(23) A. J. Aguiar, J. Krc, Jr., A. W. Kinkel, and J. C. Samyn, *J. Pharm. Sci.*, **56**, 847(1967).
(24) A. J. Aguiar, *ibid.*, **58**, 963(1969).
(25) A. J. Aguiar and J. E. Zelmer, *ibid.*, **58**, 983(1969).
(26) S. Lin and L. Lachman, *ibid.*, **58**, 377(1969).
(27) L. J. Ravin, E. G. Shami, and E. Rattie, *ibid.*, **59**, 1290 (1970).
(28) D. L. Simons, R. J. Ranz, P. Picotte, and S. Szabolcs, *Can. J. Pharm. Sci.*, **5**, 50(1970).
(29) R. R. Pfeiffer, K. S. Yang, and M. A. Tucker, *J. Pharm. Sci.*, **59**, 1809(1970).
(30) S.-L. Lin, L. Lachman, C. J. Swartz, and C. F. Huebner, *ibid.*, **61**, 1418(1972).
(31) J. H. Wood, J. E. Syarto, and H. Letterman, *ibid.*, **54**, 1068(1965).
(32) S. Lin, J. Menig, and L. Lachman, *ibid.*, **57**, 2143(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received December 22, 1971, from the *Development and Control Department, Ciba-Geigy Pharmaceutical Co., Summit, NJ 07901*

Accepted for publication April 28, 1972.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

The author thanks Dr. C. Swartz and Dr. L. Lachman for discussions and encouragement relating to the study, and Dr. R. Puckett and Miss N. Cahoon for their capable assistance.

Present address: Pharmacy Division, Ayerst Laboratories, Rouses Point, NY 12979

Use of Adsorbents in Enhancement of Drug Dissolution I

DONALD C. MONKHOUSE and JOHN L. LACH▲

Abstract □ A new approach is described for increasing the dissolution rates of relatively insoluble powders. It is based on the concept of increasing the surface available for contact with dissolution media. This is accomplished by equilibration of the drug in an organic solvent (*e.g.*, acetone) on an insoluble excipient with an extensive surface (*e.g.*, fumed silicon dioxide). The drugs studied included indomethacin, aspirin, sulfaethidole, griseofulvin, reserpine, chloramphenicol, oxolinic acid, probucol, and hydrochlorothiazide. The effects of pH, wetting agents, and agitation intensity were investigated in some systems. An increased rate of release from the minuscular drug delivery system was observed in all instances.

Keyphrases □ Adsorbents—used to increase the dissolution rates of relatively insoluble drug powders □ Dissolution rates—micronized (minuscular) drug dispersed on microparticulate adsorbents □ Drug delivery system—micronized (minuscular) drug dispersed on microparticulate adsorbents

The poor dissolution characteristics of relatively insoluble drugs has long been a problem to the pharmaceutical industry. If one accepts the premise that the absorption of such drugs is rate limited by the dissolution process, then the physicochemical factors controlling the dissolution rate may be described by the Noyes–Whitney and Nernst equations (1, 2). The terms in these equations can be modified and the dissolution rate altered through the use of soluble salts, polymorphs, hydrates or solvates, molecular complexes, eutectics, and solid solutions. These approaches to altering the dissolution rate will now be considered in detail.

As a rule, a pharmaceutical salt exhibits a higher dissolution rate than the corresponding nonelectrolyte at an equal pH, although the salt and nonelectrolyte may have the same equilibrium solubility. Thus, under the conditions that favor conversion of the salt to the nonelectrolyte, faster dissolution of the salt occurs, but the nonelectrolyte precipitates as fine particles which then have the required characteristics for proper redissolution (3). If rapid dissolution of a nonelectrolyte is desired, it can be achieved by incorporation of a buffer substance into the formulation. Such a buffer effectively alters the pH of the diffusion layer, enhancing dissolution by *in situ* salt formation (4).

The concept of employing a suitable ligand to complex with a drug substrate in the formation of a more soluble entity is not new (5), but it has not been widely exploited until recently. One such application was made with the caffeine–ergotamine combination (6).

The successful utilization of a polymorph of significantly greater thermodynamic activity (*i.e.*, solubility) than the stable modification may provide, in some instances, therapeutic blood levels from otherwise physiologically inactive drugs. The use of such metastable compounds may lead to crystal reversions on standing, and these stability aspects must be considered (7). The use of solvates and hydrates has also enjoyed limited use, although the anhydrous forms of semisynthetic penicillins have been used to give blood serum levels consistently earlier and significantly higher than those observed after administration of similar formulations containing the hydrated material (8).

Reduction of particle size remains the accepted method for increasing dissolution rates. However, upon micronization, hydrophobic drugs have a tendency to clump when exposed to the dissolution medium (9). An apparent solution to this problem was provided by Sekiguchi and Obi (10). They proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drug in a solid matrix of water-soluble carrier would increase the dissolution rate and absorption of the drug. Since then, modifications of the technique have been suggested under a variety of names, including solid solutions (11), eutectics (10), coprecipitates (12), and fast-release solid dispersions (13). The exact physical nature of these compositions is not exactly clear, but it is believed that the insoluble drug is

Table I—Dissolution Studies of Various Drugs in the Minuscular Form

Drug	Solvent Used to Prepare Samples	Quantity of Pure Drug in Sample, mg.	Dissolution Media	r.p.m.	Percent Fumed Silicon Dioxide Added	Relative Dissolution Rate, min.[a] 3	6	14
Indomethacin	Acetone	50[b]	Water	240	5	2.5	3.1	3.6
					10	14.3	13.8	11.3
					20	15.4	14.6	11.5
Aspirin	Methylene chloride	100	Water	15	2	1.2	1.2	1.2
					5	2.8	2.2	1.6
					10	3.0	2.3	1.7
Hydrochlorothiazide	Acetone	25	Water	60	5	2.6	2.2	1.6
					10	4.0	3.1	2.0
					20	4.0	3.1	2.0
Chloramphenicol	Acetone	100	Water	15	5	2.7	2.2	1.7
					10	4.1	2.9	1.9
					20	4.1	2.9	1.9
Sulfaethidole	Acetone	60	Water	240	5	2.3	1.7	1.4
					10	3.0	2.2	1.6
					20	3.0	2.2	1.6
Reserpine	Chloroform	14	0.005 *M* $HOCOCH_3$	240	5	3.3	3.1	3.0
					10	4.3	3.9	3.5
					20	4.3	3.9	3.5
Griseofulvin	Chloroform	20	Water	240	5	4.8	4.2	3.2
					10	9.8	8.0	5.5
					20	9.8	8.0	5.5
Probucol	Acetone	10	75% CH_3OH	240	5	3.0	2.4	1.7
					10	3.5	2.7	2.0
					20	3.5	2.7	2.0
Oxolinic acid	Chloroform	20	Water	240	5	1.8	2.0	2.3
					10	2.4	2.6	2.7
					20	2.6	3.0	3.1

[a] Ratio of minuscular drug in solution to th pure drug at the designated times. [b] Total amounts of sample in this case would be 52.5, 55, and 60 mg. for 5, 10, and 20% adsorbent added, respectively.

dispersed molecularly in the matrix of the soluble inert carrier. Upon exposure to the dissolution medium, the carrier dissolves rapidly and the finely dispersed particles are then released with optimum properties for dissolution. These reports attributed the observed effects principally to a decrease in particle size.

Each of these approaches for altering the dissolution rate requires a unique type of drug molecule to exhibit its effect. In the present investigation, a new delivery system is proposed which will provide an increase in the dissolution rate of a wide variety of drug types. A method is described here wherein the drug is deposited in "minuscular form" on the surface of an adsorbent. This new term implies that the drug has undergone molecular micronization when it is dispersed on the extensive surface of the microparticulate adsorbents. The present paper reports the dissolution aspects of this concept, and the second paper will report an investigation into the type of bonding involved in these systems.

EXPERIMENTAL

Materials—The following were used: hydrochlorothiazide[1], indomethacin[2], microsize griseofulvin USP[3], chloramphenicol[4], sulfaethidole (sulfaethylthiadiazole)[5], probucol[6], oxolinic acid[7], reserpine[8], aspirin USP[9], fumed silicon dioxide[10], and silicic acid (precipitated)[11]. All other chemicals were of reagent grade and were used as received.

Preparation of Minuscular Drug Sample—Fine powders of the drug and different water-insoluble adsorbents such as fumed silicon dioxide or silicic acid were accurately weighed in certain ratios. They were mechanically mixed and transferred to beakers of a suitable size. Sufficient organic solvent (acetone, chloroform, or methylene chloride) to dissolve all of the drug in the sample was then added to the beakers. These slurries or gels were stirred by a magnetic stirrer and evaporated by a stream of filtered air. The samples were then placed in a heated vacuum desiccator at 70° for 1 hr. (40° was used for aspirin) to facilitate the drying process. The solid masses were then pulverized in a mortar and sieve sized to the 80-mesh range. These powders were remixed by tumbling end over end for 15 min. A small portion of the powder was then removed and assayed for its drug content. Only those samples containing 100 ± 5% of the required amount of drug were used in the dissolution studies. The solvent method of preparation was utilized because it provided a definite control of the composition of the solid obtained. An assay resulting in a sample outside the above limits was uncommon.

Dissolution Studies—Five hundred milliliters of distilled water (or other media where indicated) was added to a 1-l. beaker and permitted to equilibrate to 37° in a constant-temperature water bath. A T-shaped two-bladed glass stirrer, about 5.5 × 0.5 cm., was vertically centered and lowered to a depth of 1 cm. above the bottom of the beaker. The stirrer was attached to a synchronous motor which could easily be adjusted to rotate accurately at speeds of 15, 60, and 240 r.p.m. These three speeds assured relatively constant hydrodynamic conditions. Accurately weighed samples, equivalent to a certain quantity of pure drug, were spread over the surface of the medium. Any large aggregates that formed at this stage were lightly broken up with a microspatula within 10 sec. of adding the

[1] Lot 39917, Merck Sharp and Dohme, West Point, Pa.
[2] Lot F-140507, Merck Sharp and Dohme, West Point, Pa.
[3] Lot MI-25012, Schering Corp., Bloomfield, N. J.
[4] Lot 702103, Parke, Davis and Co., Detroit, Mich.
[5] Lot 11,708, American Cyanamid Co., Pearl River, N. Y.
[6] 4,4′-(Isopropylidenedithio)-bis[2,6-di-*tert*-butylphenol], Lot D-1280, Dow, Indianapolis, Ind.
[7] 5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid, Lot 26, Warner-Chilcott Laboratories, Morris Plains, N. J.
[8] Aldrich Chemical Co., Inc., Milwaukee, Wis.
[9] Mallinckrodt Chemical Works, St. Louis, Mo.
[10] Grades EH5 and M7, Cabosil, Cabot Corp., Boston, Mass.
[11] Fisher Scientific Co., Fair Lawn, N. J.

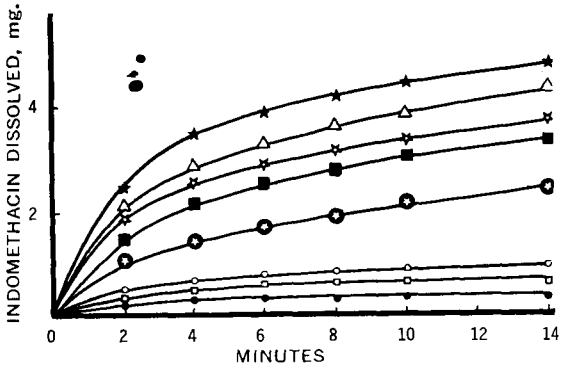

Figure 1—*Dissolution profiles of minuscular indomethacin in water at 15 r.p.m. Key: ★, 20% fumed silicon dioxide EH5; △, 10% fumed silicon dioxide EH5; ✲, 20% fumed silicon dioxide M7; ■, 10% fumed silicon dioxide M7; ◘, 20% silicic acid; ○, 5% fumed silicon dioxide EH5; □, 10% silicic acid; and ●, indomethacin powder only.*

sample. Subsequently, the surface was not disturbed except when aliquots were removed from the medium. The aliquots were withdrawn at periodic time intervals by means of a pipet adapted with a sintered-glass filter of medium porosity. The aliquot was then diluted appropriately in a volumetric flask, and absorbance measurements were determined at the required wavelength on a spectrophotometer[12]. A similar quantity of the dissolution medium was treated in the same way and used to set the instrument to zero absorbance. When 20 mg. of adsorbent (equivalent to the maximum amount used in the dissolution study) was placed in 500 ml. of medium and an aliquot was withdrawn and treated in the same manner as a normal drug sample, no significant absorbance was found over the wavelengths used for the analysis of the drugs. Beer's law was confirmed in all of the systems studied.

Unless otherwise specified, the exact experimental details for each drug system are listed in Table I. The absorbances of the samples were converted into milligrams of drug dissolved in 500 ml. of medium and plotted *versus* time in the form of a dissolution profile. Each point on the profile represents the average of at least two determinations.

Although it is theoretically preferable for sink conditions to exist in the dissolution bath throughout the process (1), this could not be accomplished in some cases because of the minute quantity of sample required and/or the drug's small absorptivity. Where these limiting factors prevailed, it was necessary to use nonsink conditions (*e.g.*, indomethacin, griseofulvin, and oxolinic acid) for comparison.

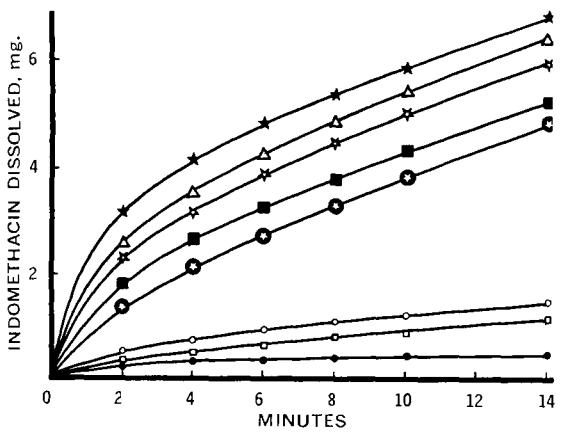

Figure 2—*Dissolution profiles of minuscular indomethacin in water at 60 r.p.m. Key: ★, 20% fumed silicon dioxide EH5; △, 10% fumed silicon dioxide EH5; ✲, 20% fumed silicon dioxide M7; ■, 10% fumed silicon dioxide M7; ◘, 20% silicic acid; ○, 5% fumed silicon dioxide EH5; □, 10% silicic acid; and ●, indomethacin powder only.*

[12] Gilford model 240.

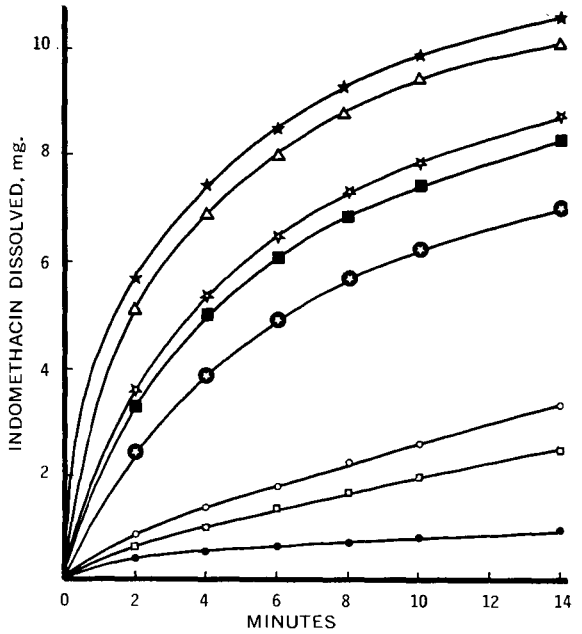

Figure 3—*Dissolution profiles of minuscular indomethacin in water at 240 r.p.m. Key: ★, 20% fumed silicon dioxide EH5; △, 10% fumed silicon dioxide EH5; ✲, 20% fumed silicon dioxide M7; ■, 10% fumed silicon dioxide M7; ◘, 20% silicic acid; ○, 5% fumed silicon dioxide EH5; □, 10% silicic acid; and ●, indomethacin powder only.*

In all cases, the drugs supplied were in a micronized form or in very fine crystals. When these drugs were treated in the same manner as the microparticulate drug samples, except that no adsorbent was added, the dissolution rate was slightly less than or equal to that measured on the original commercial product. Thus, the dissolution rate of the pure drug plotted in the profiles represents that of the original commercial product. This was considered necessary in order to report a "fair" comparison with the minuscular drug samples; consequently, it may be assumed that the enhanced dissolution rate of the drugs in the surface-coated form was not due to recrystallization *per se*. The dissolution rates of the drugs alone were similar to those of various physical mixtures of the surface materials containing the same particle-size drug. (The plots of the physical mixes were omitted to prevent overcongestion of the profiles.) This tends to preclude the possibility that the adsorbents function to increase the bulk solubility of the drug, which would result in alteration of dissolution and absorption characteristics.

Modified Silica Gels—These were prepared using a similar method to that employed for TLC (14). Basified silica gel was prepared by stirring 20 g. of silicic acid and 100 ml. of 0.5 *N* NaOH for 30 min. Acidified silica gel was prepared by stirring 20 g. of silicic acid and 100 ml. of 0.5 *N* HCl. The slurry was then filtered, and the precipitate was washed with 200 ml. of distilled water. These powders were dried in a heated vacuum desiccator at 100° for 3 hr.

RESULTS AND DISCUSSION

Indomethacin—As shown in Figs. 1–3, the rate of dissolution of indomethacin varied with the surface material component used to prepare the minuscular drug. The rank order of dissolution, as obtained from the family of curves represented in each figure, is as follows: 20% fumed silicon dioxide EH5 > 10% fumed silicon dioxide EH5 > 20% fumed silicon dioxide M7 > 10% fumed silicon dioxide M7 > 20% silicic acid > 5% fumed silicon dioxide EH5 > 10% silicic acid > indomethacin powder. This rank order of dissolution was independent of the speed of the stirrer from 15 to 240 r.p.m.

It was evident that indomethacin in the minuscular form went into solution significantly faster than the indomethacin powder alone. Since the same range of particle size (smaller than 80 mesh) was used for these systems, it is reasonable to suppose that the indomethacin in the minuscular form is available to the dissolution medium in a smaller particle-size form. If the layer of drug on the

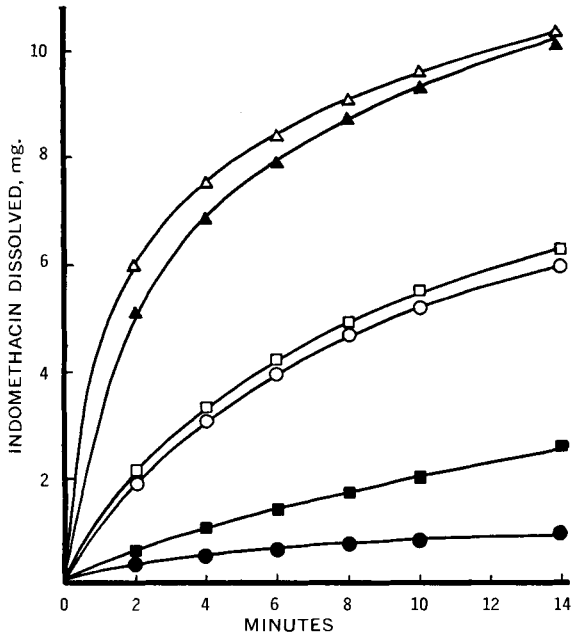

Figure 4—*Dissolution profiles of minuscular indomethacin in water and in 0.02% polysorbate 80 at 240 r.p.m. Key for 0.02% polysorbate 80: △, 10% fumed silicon dioxide; □, 10% silicic acid; and ○, pure indomethacin powder. Key for water: ▲, 10% fumed silicon dioxide; ■, 10% silicic acid; and ●, pure indomethacin powder.*

surface of the silica is weakly adsorbed, then a silica of large surface area should manifest a greater enhancement of dissolution than a silica of smaller surface area. Fumed silicon dioxide EH5 has a surface area of 390 ± 40 m.²/g. and fumed silicon dioxide M7 has a surface area of 200 ± 25 m.²/g. From Figs. 1–3, the rank order is 20% fumed silicon dioxide EH5 > 10% fumed silicon dioxide EH5 > 20% fumed silicon dioxide M7 > 10% fumed silicon dioxide M7. Thus, surface area was, in fact, a controlling factor for the increased dissolution rate of these drug samples. Also, silicic acid is much coarser than the fumed silicon dioxide samples and was, therefore, less efficient at releasing the drug. However, the efficiency of release of these silica adsorbents did not completely parallel the rank order of "total" surface (*i.e.*, g. × m.²/g.) available to the drug. Since fumed silicon dioxide EH5 was the more effective silica adsorbent, this grade was the preferred excipient in the remaining experiments.

Even though most drugs are micronized and, therefore, have a theoretically large surface available to the dissolution medium, they have an unfortunate habit of clumping together as a result of their hydrophobicity (9). It is well known that the presence of a surfactant greatly enhances the deaggregation of these types of powders. In this particular study, 0.02% polysorbate 80[13] was chosen as the dissolution medium because it has been shown to overcome the "nonwetting" character of powdered drugs (15) and it more closely resembles the surface tension of the GI fluids than distilled water. From Fig. 4, it is evident that dispersion is a problem with indomethacin. The amount of drug in solution from the untreated powder was sufficiently increased (six times), but the 10% silicic acid sample released the drug still a little more rapidly in the polysorbate 80 medium. Solubilization was considered to have only a minor contribution. Upon further examination of the plot, it was noted that the presence of polysorbate 80 was inconsequential when 10% fumed silicon dioxide was used. In this case, apparently because of its molecular size and wettability, 10% fumed silicon dioxide adequately dispersed the drug and allowed the drug to be wetted by the solvent. Since indomethacin is a weak acid, it was expected that its dissolution rate should be enhanced by coating the drug onto a basic surface such as basified silica gel. Conversely, the drug should be released more slowly when coated onto an acidic surface such as acidified silica gel. Experiments were performed which confirmed these expected results (Fig. 5).

[13] Tween 80.

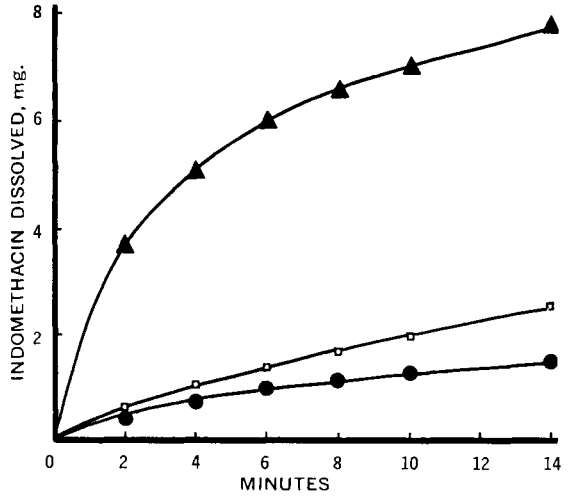

Figure 5—*Dissolution profiles of minuscular indomethacin in water at 240 r.p.m. as a function of pH of the surface. Key: ▲, 10% basified silica gel; □, 10% untreated silicic acid; and ●, acidified silica gel.*

It is well known that the solubility term in the Noyes-Whitney equation represents the concentration of a drug in the thin film of a liquid that adheres to the dissolving solids, namely "the diffusion layer." In effect, the solution rate of the acid is not dependent on its intrinsic solubility in the gross medium but upon the solubility that exists in the diffusion layer. It was found in this study that 10 mg. of the acid- or base-treated silica gel (maximum amount used in this study) changed the pH of the dissolution medium negligibly. It is apparent in this instance that the diffusion layer pH is the controlling factor.

In the case of basified silica gel, the sodium salt is most probably formed when the aqueous layer reaches the particulate surface. However, when the salt molecules diffuse out through the layer of high pH and reach the gross medium, the free acid precipitates once again but in very finely dispersed particles. These possess the desired properties for optimum redissolution. For the acidified excipient, the diffusion layer is acidic and the inherent solubility of the drug is markedly decreased. This portrays quite a comparable dissolution rate to the untreated powder in 0.1 *N* HCl (Fig. 6). From these considerations, it may be generalized that, unless the basic surface causes some decomposition (16), the coating of weak acids onto such treated surfaces might be of potential significance for increasing the dissolution rate.

It is always necessary to verify that a new process for increasing dissolution rates exhibits comparable behavior in GI fluids. In this case, the pepsin in simulated gastric fluid interfered with the analysis; but judging from results of previous studies (17), it was considered reasonable to assume that if an increase could be observed in 0.1 *N* HCl, then an improved result might be expected in human gastric juice.

Figure 6 illustrates that the amount of increase observed with 10% fumed silicon dioxide in 0.1 *N* HCl was not as great as that observed in water. This result was not entirely unexpected, as the rate of solution is proportional to solubility in the diffusion layer.

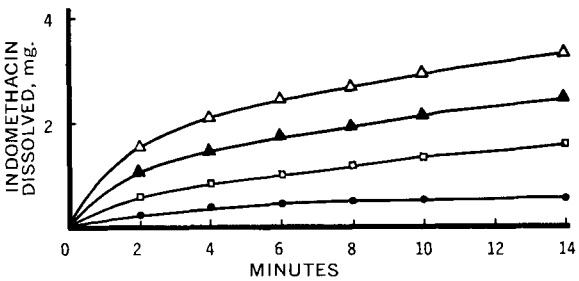

Figure 6—*Dissolution profiles of minuscular indomethacin in 0.1 N HCl at 240 r.p.m. Key: △, 10% fumed silicon dioxide; ▲, 10% basified silica gel; □, 10% untreated silicic acid; and ●, pure indomethacin powder.*

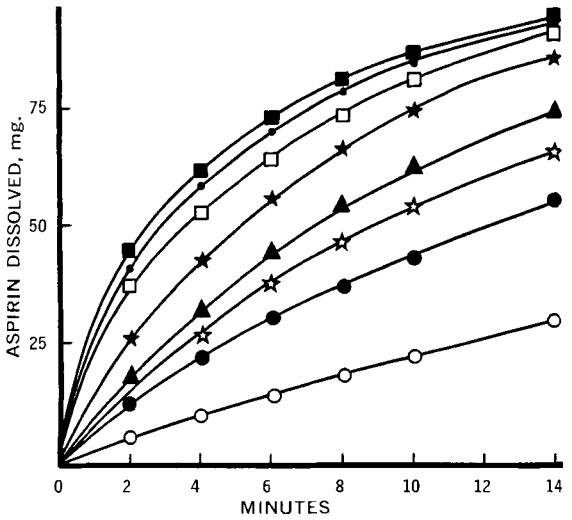

Figure 7—*Dissolution profiles of minuscular aspirin in water at 15 r.p.m. Key: ■, 10% fumed silicon dioxide; •, 5% fumed silicon dioxide; □, 10% starch and 10% lactose; ★, 10% silicic acid; ▲, commercial starch granules; ☆, 2% fumed silicon dioxide and 5% silicic acid; ●, pure aspirin crystals <100 mesh; and ○, 40-mesh aspirin commercial crystals.*

In this case, the diffusion layer could be considered as exemplifying the same pH as the gross dissolution medium. In fact, the solubility of indomethacin in 0.1 *N* HCl was decreased by one-third, which implied a slower dissolution rate. A similar decrease was observed with 10% silicic acid.

The basified silica gel also had a decreased effect in 0.1 *N* HCl. This might be explained by presuming that the depth of the diffusion layer was of a smaller magnitude in 0.1 *N* HCl than in distilled water. As a result, the molecules of free acid would precipitate earlier and the effectiveness of the alkali would be reduced. As observed initially, the rank order is invariant both in distilled water and in 0.1 *N* HCl.

It was considered that the method of preparation might be partly responsible for the observed behavior, since the evaporation technique might not have entirely discouraged the possibility of multiphase solids. For this reason, solvents such as methylene chloride and chloroform were tried for the indomethacin system and a rotary evaporator was used to remove the solvent. The amount of indomethacin dissolved as a function of time exhibited essentially the same release profiles as the original samples prepared in the manner described in the *Experimental* section. It may, therefore, be construed that the results are, for the most part, independent of the solvent and the method of preparation and are a function only of the indomethacin–fumed silicon dioxide ratio.

Aspirin—The family of curves obtained at 15 r.p.m. (Fig. 7) produced the following rank order of dissolution: 10% fumed silicon dioxide > 5% fumed silicon dioxide > 10% starch-coated, 10% lactose-coated > 10% starch granules > 2% fumed silicon dioxide, 5% silicic acid > aspirin crystals (<100 mesh) > 40-mesh commercial aspirin crystals. At the higher speeds, 60 and 240 r.p.m., the profiles further coalesced, but the rank order remained essentially the same; that is, there was no crossover of individual profiles as previously reported for aspirin tablets (18) or for different crystal sizes (19). Although it is difficult to compare results gained from different experimental conditions, it was not surprising that results varied when such different conditions as nonsink and a 0.1 *N* HCl medium were employed.

Since starch and lactose are two of the most popular "nondrug" ingredients in tablets, a comparison of their release rates with the silica compounds was desirable. A sample of a commercial aspirin granulation containing 10% starch was obtained, and its dissolution rate was compared to surface-coated samples containing 10% starch and 10% lactose. From Fig. 7, it is evident that the surface-coated samples were superior to the granulated form while there appears to be no difference between lactose and starch. The physical mixes (not shown) dissolved slightly faster than the pure drug powder, yet slower than the 2% fumed silicon dioxide and the 5% silicic acid coated samples. The commercial granulation was prepared from the 40-mesh crystals, but the method involved in their preparation is unknown. Two possibilities exist which may explain why the granulation dissolved faster than the physical mix:

1. If wet granulation was used, then some surface coating may have occurred.

2. If a slugging technique was used, then the specific surface area would have been increased by the action of the compression pressure fracturing the particles (20).

The possibility of a surface interaction occurring under the compression conditions must also be considered (21).

The swelling action of starch grains is most desirable in a tablet formulation. It is suggested that some surface coating, preferably on fumed silicon dioxide, be a prerequisite before the drug is granulated.

General—It appears that the rank order for the diffusion-controlled dissolution of the two studies discussed thus far remained constant regardless of a change in agitation intensity. For the more soluble drug, aspirin, the optimum speed for differentiation of the individual profiles seemed to be 15 r.p.m.; for the more insoluble drug, indomethacin, the better speed was 240 r.p.m. On this basis it was decided that rather than using three speeds for the remaining seven drugs, one differentiating speed was needed.

For the low solubility drugs (*e.g.*, sulfaethidole, reserpine, griseofulvin, probucol, and oxolinic acid), a high speed of 240 r.p.m. was utilized; for the moderately soluble drugs (*e.g.*, hydrochlorothiazide), 60 r.p.m. was employed; and for the higher solubility drugs (*e.g.*, chloramphenicol), a speed of 15 r.p.m. was used. Under the conditions of this experiment, 15 r.p.m. was the minimum speed that produced homogeneity in the medium and 240 r.p.m. was the maximum speed that did not cause excessive turbulence.

From the preceding two studies, it appeared that fumed silicon dioxide was the most efficient delivery system in releasing the drug as compared, for example, to silicic acid. Thus, it was resolved to test this system with a number of drugs that are known to have problems in their dissolution characteristics: chloramphenicol (22, 23), griseofulvin (10, 12, 15, 24–26), sulfaethidole (27), reserpine (11, 28, 29), and hydrochlorothiazide (30, 31). In addition, two experimental drugs[14], oxolinic acid (32) and probucol, were also tested. These seven drugs were prepared in the previously described manner with 5, 10, and 20% fumed silicon dioxide; the dissolution profiles of these systems, along with that of the pure drug, were determined (Table I).

Examination of the relative dissolution rates in Table I clearly indicates that a linear relation does not exist between the release rate and the amount of fumed silicon dioxide added. On closer inspection, observing the 3-min. interval, there seems to be a leveling off between 10 and 20% of fumed silicon dioxide added. This implies that the surface was covered by a drug monolayer that controlled the dissolution process. It can be rationalized that up to 10% the fumed silicon dioxide was being covered by a drug layer, while a monolayer was formed at or about 10%. Above this amount, multilayers or clusters of multilayer aggregates coated the silica surface or, alternatively, the excess silica coated the drug. Hence, when the samples were placed in the dissolution medium, the competition between the water molecules and the drug for the surface became maximal once a monolayer was present. The dissolution rate was then minimally improved with further addition of fumed silicon dioxide above 10%.

The increases in dissolution rates of the compounds listed in Table I are comparable to those reported in most of the studies cited previously. The approach taken in this study was, however, essentially different. The other methods, which include mixed melts, high energy polymers, molecular complexes, and solubilizing agents, are all capable of releasing "bound" drug. Present analytical techniques are not selective—they all measure total drug in solution. This total drug can include bound drug (33) which may be a nonadsorbable species. Preliminary data from other studies in this laboratory are conclusive in showing that the dialysis rate across a membrane is markedly influenced by binding phenomena. Since fumed silicon dioxide and silicic acid are insoluble, the minuscular drug system releases only free, adsorbable drug into solution.

[14] Supplied by commercial drug companies.

Another apparent disadvantage of these other methods is that the total bulk quantity of final dosage form required becomes prohibitive when the dose is of the order of 250 mg. The impracticality becomes evident when it is realized that a 1:9 drug–excipient ratio is frequently necessary to observe the increased rates. In the current study, a high drug–excipient ratio of 10:1 is indicated.

From the foregoing results, it is quite evident that the use of adsorbents can facilitate the dissolution process of relatively insoluble powders. Surface degradation is, however, a possibility with such systems (34, 35), but this aspect will be considered in the second article. The minuscular drug delivery system can be regarded as drug in a microparticulate form molecularly dispersed on the very extensive surface of fumed silicon dioxide. The resulting decrease in particle size and the concomitant increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which, in turn, greatly enhances the rate of solution of the drug.

REFERENCES

(1) A. A. Noyes and W. R. Whitney, *J. Amer. Chem. Soc.*, **19,** 930(1897).

(2) W. Nernst, *Z. Phyz. Chem.*, **47,** 52(1904).

(3) W. I. Higuchi, E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **47,** 376(1958).

(4) E. Nelson, *ibid.*, **47,** 300(1958).

(5) T. Higuchi and J. L. Lach, *ibid.*, **43,** 349(1954).

(6) M. A. Zoglio, H. V. Maulding, and J. J. Windheuser, *J. Pharm. Sci.*, **58,** 222(1969).

(7) J. Haleblian and W. McCrone, *ibid.*, **58,** 911(1969).

(8) J. W. Poole and C. K. Bahal, *ibid.*, **57,** 1945(1968).

(9) A. J. Aguiar, J. E. Zelmer, and A. W. Kinkel, *ibid.*, **56,** 1243 (1967).

(10) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9,** 866(1961).

(11) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **54,** 1145(1965); *ibid.*, **55,** 482(1966); *ibid.*, **55,** 487(1966).

(12) R. G. Stoll, T. R. Bates, K. A. Nieforth, and J. Swarbrick, *ibid.*, **58,** 1457(1969).

(13) W. L. Chiou and S. Riegelman, *ibid.*, **58,** 1505(1969).

(14) E. Stahl, *Arch. Pharm.*, **292/64,** 411(1959).

(15) M. Mayersohn and M. Gibaldi, *J. Pharm. Sci.*, **55,** 1323 (1966).

(16) S. Goto, T. Wen-yung, M. Kai, S. Aizawa, and S. Iguchi, *Arch. Pract. Pharm.*, **29,** 118(1969).

(17) P. Finholt and S. Solvang, *J. Pharm. Sci.*, **57,** 1322(1968).

(18) G. Levy, J. R. Leonards, and J. A. Procknal, *ibid.*, **56,** 1365 (1967).

(19) P. Finholt, H. Kristiansen, O. C. Schmidt, and K. Wold, *Medd. Norsk Farm. Selskap.*, **28,** 17(1966).

(20) T. Higuchi, A. N. Rao, L. W. Busse, and J. V. Swintowsky, *J. Amer. Pharm. Ass., Sci. Ed.*, **42,** 194(1953).

(21) J. L. Lach and M. Bornstein, *J. Pharm. Sci.*, **54,** 1730(1965).

(22) A. H. Goldberg, M. Gibaldi, J. L. Kanig, and M. Mayersohn, *ibid.*, **55,** 581(1966).

(23) A. J. Aguiar, L. M. Wheeler, S. Fusari, and J. E. Zelmer, *ibid.*, **57,** 1844(1968).

(24) P. H. Elworthy and F. J. Lipscomb, *J. Pharm. Pharmacol.*, **21,** 273(1969).

(25) S.-L. Lin, J. Menig, and L. Lachman, *J. Pharm. Sci.*, **57,** 2143(1968).

(26) T. R. Bates, M. Gibaldi, and J. L. Kanig, *ibid.*, **55,** 191(1966).

(27) K. Kakemi, T. Arita, and S. Ohashi, *Yakagaku Zasshi*, **82,** 261(1962).

(28) M. H. Malone, H. I. Hochman, and K. A. Nieforth, *J. Pharm. Sci.*, **55,** 972(1966).

(29) T. R. Bates, *J. Pharm. Pharmacol.*, **21,** 710(1969).

(30) D. Cook, H. S. Chang, and C. A. Mainville, *Can. J. Pharm. Sci.*, **1,** 69(1966).

(31) D. C. Baun and G. C. Walker, *J. Pharm. Sci.*, **58,** 611(1969).

(32) T. H. Simon, paper presented to the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, Apr. 1967.

(33) Z. Mansour and E. P. Guth, *J. Pharm. Sci.*, **57,** 404(1968).

(34) W. Wu, T. Chin, and J. L. Lach, *ibid.*, **59,** 1122(1970); *ibid.*, **59,** 1234(1970).

(35) K. C. Wichman, Ph.D. thesis, University of Iowa, Iowa City, Iowa, 1970.

ACKNOWLEDGMENTS AND ADDRESSES

Received October 28, 1971, from the *College of Pharmacy, University of Iowa, Iowa City, IA 52240*

Accepted for publication May 9, 1972.

Abstracted in part from a dissertation submitted by D. C. Monkhouse to the Graduate College, University of Iowa, in partial fulfillment of the Doctor of Philosophy degree requirements.

▲ To whom inquiries should be directed.

Use of Adsorbents in Enhancement of Drug Dissolution II

DONALD C. MONKHOUSE and JOHN L. LACH▲

Abstract □ Using the instrumental techniques of diffuse reflectance spectroscopy, differential thermal analysis, and X-ray analysis, it was possible to characterize the type of bonding forces involved in the minuscular drug systems prior to the dissolution process. Hydrogen bonding and van der Waals' forces accounted for the rapid desorption of the drugs from the adsorbent surface. A decrease in particle size was suggested as a major factor improving the dissolution rate of these equilibrated systems. Two polymorphic forms of indomethacin and probucol were identified as being present in the samples, the proportion of the metastable form being dependent on the percentage of fumed silicon dioxide added to the system.

Keyphrases □ Adsorbents—used to increase dissolution rates of drugs, characterization of drug–excipient binding □ Drug–excipient binding—dissolution characterization of micronized (minuscular) drug dispersed on adsorbents □ Diffuse reflectance spectroscopy—characterization of drug–excipient binding □ Differential thermal analysis—characterization of drug–excipient binding □ X-ray crystallography—characterization of drug–excipient binding □ Dissolution rates—micronized (minuscular) drug dispersed on adsorbents, characterization of binding forces

Reports in the literature in the last 5 years brought to light the importance of drug–excipient interactions. These interactions have been responsible in part for difficulties experienced in formulating pharmaceutical dosage forms. The most pertinent consequence associated with these interactions is often a decreased thera-