dissolution of phenobarbital and sodium phenobarbital from granules and tablets has been determined using 0.1 *N* HCl and diluted gastric juice as dissolution media. Comparisons with the rate of dissolution of the pure drug have been made.

Figures 7 and 8 show that the rate of dissolution of the sodium salt in both dissolution media is lowered by granulating a mixture of the drug and potato starch with gelatin. Compression of the granules into tablets results in a further reduction of the dissolution rate. If the free acid is used instead of the sodium salt, the granulation procedure and the tableting have—as mentioned earlier—the opposite effect: the dissolution rate is increased by granulation of the drug and further increased by compression of the granules.

By comparing the curves for sodium phenobarbital powder in Figs. 7 and 8 it will be seen that the precipitation of the free acid is much faster in 0.1 *N* HCl than in diluted gastric juice. It is also evident from these figures that granulated sodium phenobarbital forms a supersaturated solution of the free acid in diluted gastric juice but not in 0.1 *N* HCl. The rate of precipitation of the free acid in diluted gastric juice is obviously so low compared with the rate of dissolution of the granules that a supersaturated solution may be formed, whereas in 0.1 *N* HCl this is not the case.

Figures 7 and 8 also show that granulation of the free acid leads to a greater increase of the dissolution rate in 0.1 *N* HCl than in diluted gastric juice. This was expected since 0.1 *N* HCl has a much higher surface tension than diluted gastric juice.

Tablets prepared from the free acid had a much higher dissolution rate in both media than tablets prepared from the sodium salt. This was due to the fact that tablets containing the free acid disintegrated rapidly in 0.1 *N* HCl and diluted gastric juice, whereas tablets containing the sodium salt, although disintegrating fast in water, did not disintegrate in the acidic media, but swelled and dissolved slowly from the surface.

Some experiments were done to prepare sodium phenobarbital tablets with better dissolving properties in acidic media. Dry granulation of a mixture of the drug and potato starch instead of wet granulation of the same mixture with gelatin did not cause any improvement. Better results were obtained by direct compression of a mixture of the drug with microcrystalline cellulose. But even these tablets exhibited much slower dissolution rate than phenobarbital tablets prepared according to Formula I.

SUMMARY AND CONCLUSIONS

1. The rate of release of phenobarbital, phenacetin, and prednisone from granules and tablets prepared with gelatin as granulating agent was faster than the rate of dissolution of the pure drugs. Phenobarbital and prednisone were released at a higher speed from the tablets than from the granules. It is thus evident that both the granulation process and the compression of the granules may increase the rate of dissolution of drugs in human gastric juice.

2. The rate of dissolution of phenobarbital from tablets prepared with gelatin as granulating agent increased with decreasing particle size of the drug.

3. Phenobarbital tablets prepared with gelatin as granulating agent were found to dissolve much faster in human gastric juice than tablets prepared with sodium carboxymethylcellulose or polyethylene glycol 6000 as binders, probably because gelatin makes the originally hydrophobic surface of the drug particles hydrophilic, whereas sodium carboxymethylcellulose at the pH of the dissolution medium is converted into the less hydrophilic free acid and polyethylene glycol 6000 forms a complex of reduced solubility with phenobarbital.

4. The rate of dissolution of sodium phenobarbital in human gastric juice and in 0.1 *N* HCl was lowered by granulating a mixture of the drug and potato starch with gelatin. Compression of the granules into tablets resulted in a further reduction of the dissolution rate. These tablets dissolved much slower in both media than tablets prepared in a similar way from phenobarbital. The reason for this was that the sodium phenobarbital tablets, although disintegrating rapidly in water, did not disintegrate in the acidic media, but swelled and dissolved slowly from the surface. In contrast to this the phenobarbital tablets disintegrated very rapidly in acidic media as well as in water. Attempts to use dry granulation or direct compression in order to obtain sodium phenobarbital tablets dissolving as fast as the phenobarbital tablets in acidic media were not successful. It appears thus to be more difficult to prepare fast dissolving tablets from the highly soluble sodium salt of phenobarbital than from the corresponding poorly soluble free acid. It has often been claimed that rapid dissolution of the active ingredient of tablets in the stomach represents a problem only as far as poorly soluble drugs are concerned, but it may certainly be a problem also when the drug in question is very soluble.

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