removed, and a small amount of ethanol was added to destroy residual sodium amide. The ethanol was removed, the residue was suspended in a saturated solution of potassium carbonate, and extracted with ether. The ether was removed and the residue distilled at reduced pressure. This is a modification of a procedure reported by Huttrer (4).

Isopropyl N-(N'-Diethylaminopropyl)-aminophenyl Sulfide (VIII).—This compound was prepared in the same manner as compound IX. Isopropyl 2-methylaminophenyl sulfide (0.13 mole) was reacted with sodium amide (0.25 mole) in 200 ml. of toluene. After heating the mixture for 24 hours, 3-diethylaminopropylchloride hydrochloride was added and heated for 24 hours. The product was isolated in the manner described above in a yield of 82%. Compounds of this type have been previously reported (5).

These compounds were screened for gross pharmacologic activity using the Hippocratic screen method (6). Biphasic activity was exhibited by an initial increase in motor activity accompanied by evidence of disorientation and stereotypy in the form of head shaking, chewing motions, and prancing of the forelimbs. This was followed by ataxia and decreased motor activity 1 hour after intraperitoneal injection. One compound, isopropyl N-(N'-diethylaminopropyl)-aminophenyl sulfide exhibited only motor activity depression without an initial increase.[1]

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

Tablet Lubricants

By GERHARD LEVY and ROBERT H. GUMTOW

A hydrophobic tablet lubricant (magnesium stearate) has been found to retard the dissolution of salicylic acid from model compressed tablets, while a water-soluble, surface-active lubricant (sodium lauryl sulfate) enhanced markedly the dissolution rate. Experiments with nondisintegrating disks indicate that the more commonly used hydrophobic lubricants (magnesium stearate, aluminum stearate, stearic acid, talc) decrease the effective drug-solvent interfacial area and thereby decrease the rate of dissolution of the drug, while water-soluble lubricants (sodium oleate, sodium lauryl sulfate) do not have this effect. The dissolution rate enhancing effect of sodium lauryl sulfate (in the case of conventional tablets) is not due to any modification of microenvironmental pH or solubilization by micelles, but rather to the better penetration of solvent into tablets and their component granules and the resulting greater availability of drug surface.

THE EFFECT of formulation and processing factors on the dissolution rate of active ingredients of compressed tablets has been the subject of extended investigation in this laboratory (1, 2). The present report deals with the effects of tablet lubricants and the mechanisms by which they may modify the dissolution rate of pharmaceuticals contained in tablets.

The more commonly used tablet lubricants are hydrophobic substances. Their water-repellent effect is evidenced by their tendency to increase markedly the disintegration time of tablets (3–5). When lubricants are added to a tablet granulation, they form a coat around individual granules which remains more or less intact during the process of tablet compression (3). Interference by these agents with the dissolution of drugs in aqueous media is therefore a likely possibility.

An extensive study of currently used and potentially useful tablet lubricants by Strickland, *et al.* (6), revealed that a few water-soluble substances are effective lubricants. Presumably, these substances, unlike hydrophobic lubricants, will not interfere with the dissolution of tablet ingredients. For this reason, both hydrophobic lubricants as well as certain water-soluble lu-

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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 60–80 mesh	2150	20–40	SA granules, 300 mg. Starch, 60 mg. Lubricant, 9 mg.	715
B	SA 60–80 mesh Starch, 10%	1430	20–40	SA Starch granules 300 mg. SA equiv. Starch, 15 mg. Lubricant, 9 mg.	715

[a] SA = Salicylic acid. [b] Kg./cm.^{2} [c] U.S.P. mesh size of granules used for preparation of tablets.

bricants were used in this study. They were selected on the basis of high R value[1] and ejection force lowering capability from among those evaluated by Strickland, *et al.* (6). The particular dissolution test for compressed tablets (beaker method) and the experimental tablet formulations used in this study were chosen for reasons that have been discussed previously (1, 2).

EXPERIMENTAL

Preparation of Tablets

Salicylic acid tablets were prepared according to a method described previously (2). Composition and processing conditions of the two experimental preparations are listed in Table I. All lubricants were passed through a 100-mesh sieve.

Dissolution Rate Determination for Tablets.—Dissolution rates were determined by the beaker method (7) and in one instance also by the oscillating tube method (1). For the latter procedure, the volume of dissolution medium was reduced to 300 ml.

Preparation of Disks

Salicylic acid powder was precompressed at 6000 lb. total force into 0.5-in. diam. slugs by a modified hydraulic press (Carver, model B). The slugs were crushed into granules with mortar and pestle, and the 20–40-mesh granule fraction was collected by sieving. Lubricant was added to the granules in a small plastic vial, and these were mixed gently but thoroughly by rotating the vial. The granulation was compressed into thin, nondisintegrating disks of $^1/_2$ in. diam. with the modified hydraulic press, using 20,000 lb. total force. In one instance, disks were prepared directly from 100-mesh salicylic acid powder and from a mixture of salicylic acid powder (100 mesh) and lubricant.

Dissolution Rate Determinations for Disks.—Dissolution rates were determined by the rotating disk (8, 9) and static disk (1) methods, using 0.1 *N* hydrochloric acid at 37° as the dissolution medium. Speed of rotation for the rotating disk experiments was 555 r.p.m. Except where otherwise indicated, all data shown in the figures represent the average of duplicate determinations.

RESULTS AND DISCUSSION

Studies with Compressed Tablets.—A commonly used and very effective hydrophobic lubricant (magnesium stearate) and a very effective (6) water-soluble lubricant (sodium lauryl sulfate) were used in these studies. Figure 1 shows the effect of these agents on the dissolution rate of salicylic acid in compressed tablets made from granules containing pure drug. Magnesium stearate decreased dissolution rate appreciably, while sodium lauryl sulfate had the opposite effect. Figures 2 and 3 show the effect of magnesium stearate and sodium lauryl sulfate, respectively, on the dissolution rate of salicylic acid tablets made from granules that contained salicylic acid and starch. Again, magnesium stearate decreased and sodium lauryl sulfate increased the dissolution rate of salicylic acid. Comparison of Fig. 1 with Fig. 3 shows that sodium lauryl sulfate had a greater enhancing effect when it was incorporated in tablets that were made from starch-containing, *i.e.*, disintegrating granules. The latter formulation was also tested by means of the oscillating tube method (compared with the

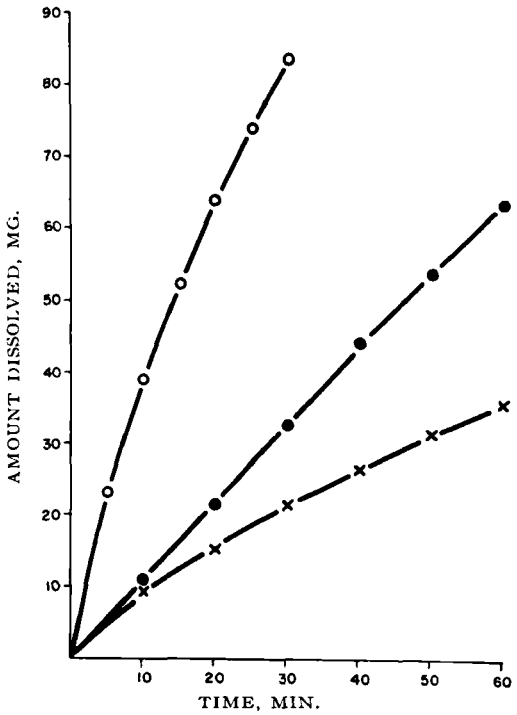

Fig. 1.—Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (formula A). Key: ×, 3% magnesium stearate; ●, no lubricant; ○, 3% sodium lauryl sulfate. (Average of 10 tablets each).

[1] This is the ratio of lower to upper punch forces at maximum compression. A hypothetical perfect lubricant has a R value of unity (6).

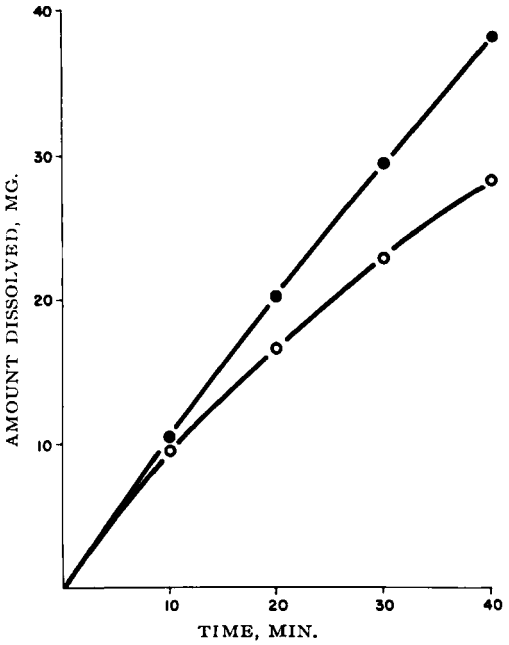

Fig. 2.—Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (formula B). Key: O, 3% magnesium stearate; ●, no lubricant. (Average of five tablets each).

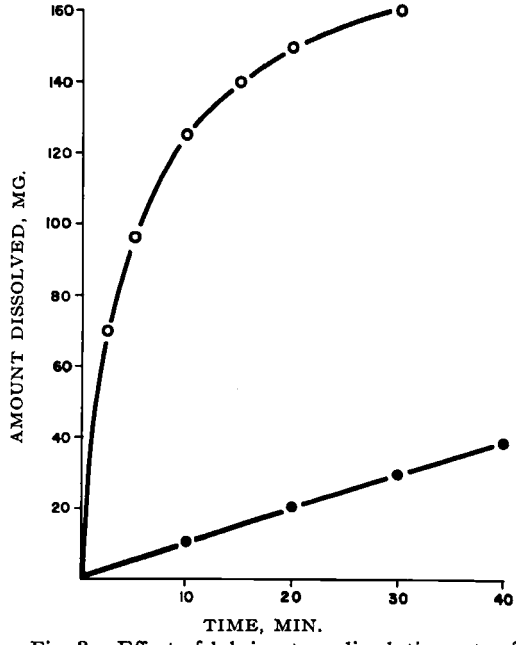

Fig. 3.—Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (formula B). Key: O, 3% sodium lauryl sulfate; ●, no lubricant. (Average of five tablets each).

beaker method). The results of this experiment, shown in Fig. 4, though quantitatively different, are qualitatively similar to those obtained with the beaker method.

Cooper and Brecht (10) have found that incorporation of surfactants into tablet formulations was an effective means of reducing tablet disintegration time. Sodium lauryl sulfate had no significant effect in their experience, but this is probably due to their use of calcium lactate tablets as the test system. Sodium lauryl sulfate reacts with calcium ion to yield a water-insoluble compound. Ward and Trachtenberg (11) have found that sodium lauryl sulfate did reduce the disintegration time of tablets made from amphenidone and sulfadiazine, respectively.

The experimental results depicted in Figs. 1–4 parallel those obtained from studies of the effect of stearates (3–5) and surfactants (10, 11), respectively, on the disintegration rate of tablets. However, this does not mean that the effect of these lubricants on dissolution rate is mediated solely or even primarily by their modification of tablet disintegration rates. In fact, the experimental tablet preparations used in this study were formulated in a manner which resulted in their rapid disintegration in order to minimize the effect of differences in tablet disintegration rates.

In the case of sodium lauryl sulfate, the dissolution rate enhancing effect could be due in part to an increase in microenvironmental pH (2),[2] to solubilization by micelles (12), and to more complete wetting of the drug solids (12). The dissolution rate retarding effect of magnesium stearate could be partially the result of delayed granule disintegration and reduced contact between drug and solvent. To investigate most of these possibilities it was desirable to eliminate totally tablet disintegration rate as an experimental variable. This was accomplished by the use of nondisintegrating pellets (disks) made from pure drug granules and lubricant.

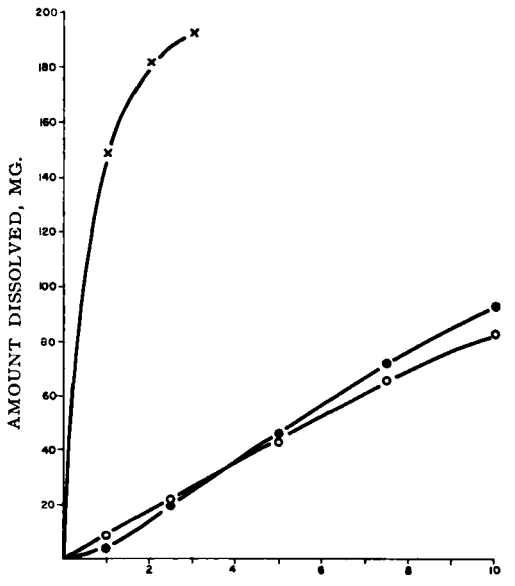

Fig. 4.—Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets (formula B) as determined by the oscillating tube method. Key: O, 3% magnesium stearate; ●, no lubricant; ×, 3% sodium lauryl sulfate. (Average of five tablets each).

[2] A slurry of sodium lauryl sulfate in 0.1 *N* hydrochloric acid at 37° has a pH of approximately 9.2.

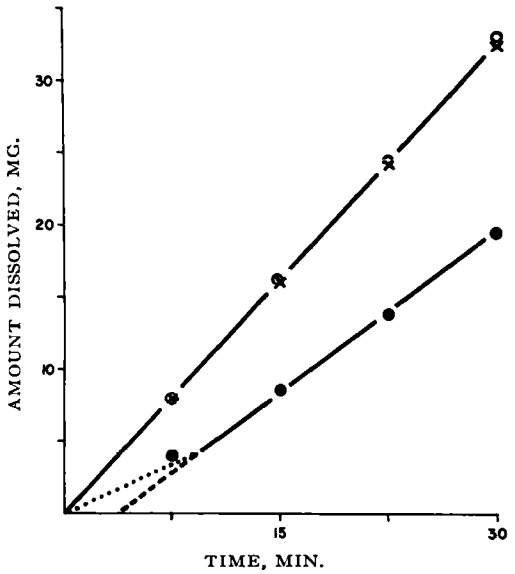

Fig. 5.—Effect of lubricant on the rate of dissolution of salicylic acid from rotating disks. Key: ●, 3% magnesium stearate; O, no lubricant; ×, 3% sodium lauryl sulfate; ---, extrapolation of experimental line; ..., line from Fig. 8. (Average of five disks each).

Studies with Nondisintegrating Disks.—As shown in Fig. 5, sodium lauryl sulfate had no effect on the dissolution rate of salicylic acid from the surface of nondisintegrating disks. This indicates that neither increased microenvironmental pH nor micellular solubilization are the cause for the dissolution rate enhancing effect of sodium lauryl sulfate observed in experiments with compressed tablets.

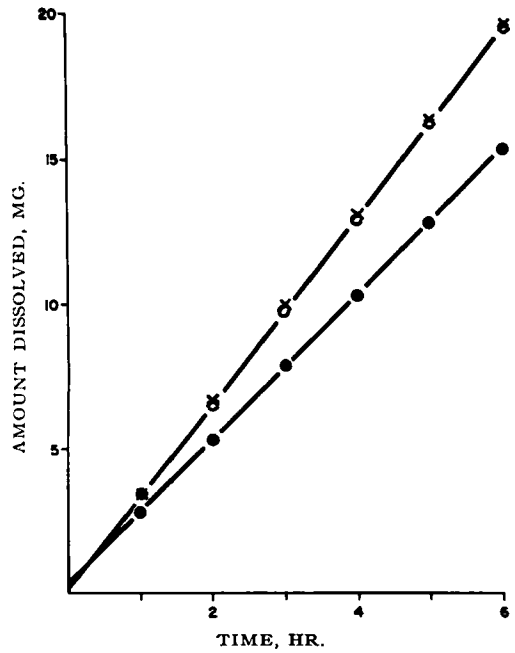

Fig. 6.—Effect of lubricant on the rate of dissolution of salicylic acid from static disks. Key: ●, 3% magnesium stearate; O, no lubricant; ×, 3% sodium lauryl sulfate.

The plot of amount dissolved *versus* time for disks containing magnesium stearate, also shown in Fig. 5, was somewhat unusual. Though linear (except for the first experimental point), it yielded a positive time intercept upon extrapolation. This suggested that magnesium stearate formed an impervious surface barrier which had to be removed before dissolution of drug could occur. If the surface of magnesium stearate–containing disks is, indeed, covered by an impervious barrier of the lubricant, then the apparent "lag-time" should be even greater under conditions where the mechanical effect of stirring is absent. However, when the dissolution rate was determined by the static disk method, there was no increase in apparent "lag-time," but rather, there was no apparent "lag-time" whatsoever (Fig. 6).

To determine whether the apparent "lag-time" found with rotating disks was real, experiments were carried out in which the dissolution medium was sampled every 2 minutes. This established that the apparent "lag-time" was because of an apparent increase in dissolution rate after about 5 mg. of drug had dissolved. Specifically, dissolution rate was constant until about 4 mg. of drug had dissolved, then gradually increased until it became constant once again after about 7 mg. had dissolved. The dotted line in Fig. 5 represents the experimentally determined initial dissolution rate of salicylic acid from magnesium stearate–containing disks. The subsequent change in apparent rate is seen readily.

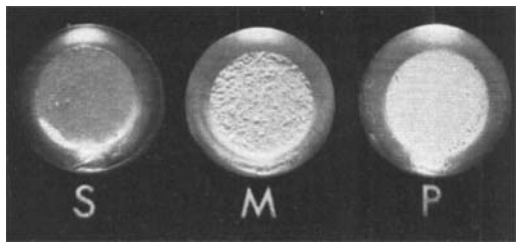

Fig. 7.—Surface of disks after dissolution of 10 mg. salicylic acid. Key: S = containing 3% sodium lauryl sulfate, M = containing 3% magnesium stearate, P = containing only pure salicylic acid.

These results may be explained on the basis of the changing surface characteristics of disks made from salicylic acid granules and magnesium stearate. The lubricant is confined to the surface and intergranular regions of the disks (3) and, as a result, the granules are surrounded by a water-insoluble matrix. As some of the salicylic acid dissolves, it leaves pits on the surface of the disk. This

TABLE II.—SURFACE PITTING TENDENCY OF LUBRICANTS

Lubricants with Which Pitting Occurs
Aluminum Stearate
Magnesium Stearate
Sodium Stearate
Stearic Acid
Stearyl Alcohol
Talc
Lubricants with Which Pitting Does Not Occur
Sodium Lauryl Sulfate
Sodium Oleate

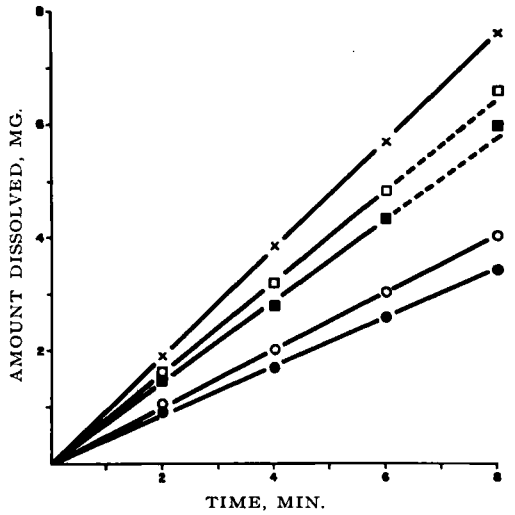

Fig. 8.—Effect of lubricants on initial dissolution rate of salicylic acid from rotating disks. Key: ●, 3% magnesium stearate; O, 1.5% magnesium stearate; ■, 3% aluminum stearate; □, 3% stearic acid; ×, no lubricant.

represents an increase in surface area which results in a more rapid dissolution of drug from the rotating disks. Although pits develop also on the surface of static disks, no increase in apparent dissolution rate occurs because the boundary layer at the solid-solvent interface of static disks is sufficiently thick to cover the pits (1). Pitting does not occur on the surface of disks which contain a water-soluble lubricant or no lubricant at all (Fig. 7). It does occur whenever any of the hydrophobic lubricants that were studied are used (Table II).

A comparative evaluation of the effect of various lubricants on dissolution rate by the rotating disk method had to be carried out in a manner which prevented complications because of pitting. This was accomplished by determining only initial dissolution rates, (*i.e.*, before apparent increases due to pitting had occurred). The results of the experiments are shown in Figs. 8 and 9. Magnesium stearate, aluminum stearate, sodium stearate, stearic acid, and talc all decreased the dissolution rate. Evaluation of relative effects of these agents is complicated because there is no assurance that their specific and/or effective surface areas were exactly equal, but magnesium stearate appears to have the most pronounced retarding effect. A concentration dependency is evident from the difference between the dissolution rate from disks containing 1.5% and 3%, respectively, of magnesium stearate. It is interesting that magnesium stearate not only retards dissolution rate more than does stearic acid, but that it also prolongs tablet disintegration time more than stearic acid (3).

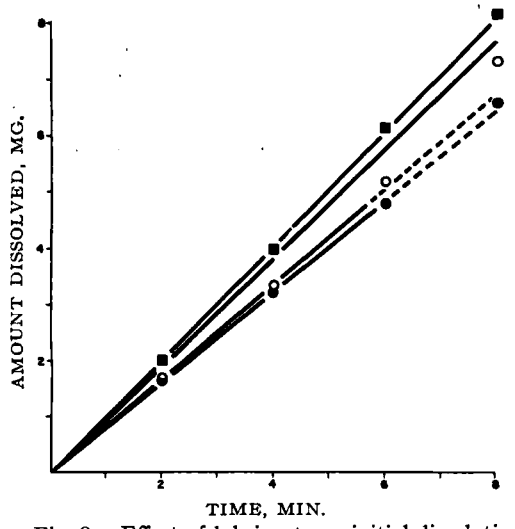

Fig. 9.—Effect of lubricants on initial dissolution rate of salicylic acid from rotating disks. Key: ●, 3% sodium stearate; O, 3% talc; ■, 3% sodium oleate; ——, no lubricant (from Fig. 8).

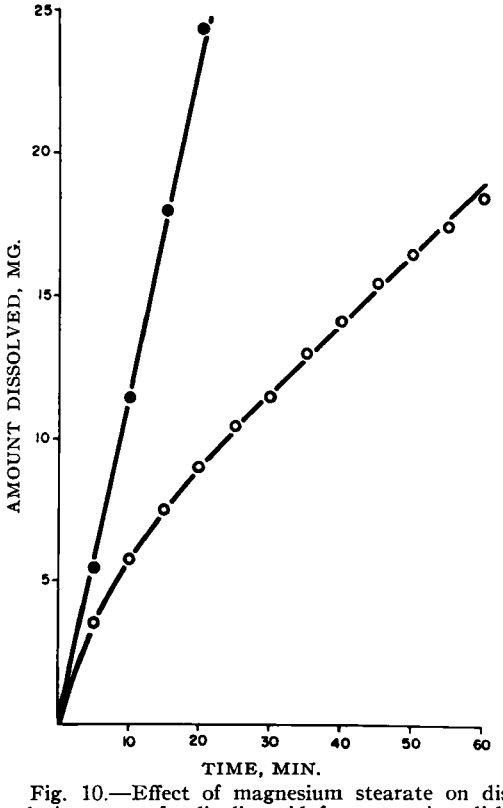

Fig. 10.—Effect of magnesium stearate on dissolution rate of salicylic acid from rotating disks made from fine salicylic acid powder. Key: O, 3% magnesium stearate; ●, no lubricant added.

The water-soluble sodium oleate had no significant effect on dissolution rate from disks and neither did sodium lauryl sulfate (Figs. 5 and 9). The dissolution rate retarding and pitting effect of sodium stearate appears unusual since this substance is stated to be water-soluble (13). However, it is also stated to be slowly dissolving (13). Addition of milligram amounts of sodium stearate to 0.1 *N* hydrochloric acid at 37° (the dissolution medium used in these studies) did not result in solution (and possible reprecipitation) of the substance, and it must be assumed that sodium stearate acts like a poorly soluble and hydrophobic agent under the conditions of this study.

One experiment was conducted with rotating disks

made from salicylic acid powder (100 mesh) and 3% magnesium stearate in order to determine whether a marked increase in the ratio of surface areas of drug:lubricant would result in a quantitative modification of the dissolution-retarding effect. The results of the experiment (shown in Fig. 10) indicate that the dissolution-retarding effect of magnesium stearate was somewhat greater in the case of disks prepared from salicylic acid powder (compared with disks made from granules). Therefore, the lubricant content of disks made from granules was sufficient to cover the surface of all granules; otherwise the retarding effect of lubricant would have decreased when drug granules were replaced by finely powdered drug. The initial curvature in the dissolution curve of magnesium stearate–containing disks made from salicylic acid powder (Fig. 10) was found repeatedly and may be because of a lower concentration of lubricant at the surface of the disk, from which it could have been removed mechanically by handling or during compression of the disk.

On the basis of these experiments it may be concluded that hydrophobic lubricating agents may retard the dissolution of drugs contained in compressed tablets not only by prolonging the disintegration time of both tablets and granules but also by reducing the area of the interface between drug particles and solvent. The surface of pellets made from salicylic acid and a hydrophobic lubricant represents a complex physicochemical system because the "true" surface area with respect to salicylic acid is difficult to estimate. This is the reason why the boundary layer thickness calculations in the first paper of this series were stated to be only reasonable approximations (1).

The dissolution rate enhancing effect of sodium lauryl sulfate appears to be due to increased wetting and to better solvent penetration into the tablets and granules as a result of the interfacial tension lowering effect of the surfactant. This conclusion is in accord with observations by Wurster and Seitz (12), who have found that dissolution of pellets with artificial pores is more rapid when the dissolution medium contains sodium lauryl sulfate, due mainly to better contact between solvent and the drug surface. Since sodium lauryl sulfate has excellent tablet lubricating activity (6), its use for this purpose appears advantageous, except where specific incompatibility or stability problems are present.

Of interest is a recent case where the addition of a surfactant to a tablet formulation resulted in better absorption of the drug (14). This was attributed first to a physiologic effect of the surfactant (an unlikely possibility because of the small amount of surfactant involved), but subsequent studies revealed that this was a dosage form effect (15, 16). It is apparent from the results of the present study that a surfactant can enhance the dissolution rate of drugs contained in compressed tablets and thereby cause them to be more rapidly and more completely absorbed.

CONCLUSIONS

It may be concluded from the results of this investigation that hydrophobic tablet lubricants can retard the dissolution of drugs from compressed tablets. The magnitude of this effect may be expected to depend, among other factors, upon the particular lubricant, its concentration, its particle size, the drug, the tablet formulation, various processing variables, and the conditions (particularly with respect to agitation intensity) under which dissolution is taking place. Hydrophilic lubricants apparently do not retard dissolution[3] and, if they have surface-tension lowering capability, may enhance the rate of dissolution of drugs contained in compressed tablets.

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[3] This statement is made with the qualification that surfactants can retard dissolution in certain systems because of their adsorption on the surface of the dissolving substance (17) or possibly by facilitating particle aggregation (18). However, it is felt that these effects would not be important with compressed tablets containing very small amounts of a surface active lubricant.