Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient II

Granule Size, Starch Concentration, and Compression Pressure

By GERHARD LEVY, JANET M. ANTKOWIAK, JOSEPHINE A. PROCKNAL, and DONALD C. WHITE

The effect of various tablet formulation and processing factors on the rate of dissolution of the active ingredient of model tablets (prepared by double compression) was investigated. Dissolution rate increased with decreasing granule size (over the range 16–20 mesh to 60–80 mesh), but not strictly proportionally to the corresponding increase in the apparent surface area of the granules. Increasing starch content of granules (varied from 0 to 20 per cent) resulted in an increase in dissolution rate. Increasing precompression pressure (varied from 715 to 5720 Kg./cm.^{2}) caused an increase in dissolution rate. This was probably due to fracturing of the harder granules into smaller particles with greater specific surface area or bonding of the softer granules (prepared at lower slugging pressure) during their compression into tablets.

THE RATE of absorption and the physiologic availability of many drugs that are administered orally in solid form is a function of their rate of dissolution in gastrointestinal fluids (1–3). Certain tablet formulation and processing factors apparently affect the dissolution rate of drugs contained in tablets, since it has been found that generically identical tablet products made by different manufacturers exhibit significant differences in dissolution rate of the active ingredient (4). In a number of instances, poor tablet formulation has been shown to cause a significant reduction of physiologic availability of the active ingredient and impairment of clinical response (for example, see References 5–8).

There is frequently no correlation between tablet disintegration time and dissolution rate (2–4), or the nature of this correlation (if it exists) is variable and may be affected significantly by the nature of the formulation (9). Various aspects of tablet formulation and production have been the subject of extensive studies; but, unfortunately, disintegration tests rather than dissolution tests have been used to determine the effect of formulation and processing variables on the rate of release of the active ingredient. The need for information concerning the effect of tablet formulation factors on dissolution rate has led to studies that are the subject of this series of communications. The present communication deals with the effect of granule size, starch content of granules, and precompression (slugging) pressure on the rate of dissolution of the active ingredient of compressed tablets.

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EXPERIMENTAL

Preparation of Tablets.—Compressed tablets were made by double compression with a Carver hydraulic press, model B, using a conventional set of punches and die placed in a special holder. The punches were flat-faced and 1.27 cm. diam. Slugs were prepared from approximately 1 Gm. of powder and were subsequently broken into granules with a mortar and pestle. The granules were separated into the desired size fractions by sieving. Small amounts (sufficient for approximately 12 tablets) of the different granulations were mixed gently but thoroughly with other components of the formulation in small plastic vials. Quantities of mixture necessary to prepare a single tablet were weighed on an analytical balance and compressed into tablets. Preparation of mixtures and tablets took place on the same day on which the dissolution tests were made. The composition and other specifications of the experimental tablet preparations are listed in Table I.

Dissolution Rate Determinations.—Dissolution rates were determined by the beaker method, which has been described in detail (4). In one instance, the oscillating tube method (10) was used, except that the volume of dissolution medium was reduced to 300 ml.

GENERAL COMMENTS

In terms of physiologic realities, poor tablet formulation resulting in decreased dissolution rate of the active ingredient is most likely to affect the rate of gastrointestinal absorption of relatively poorly water-soluble weak acids. This is so because weak acids are generally well absorbed from the stomach (11) but dissolve much more slowly in acidic than in neutral or basic media (12, 13). On the other hand, weak bases dissolve much more rapidly in acidic than in basic media and generally are not absorbed to a significant extent from the stomach. Any retardation in dissolution of a weakly acidic drug may be reflected readily by slower absorption rate (2). A similar effect is less likely in the case of weak bases because of their more rapid dissolution

TABLE I.—SPECIFICATIONS FOR EXPERIMENTAL TABLETS

Formula Designation	Granules: Compn.[a]	Granules: Precompression Pressure[b]	Granules: Size[c]	Tablets: Compn.	Tablets: Compression Pressure[b]
A	SA, 80–100 mesh	2150	40–60	SA granules, 300 mg. Starch, 60 mg. Sodium lauryl sulfate, 9 mg.	715
B	SA, 80–100 mesh	2150	16–20 20–40 40–60 60–80	SA granules, 300 mg. Starch, 60 mg.	715
C	SA, 60–80 mesh Starch, 5% 10% 20%	1430	20–40	SA-starch granules, 300 mg. SA equiv. Starch, 15 mg.	715
D	SA, 60–80 mesh Starch, 15%	715 1430 2860 5730	20–40	SA-starch granules, 300 mg. SA equiv. Starch, 15 mg.	715

[a] SA = Salicylic acid. [b] Kg./cm.^{2} [c] U.S.P. mesh size.

in the acidic gastric fluids and because their absorption is restricted almost exclusively to the intestine. Therefore, gastric emptying rate rather than dissolution is likely to be the rate-limiting factor in the absorption of weak bases.[1]

These considerations have led to the use of a poorly water-soluble weak acid as the active ingredient in the tablet formulations prepared for this study. In view of the availability of an *in vitro* dissolution test method which has been shown to yield data which correlate with human absorption rate studies of salicylates (2), the weak acid salicylic acid was chosen. This compound has the additional advantages of stability and availability of a simple and direct method of analysis.

Studies described in this and the following communication (15) deal with certain formulation and processing variables encountered in the preparation of compressed tablets by double compression. This method of preparation does not involve the use of binders and liquids which could complicate considerably any reasonably well controlled study of variables associated with the preparation of tablets by wet granulation. However, many aspects of the results of the present study should be equally applicable to the preparation of tablets by wet granulation. It is recognized that the results obtained with tablets compressed with a hydraulic press may, in some instances, differ from those obtained with tablets compressed by means of a conventional tablet machine.

The effect on dissolution rate of some of the formulation variables studied may be mediated in some instances by a modification of granule and/or tablet disintegration rates. No attempt was made to evaluate the relative contribution of these as well as of certain microenvironmental factors.[2] The formulations, methods of preparation, and particularly the active ingredient, were chosen primarily for the purpose of obtaining model systems capable of yielding useful information. Accordingly, the choice of formulations was not restricted to those which might be of direct commercial pertinence.

RESULTS AND DISCUSSION

Aging Effects.—Preliminary experiments were carried out to determine the effect of aging on the dissolution rate of drug contained in compressed tablets because others have found that granulations prepared at different times may exhibit differences in properties (16). Salicylic acid granules were stored at room temperature in a desiccator containing Drierite; tablets were prepared from these granules after 1, 3, and 5 weeks of storage. Dissolution rates were determined on the same day on which the tablets were compressed. The results (shown in Fig. 1) indicate that dissolution rate changed significantly with granule age. To prevent significant bias or distortion of results because of

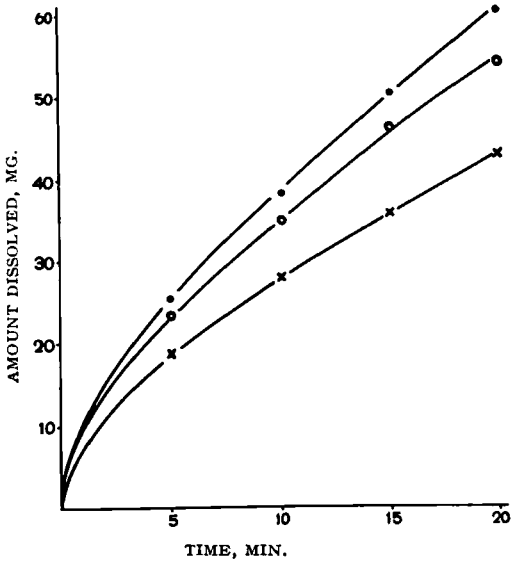

Fig. 1.—Effect of granule age on dissolution rate of salicylic acid contained in compressed tablets. Key: ●, one week; ○, 3 weeks; ×, 5-week-old granules. (Average of 10 tablets each, formula A.)

[1] Relatively rapid dissolution in acidic media and poor absorption from the stomach may be the reasons why the rate of absorption of tetracycline hydrochloride has been found to be independent of particle size (14).

[2] The reader may refer to the first paper of this series (10) for an explanation and description of microenvironmental factors.

aging effects, all subsequent experiments were conducted in the form of a latin-square design; dissolution tests for a given experiment were carried out as rapidly as possible to make all measurements within a few days. This also reduced possible bias because of effects resulting from fluctuations of temperature and humidity.

Effect of Granule Size.—Figures 2 and 3 show dissolution rate data for tablets made from 16–20-mesh, 20–40-mesh, 40–60-mesh, and 60–80-mesh granules, respectively. It is evident that the dissolution rate increases with decreasing granule size. However, this increase is not strictly proportional to the increase in the apparent surface area of the granules (Table II). The surface area ratios listed in Table II were calculated on the assumption that the granules were spherical and had smooth surfaces. The ratios should be approximately correct even if these assumptions do not obtain, because shape factor and surface roughness should be about the same for granules of all sizes used.[3] Dissolution rate ratios could be calculated from initial dissolution rates because these were approximately constant until 15% of the drug content of a tablet had dissolved. The increase in dissolution rate from

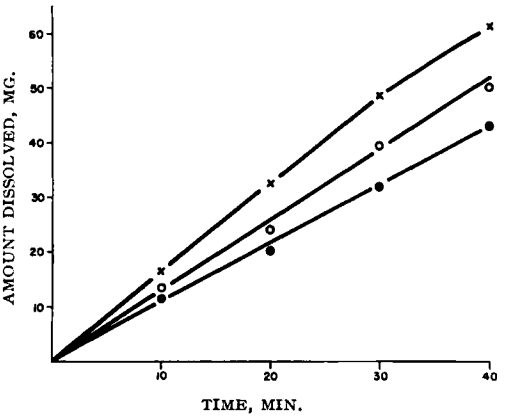

Fig. 2.—Effect of granule size on dissolution rate of salicylic acid contained in compressed tablets. Key: ●, 16–20 mesh; O, 20–40 mesh; ×, 40–60 mesh granules. (Average of 10 tablets each, formula B.)

tablets containing 20–40-mesh and 40–60-mesh granules (compared with tablets made from 16–20-mesh granules) was not so great as the increase in apparent surface area. This is because the disintegrated tablet particles remain as an aggregate on the bottom of the beaker (due to the low intensity of agitation), and the surface area of drug exposed to the solvent is primarily the surface of the aggregate. This effect has been explained in greater detail in the first paper of this series (10).

The much greater dissolution rate of tablets prepared from the smallest granules (60–80 mesh) is because these granules are small enough to be dispersed somewhat in the medium despite the low intensity of agitation. This permits moving solvent to come in contact with a greater portion of the potentially available surface. The granule size which would show such an effect in the human stomach

[3] It has been shown recently that the shape factor for 20–30-mesh anisometric crystals of salicylamide could be assumed to remain constant at least until about 30% was dissolved (17).

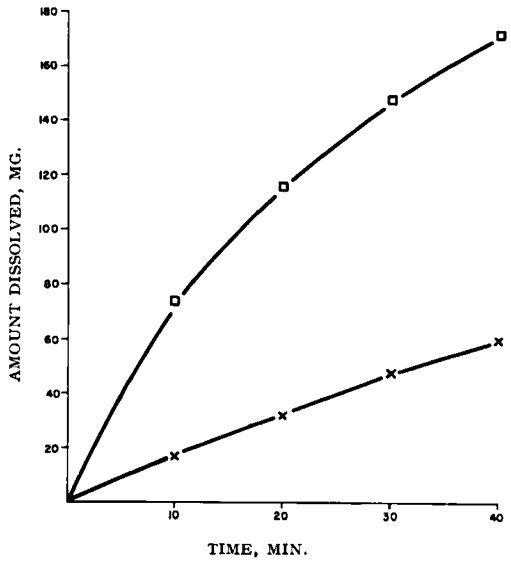

Fig. 3.—Effect of granule size on dissolution rate of salicylic acid contained in compressed tablets. Key: ×, 40–60 mesh; □, 60–80-mesh granules. (Average of 10 tablets each, formula B.)

would depend on the specific gravity of the granules and on gastric motility and cannot be estimated readily except by *in vivo* X-ray studies.

Effect of Starch Content of Granules.—Increasing the starch content of granules from 5 to 20% resulted in an increase in the dissolution rate of salicylic acid (Fig. 4), probably because of more rapid and thorough disintegration of the granules. (It is known that tablets disintegrate more rapidly when the starch content is increased (18, 19).) In this instance, dissolution rate determinations were also made with the oscillating tube apparatus (Fig. 5), and the results, although qualitatively similar, differ somewhat from those obtained by the beaker method. This illustrates again the need to use appropriate methodology for dissolution rate studies of compressed tablets (10.)

Effect of Granule Compression Pressure.—Tablets were prepared from granules made from slugs compressed at pressures ranging from 715 to 5730 Kg./cm.[2] As shown in Fig. 6, dissolution rates increased with increasing precompression pressure. This may be due to fracturing of drug particles at higher slugging pressure, yielding smaller primary particles. Such an effect was observed by Higuchi, *et al.*, with aspirin (19). Fragmentation

TABLE II.—ESTIMATED RATIOS OF SURFACE AREAS AND RATIOS OF INITIAL DISSOLUTION RATES OF SALICYLIC ACID CONTAINED IN COMPRESSED TABLETS[a] AS A FUNCTION OF GRANULE SIZE

Granule Size, U.S.P. mesh	Av. Granule Diam. cm.	Surface Areas,[b] Estimated Ratios	Initial Dissolution Rates, Ratios
16–20	0.102	1.0	1.0
20–40	0.063	1.6	1.2
40–60	0.034	3.0	1.5
60–80	0.021	4.9	6.9

[a] Tablet formula B. [b] Based on assumed sphericity of granules.

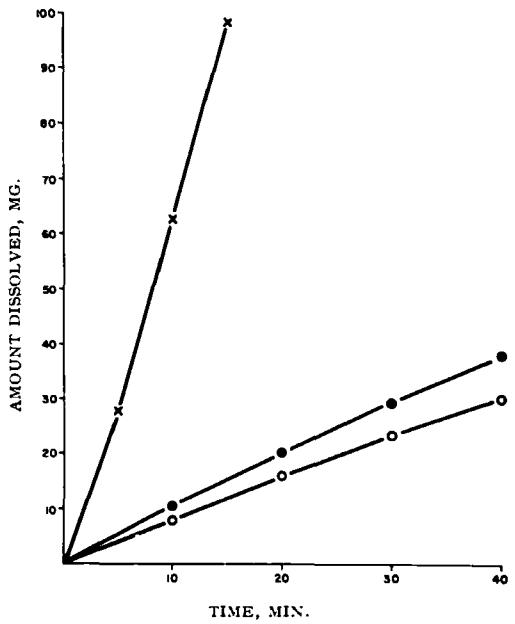

Fig. 4.—Effect of starch content of granules on dissolution rate of salicylic acid contained in compressed tablets. Key: O, 5%; ●, 10%; ×, 20% starch in granules. (Average of five tablets each, formula C.)

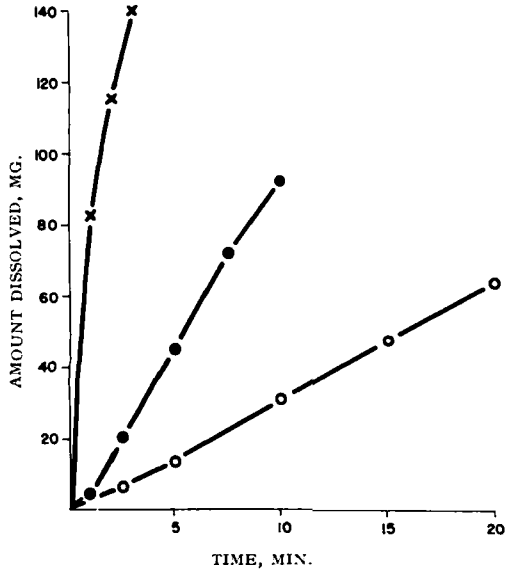

Fig. 5.—Effect of starch content of granules on dissolution rate of salicylic acid contained in compressed tablets, determined by the oscillating tube method. (Symbols, etc., same as in Fig. 4.)

of the more highly compressed granules during subsequent tableting may also occur. Finally, the softer granules obtained at lower precompression pressures are more likely to undergo bonding during tableting, and thus yield larger granules. Visual observations suggest that the latter effect is operative, but this does not exclude a possible contribution because of one or both of the other effects.

It has been found that aspirin administered in

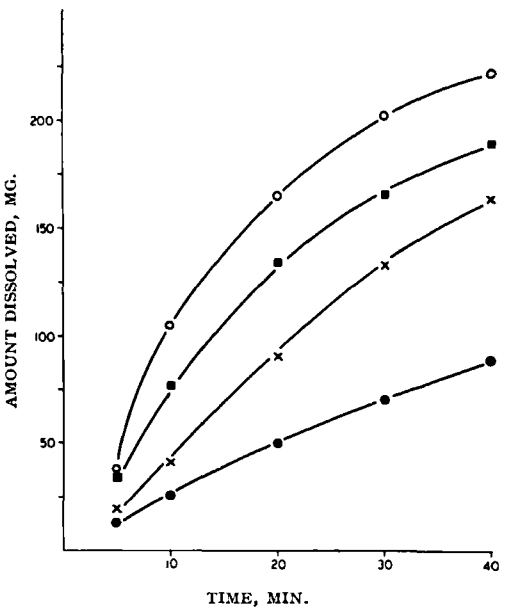

Fig. 6.—Effect of precompression pressure on dissolution rate of salicylic acid contained in compressed tablets. Key: ●, 715 Kg.; ×, 1430 Kg.; ■, 2860 Kg.; O, 5730 Kg. pressure per cm.^{2} (Average of five tablets each, formula D.)

tablets made at very high compression pressure was more rapidly absorbed by humans than aspirin administered in tablets compressed at lower pressure (20); this could be because of the same effects reported here.

Although the data shown in Figs. 4 and 6 represent separate experiments carried out at different times, the dissolution rate curve in Fig. 6 for the tablets made from granules prepared at 1430 Kg./cm.^{2} pressure (and containing 15% starch) falls between the curves for tablets made from granules that were also compressed at 1430 Kg./cm.^{2} and contain 10 and 20% of starch, respectively (as shown in Fig. 4).

CONCLUSIONS

Results of this study indicate that some of the more important tablet formulation and processing variables may affect the dissolution rate of the active ingredient. The magnitude of these effects must be determined individually for each tablet product, and their significance with respect to the rate of gastrointestinal absorption and the physiologic availability of the active ingredients must be assessed on the basis of several additional considerations (10, 21). The results of the present investigation should only be interpreted as indicative of the general nature of the effects on dissolution rate of the tablet formulation and processing factors studied.

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Nonclassical Antimetabolites XIV

Some Factors in Design of Irreversible Inhibitors Effective at Low Concentration

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5-(Bromoacetyl)salicylic acid (XII) irreversibly inhibits glutamic dehydrogenase and lactic dehydrogenase about as well as the standard exoalkylating agent, 4-(iodoacetamido)salicylic acid, at one-tenth the concentration of the standard; most of this increased reactivity is because of the higher reactivity of the halogen in XII. Three of the four iodoacetamido compounds that reversibly bound to lactic dehydrogenase more tightly than the standard gave irreversible inhibition at 10–20 per cent the concentration necessary for the standard. Three carbophenoxyamino heterocyclic acids showed no irreversible inhibition of lactic dehydrogenase, but were effective irreversible inhibitors of glutamic dehydrogenase at one-tenth the concentration of the standard compound.

THE CONCEPT (2) that a properly designed inhibitor can reversibly complex with the active site of an enzyme, then become irreversibly bound within the complex by alkylation adjacent to the active site (exo-alkylation) has had strong experimental support (3, 4). Similar observations have been independently and subsequently made in the area of hapten immunochemistry (5) and with chymotrypsin (6).

The exo-alkylation phenomenon is illustrated (4) by Eq. 1. In the experimental evidence for this phenomenon, it was shown that the rate of irreversible reaction between the inhibitor AB and the enzyme, to form the irreversible complex, II, was dependent upon the concentration of reversible complex, I; that is, the rate of inactivation could not be increased once the enzyme was saturated with the inhibitor. The amount of reversible complex, I, can be calculated from the measurable dissociation constant, K_I, of the enzyme-inhibitor complex.

$$E\!\!<^{H} + AB \rightleftharpoons E\!\!<^{H} \cdots AB \rightarrow \underset{\text{I}}{} \quad E\!\!\overset{\frown}{\cdots A} + BH \quad \text{(Eq. 1)}$$
II

Of obvious importance to chemotherapy is that a sufficient intracellular concentration of an inhibitor must be obtained to effect the target enzyme site of an invading cell. In order to overcome an insufficient intracellular concentration of inhibitor, it would be necessary to find inhibitors that will operate at lower concentrations. There are two ways in which exo-alkylating irreversible inhibitors effective at lower concentrations could be obtained. First, a compound that can saturate the enzyme at a lower concentration (smaller K_I) will operate equally as effectively as an agent that requires a higher concentration to saturate the enzyme (larger K_I); second, if a more active alkylating group, B, in structure I is employed, the rate of inactivation of the enzyme should be the same at proportionally lower inhibitor concentrations. The design, synthesis, and evaluation of both types are the subject of this paper.

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For previous paper in this series see Reference 1.