Dissolution of Poorly Water-Soluble Drugs I: Some Physical Parameters Related to Method of Micronization and Tablet Manufacture of a Quinazolinone Compound

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Abstract □ An investigation was conducted to analyze the dissolution behavior of a poorly water-soluble drug. Two specific methods of micronization were employed which provided drug forms of different physical characteristics, specific surface area, and particle-size range. The drug, a quinazolinone compound, was micronized by employing spray drying and air attrition. The micron-sized drugs, pelletized pure drugs, and tablets prepared from same by direct compaction were subjected to dissolution-rate studies at pH 1.2 and 3. *In vitro* dissolution data obtained have demonstrated a significant variation for the pure spray-dried and air-attritioned drugs at pH 1.2, although physical specifications had suggested the contrary of that reported. The pure drug forms, when pelletized, resulted in elimination of the difference observed for dissolution rates with the pure drug powders. Dilution of the pure drugs with tablet excipients and subsequent direct compaction into tablets resulted in an improvement of dissolution behavior compared to that obtained with the pure drug forms.

Keyphrases □ Dissolution behavior—poorly water-soluble drugs □ 1 - Isopropyl - 7 - methyl - 4 - phenylquinazolin - 2(1*H*) - one—dissolution □ Micronization effect—poorly water-soluble drug □ Spray-drying effect—poorly water-soluble drug □ Pellets, poorly water-soluble drug—dissolution

During the past decade, numerous publications have related biological availability data with the particle size of various drugs which are orally administered. The importance of the technological understanding and improvement of the dissolution rate for poorly water-soluble drugs has been well documented (1). *In vitro* dissolution-rate information has readily permitted distinction between different dosage forms containing the same drug with relationship to their gastrointestinal absorption characteristics. Solubility rate of a substance has been quantified directly to surface area for nearly a century (2). Reduction to a smaller workable particle-size range for poorly water-soluble drugs has been the general practice during the past decade. The research pharmacist, when formulating a solid or liquid dosage form of an insoluble drug, has relied upon a variety of processes, *i.e.*, grinding, air attrition, ball milling, and controlled precipitation, to obtain the ultimate in particle-size reduction. Air attrition has gained the most widespread acceptance, which has led to the availability of a variety of fluid energy mills (3).

A review article (1) was recently published which dealt in depth with particle size of drugs and its relationship to absorption and activity. Sulfadiazine, griseofulvin, and sulfaethidole (4–6) are a few of those compounds studied in an effort to establish the clinical effect of reduced particle size.

The twofold purpose of the present research was to study the dissolution behavior for a pure water-insoluble drug, which was micronized by spray-drying and air-attrition processes, with a compressed dosage form of the same, and to investigate the acceptability of spray drying as an alternative method for the preparation of micron-sized particles. Dissolution behavior has been compared for both physical forms with relationship to two different physical parameters: particle-size range and specific surface area.

EXPERIMENTAL

Spray-drying and air-attrition processes were selected for the manufacture of micron-sized particles of a poorly water-soluble drug. Spray drying appeared interesting to study in this instance, since it was thought that the process would impart certain desirable physical characteristics not typical of air-attritioned material such as unrestricted particle flow and ease of uniform dispersion of hydrophobic particles in an aqueous system as well as the possible presence of small holes in the spherical particles which would provide additional surface area.

Materials—1-Isopropyl-7-methyl-4-phenylquinazolin-2(1*H*)-one was synthesized in accordance with quality control standards for a pure drug.[1] The drug chosen for this study is indicative of a heterocyclic nitrogen base which does not readily form salts except at extremely low pH. The saturation concentration of the spray-dried and air-attritioned drugs in distilled water with a pH 6.0 and after 6-hr. exposure was found to be 2.7×10^{-4} moles/l. at 37° employing a rotational dissolution apparatus. Initially, the drug was twice passed through a laboratory hammer mill[2] which utilized a plate with 1-mm. perforations. The drug was then micronized by air attrition, employing a conventional fluid energy mill.[3] The micronized drug exhibited large particle aggregates which resulted from the high degree of surface energy developed by particle friction during processing. Additional drug from the same batch was used for preparing material by a spray-drying process which is described in the next section.

Spray-Drying Process—A 50-g. quantity of the quinazolinone compound was dissolved in 50 ml. chloroform, reagent grade, employing mechanical stirring. Special denatured alcohol (90% ethyl alcohol–10% methyl alcohol) was added to bring the solution to 125 ml.

A portable laboratory spray dryer[4] equipped with a centrifugal atomizing wheel, which functioned from air-turbine drive with a velocity of about 40,000 r.p.m., was employed in this study. The heated chamber of the spray dryer was maintained at 100–120° and the outlet temperature at 75–85°. The drug solution was introduced to the atomizing wheel by employing a Sigmamotor pump[5] which was adjusted to a flow rate of 15 ml./min. A cyclone collector separated the spray-dried drug from the solvent system. The solvent was not recovered; however, if scale-up was considered, a solvent-recovery method could be designed. The micron-sized drugs were both stored in tightly closed glass containers.

Physical Form and Particle-Size Range of the Pure Drug Forms—The particle-size range for the spray-dried and air-attritioned quinazolinone compounds was determined by a photomicroscopic method utilizing a grid graduated in microns. Observation of the photographs of the spray-dried drug depicted sphere-shaped amorphous particles which ranged in diameter from 1 to 15 μ. The irregular crystalline fragments of the air-attritioned drug measured from 1 to 5 μ.

[1] Sandoz Pharmaceuticals, Chemical Development Dept., Hanover, N. J.
[2] Raymond Mill, Combustion Engineering Co., Chicago, Ill.
[3] Reductionizer, Reduction Engineering Corp., Newark, N. J.
[4] Nerco-Niro, distributed by Nichols Engineering and Research Corp., New York, N. Y.
[5] Sigmamotor, Inc., Middleport, N. Y.

Specific Surface Area of the Pure Drug Forms—The spray-dried and air-attritioned quinazolinone compounds were subjected to the classical low-temperature adsorption Brunaner, Emmett, and Teller (B.E.T.) technique[6] for specific surface area measurement. Krypton gas was used as the adsorbate. The method permitted sample outgassing to less than 1 μ of pressure. One-gram samples of the spray-dried and air-attritioned materials were heated to 50° and outgassed for 8 hr. to evacuate gasses and vapors acquired from exposure to the atmosphere. The surface area analysis involved incremental gas volume adsorption measurements which were made by accurately determining the equilibrium pressure following the introduction of gas quantities into the system. The specific surface area was found to be 1.37 $m.^2/g.$ for the spray-dried drug and 2.78 $m.^2/g.$ for the air-attritioned drug.

Pellets of the Pure Drug Forms—A comparative study was designed to determine the effect on dissolution when the two pure drug forms were compressed into pellets. Fifty milligrams of the drug was compressed using a single station tablet press,[7] employing 6-mm. shallow-concavity punches. Each pellet was formed with a thickness that was maintained at 1.80 mm., which assured equivalent surface area for both materials tested. Although the hardness was measured as 3 kg. with an air-operated Strong-Cobb tester, the pellets did not fracture during the dissolution runs but remained intact with slow dissolution.

Tablet Manufacture Employing Spray-Dried and Air-Attritioned Quinazolinone Compounds by Direct Compaction—The composition for tablets manufactured by direct compaction (D.C.) utilizing spray-dried and air-attritioned drugs are given in Table I.

Direct Compaction Manufacturing Procedure—The ingredients listed in Table I were accurately weighed and passed through a No. 20-mesh screen. The materials were transferred to a glass mortar and gently blended so that the drug's particle structure would not be altered. Then 160 mg. of the blended powders was placed into the die cavity of the single station tablet press and compressed, using 8-mm. flat, beveled-edge punches. The tablet hardness was maintained at 6.5 ± 0.5 kg. which was monitored by using a compressed air-operated Strong-Cobb tester. The tablet thickness was measured using a micrometer; each tablet employed in this study had to adhere to a measurement of 2.75 ± 0.01 mm. This physical measurement assured compliance of each tablet to the hardness range established for this study. The direct compacted tablets were subjected to the USP disintegration test and were found to disintegrate within 25 ± 5 sec. These tablets were formulated to give fast disintegration in an attempt to observe uninhibited drug dissolution. Tablet disintegration occurred with the rapid formation of discrete particles of drug-diluent which resulted from rupture of the tablet matrix.

Dissolution Rate Analysis of the Pure Drugs, Pellets, and Tablets—The dissolution apparatus that was initially employed in this study was the beaker-stirrer method. The poor wetting property exhibited by the pure drug forms required selection of another method that would permit a more uniform contact of solvent and powders. The rotating-bottle method was found most suitable for attaining reasonably precise data for consecutive experiments, whereas with the beaker-stirrer method it was not possible. Preliminary experiments revealed that 20 r.p.m. was a suitable speed for demonstrating definite differences in dissolution behavior for the pure materials investigated. Rotational rates less than 20 r.p.m. did cause a substantial decrease in the dissolution rate from that reported in this paper. Each sample bottle was immersed in a water bath maintained at 37 ± 0.5°. The powder, pellet, or tablet was placed in a 75-ml. capacity, amber glass bottle containing 50 ml. of aqueous solvent which had been previously adjusted to a pH of 1.2 or 3 with hydrochloric acid. The solvent had been preheated to 37° prior to the addition of the sample. At the moment of sample addition, the time was recorded as $t = 0$. The vessel was tightly closed with a bakelite cap lined with a polyethylene sealer. Dissolution of the drug and tablets was studied over a 30-min. interval, and each sample was carried through a 60-min. period to establish whether total availability of the drug in solution was reached. Preliminary studies indicated that a 60-min. test period was sufficient, since two half-lives were encompassed which permitted valid comparison of the $t_{25\%}$, $t_{50\%}$, and $t_{75\%}$.

[6] Model 2100 surface-area analyzer, Micromeritics Instrument Corp., Norcross, Ga.

[7] Stokes E Machine, Pennsalt Chemicals Corp., Warminster, Pa.

Table I—Tablet Composition for D.C. Tablets Prepared from Spray-Dried and Air-Attritioned Quinazolinone Compounds

Materials	Quantity per 160-mg. Tablet
Isopropylmethylphenylquinazolinone, spray-dried or air-attritioned	50.0 mg.
Microcrystalline cellulose[a]	25.0 mg.
Colloidal silica[b]	0.5 mg.
Corn starch USP	12.0 mg.
Lactose, spray-dried USP	69.5 mg.
Stearic acid powder USP	3.0 mg.

[a] Avicel, FMC Corp., Marcus Hook, Pa. [b] Cab-o-Sil, Cabot Corp., Boston, Mass.

The dissolution studies for the pelletized substances were carried out for 6 hr. at pH 1.2 in the same manner employed for the tablets. A quantity of 50 mg. of the quinazolinone compound was chosen since it represented a concentration below the aqueous saturation point of 60.5 mg./50 ml. at pH 1.2. The closer the quantity of drug in solution is to the saturation equilibrium the slower the approach to total solubility. The present investigation included the following test samples: 50 mg. spray-dried and air-attritioned drugs. In addition, pellets and tablets were studied which contained 50 mg. of spray-dried and air-attritioned drugs. These materials were all subjected to the outlined dissolution rate analysis at pH 1.2 and, in most cases, pH 3.

Nonsink conditions were employed in these experiments to observe the dependence upon limited hydrogen-ion concentration as related to dissolution. An unusual situation was observed: the pH's of the systems at the termination of the dissolution runs did not vary more than ±0.1 unit from the starting value for both pH 1.2 and 3. This was explained by the particular pKa of the drug, which was determined by spectrophotometric and solubility–pH data to be 2.51.

The analytical details of the dissolution experiments involved the withdrawal of a 1-ml. sample at the specified time interval using a pipet with filter-tip. The aliquot was diluted with the specified acid solution, utilized in the dissolution study, to 100 ml. The adsorption of the diluted solution was measured in a Cary recording spectrophotometer over the UV spectra, and the maximum absorbance at 232 mμ was used to calculate the drug concentration per 50 ml. of test solution. A correction factor was calculated for each sequential sampling as a result of the volume change that occurred because the test solution withdrawn for the pellet and tablet runs was not replaced after each sampling.

Individual sample containers were employed for the pure drug forms for each time segment; otherwise, some of the drug would have adhered to the filter-tip of the pipet with each withdrawal, which would have introduced a recurring error.

RESULTS AND DISCUSSION

The quinazolinone compound utilized in this study may be classified as a heterocyclic nitrogen base which exhibited poor aqueous solubility that was shown to be a function of hydrogen-ion concentration and method of micronization. The drug undergoes solubilization by interaction with hydronium ion to form a salt.

The concentration of the compound (mol. wt. 278) at 50 mg./50 ml. was calculated to be 3.6×10^{-3} moles/l. The unprotonated form of the compound formed a saturated solution in distilled water with a concentration of 2.7×10^{-4} moles/l. The hydrochloric acid solution at pH 1.2 contained about 6.3×10^{-2} moles/l. hydrogen ion, which provided about an 18 times greater hydrogen ion than the concentration of the compound. Therefore, complete solution of the 50 mg. at this pH was obtained. At pH 3 the hydrogen-ion concentration was about 1×10^{-3} moles/l., which limited the solubility of the compound since there was a fourfold excess of drug over hydrogen ion. Henceforth, one would expect only about 13 mg. of the compound to go into solution in the protonated form at pH 3. This approximates the values recorded in Table II, which were obtained experimentally.

The dissolution data obtained for the spray-dried and air-attritioned drugs at pH 1.2 and 3 can be compared by observing Table II. The spray-dried and air-attritioned drugs possessed dissimilar particle-size distributions in the low micron range. These

Table II—Dissolution Data at pH 1.2 and 3 of Spray-Dried and Air-Attritioned Quinazolinone Compounds

Sample Intervals, min.	Amount Dissolved, mg./50 ml.[a] Spray-Dried pH 1.2	Spray-Dried pH 3	Air-Attritioned pH 1.2	Air-Attritioned pH 3
1	9.1		6.1	
3	19.2		10.5	
5	27.8	5.6	13.6	4.1
10	34.1	12.6	20.6	9.0
15	37.9		24.1	
20	39.3	12.2	29.5	11.5
30	41.5	12.4	34.1	12.4
60	45.3	12.6	43.3	12.9

[a] Represents the average of four experiments with standard deviation of not more than 1.4 for all data recorded.

data indicate that at pH 1.2 an increase in dissolution rate was observed for the drug when micronized by spray drying as compared with the air-attritioned form. The results were unexpected since the specific surface area of the air-attritioned drug was determined to be twofold that found for the spray-dried drug. The apparent surface area of a poorly water-soluble material in contact with the aqueous medium appears to be unrelated to its specific surface area. Based on this factor, correlation of specific surface area with dissolution behavior without experimental verification could be quite deceptive. It was thought possible that the smaller air-attritioned particles were not subjected to the same intensity of agitation as were the large spray-dried particles; however, by physical observation it was quite apparent this was not the case. In fact, the air-attritioned drug had a definite tendency to form large particle aggregates which diminished the surface area, thereby resulting in a dissolution rate that was less than expected. Furthermore, it was also possible that surface hydration and solubility characteristics varied for both physical forms as a result of their different physical characteristics.

Pellets prepared from the spray-dried and air-attritioned materials, possessing equal surface area, were evaluated with regard to their respective dissolution rates, and Fig. 1 indicates the results obtained. The intended incorporation of the drugs, at a later stage, into a tablet matrix required an interpretation of the interparticle bonding forces that existed for each of the physical drug forms. If the specific particle structure of the drug resulted in dissimilar interparticle adhesion, subsequent inclusion into a tablet could possibly influence the dissolution behavior. The interparticle adhesion that occurs in a solid system may result from either partial fusion or partial dissolution at the surface of the particles induced by energy added during the compression (7).

From Fig. 1 it appears evident that pellets from the two physical drug forms have no significant difference in their dissolution rates.

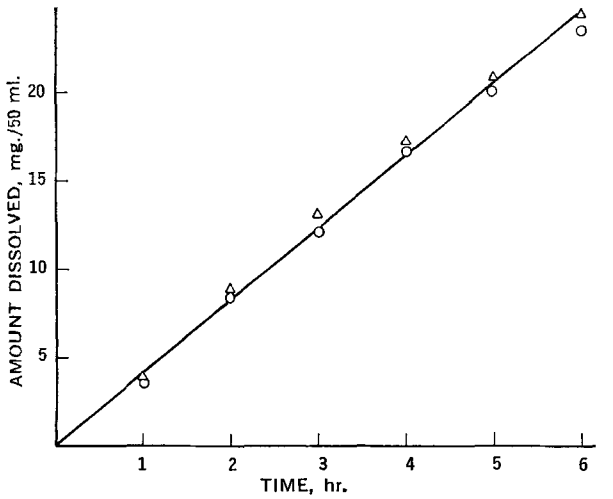

Figure 1—*Apparent zero-order dissolution rates of pelletized spray-dried and air-attritioned drugs were performed in 50 ml. aqueous solution at pH 1.2. Each plot is corrected to origin and the average of three experiments with standard deviation of not more than 0.7 for all data recorded. Key: △, spray-dried drug; and ○, air-attritioned drug.*

Table III—Dissolution Data at pH 1.2 and 3 of Spray-Dried and Air-Attritioned Quinazolinone Compounds Contained in Tablets Manufactured by Direct Compaction

Solution Time, min.	Amount Dissolved,[a] mg./50 ml. Direct Compression Spray-Dried pH 1.2	Spray-Dried pH 3	Air-Attritioned pH 1.2	Air-Attritioned pH 3
1	11.2	1.1	13.3	1.3
3	22.7	3.4	28.3	2.5
5	28.6	3.1	34.6	3.8
10	36.9	4.8	42.2	3.5
15	40.3		46.7	
20	42.9	4.4	50.4	4.8
60	46.4	13.0	50.4	12.9

[a] Represents the average of three experiments with standard deviation of not more than 1.1 for all data recorded.

An apparent zero-order equation for the dissolution data for both pellets was adhered to, which is in accord with the experimental conditions of constant dissolution surface area. By pelletizing the drug forms, the variation of surface wetting observed with the pure drug powders was eliminated. This phenomenon resulted in a need for clarification of the effect on dissolution when the pure drug form was diluted with common tablet excipients and then compressed into tablets.

The experiments designed to study the effect on dissolution with the drug forms in directly compressed tablets revealed certain definite departures from the results obtained with the pure drugs. The direct compaction method was utilized to prepare the tablets, since it permitted dilution of the drug without significant alteration of their physical forms. For this reason, the wet granulation method data were not included in this paper since it was shown to manifest additional complexities in following dissolution of the drug. A retarding effect on dissolution was experienced as a result of materials utilized in wet granulation, *i.e.*, granulating liquid and water-insoluble excipients, which tend to form a barrier layer on the surface of the drug particles during the granulating process.

The physical parameters, *i.e.*, tablet disintegration and thickness, were strictly controlled for the tablets prepared by direct compac-

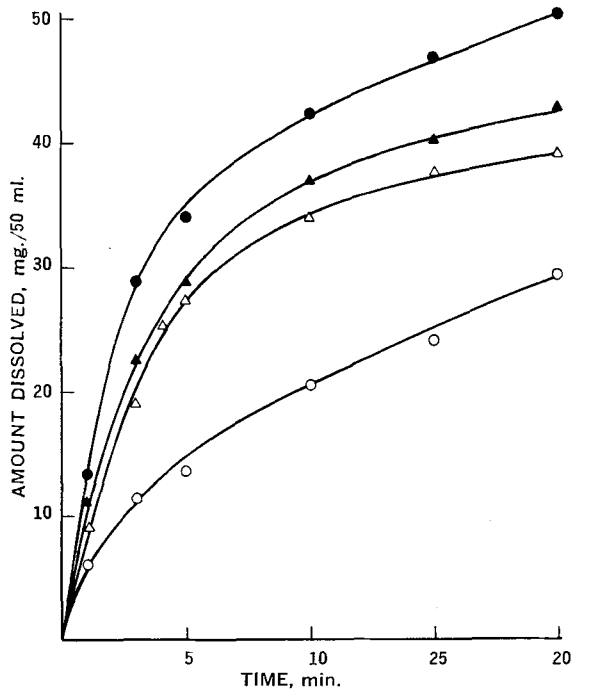

Figure 2—*Dissolution of spray-dried and air-attritioned powders and compressed tablets in 50 ml. aqueous solution at pH 1.2. Key: △, spray-dried powder; ○, air-attritioned powder; ▲, spray-dried tablet; and ●, air-attritioned tablet.*

Table IV—Amount of Spray-Dried and Air-Attritioned Drugs Dissolved (mg.) within a Specific Time Interval[a] in 50 ml. Aqueous Solution at pH 1.2, 37 ± 0.5°, and Rotated at 20 r.p.m.

	$t_{25\%}$, min.	$t_{50\%}$, min.	$t_{75\%}$, min.
Pure Drug			
Spray-dried	2.0	4.1	16
Air-attritioned	5.7	15.5	40
Compressed Tablets			
Spray-dried	1.6	3.5	10.5
Air-attritioned	1.3	2.6	6.5

[a] Each time interval was determined from the plotted data in Fig. 2.

tion. The tablets were formulated to give rapid disintegration, 25 ± 5 sec., in an attempt to observe uninhibited drug dissolution.

Dissolution data obtained for both sets of direct compacted tablets manufactured from the two drug forms have been tabulated in Table III for pH 1.2 and 3.

The dissolution rate obtained for the tablets prepared from air-attritioned and spray-dried drug proved to be quite similar in dissolution behavior (Fig. 2). These results indicate a substantial change from the comparative dissolution rates obtained with the pure air-attritioned drug under the same experimental conditions. The incorporation of the air-attritioned drug into a tablet matrix resulted in omission of the particle aggregates experienced with the pure drug. In addition, the improved dissolution rates for the tablets were probably a result of the hydrophilic property of the solid system and the increased surface area of the drug due to the force of compression.

Dissolution data obtained with the spray-dried drug and tablets of the same at pH 1.2 appear to have parallel dissolution patterns. The dissolution behavior experienced with both tablets compares more closely with the particle size and specific surface area data obtained for the pure drugs.

Table IV provides a tabulation of the time required for the dissolution of 25, 50, and 75% of the drug from both the powders and tablets, which is a convenient method for comparing dissolution data. The solid systems studied in this research were too complex for the application of reaction-order equations and, if utilized, would have possibly led to their misuse.

SUMMARY AND CONCLUSIONS

The results of dissolution studies at low pH provided information that rationalized the practical application of spray drying for the micronization of poorly water-soluble drugs. The air-attritioned drug had a tendency to form large particle aggregates which hindered its apparent dissolution rate in the pure form. In addition, the air-attritioned particles differed from the spray-dried inasmuch as they possessed a high degree of surface energy which gave rise to their sticking to each other and the sides of the storage container. Difficulty existed in handling and formulating the drug into the various forms.

The significantly greater dissolution rate that was observed for the pure spray-dried drug at pH 1.2 despite the smaller particle-size range of the air-attritioned drug would lead one to criticize the selection of a particular physical form of a poorly water-soluble drug by analyzing only physical dimension data. Particle-size range and specific surface area measurements for different physical forms of the drug studied were misleading and quite unrelated to their dissolution behavior. More pertinent is the apparent surface area of the drug available for solvent wetting for a poorly water-soluble material. The apparent surface area was not directly measured in these studies; however, dissolution is an indirect approach to the matter. The large particle aggregates, such as those observed with the air-attritioned drug, interfered with the apparent dissolution rate and gave data that would not normally be expected.

With this hydrophobic drug, it was found that the rotating-bottle method permitted acceptable reproducibility of the dissolution results. On the other hand, the beaker-stirrer method failed in this aspect as a result of discontinuous wetting of the powder by the acidic medium. With the appearance of a variety of dissolution systems in the literature (8), the authors would like to emphasize that the ability to repeat an experiment and obtain valid reproducibility should be the prime objective. A base line for dissolution behavior should always be established with the pure drug powder by employing an *in vitro* dissolution technique, and this should be done prior to fabrication of the dosage form. In this manner, the necessary properties of the tablet or capsule matrix can be more accurately determined.

The quinazolinone compound studied was insoluble in distilled water; however, by reducing the pH, limited solution did occur. The heterocyclic nitrogen in the quinazolinone structure was protonated in solution and the lower the pH of the aqueous system, the greater was its total solubility under nonsink conditions.

The dissolution data obtained for the two pure drug forms could have resulted in selection of the spray-dried drug for use in a solid dosage form; however, with additional experimentation employing a compressed tablet formulation, greater insight was obtained. Incorporation of the drug powders into a compressed tablet was helpful in clarifying possible false conclusions that could have been drawn from the dissolution data for the pure drugs. The dilution factor which resulted when the air-attritioned drug was combined with tablet excipients decreased the interparticle aggregation effect experienced with the pure form. When the tablet was placed in the aqueous medium, it released discrete particles, composed of drug and diluent, upon disintegration. This phenomenon greatly improved the dissolution behavior for the air-attritioned drug in the tablet form, since the discrete particles eliminated the particle aggregation observed with the pure drug powder. The dissolution rates for the pure spray-dried drug and tablets (Fig. 2) were not greatly different, since particle aggregation was not operative during the powder's dissolution experiments. The tablet diluents employed for the compressed tablets were selected where possible for their water-soluble or hydrophilic properties. This particular consideration can assist the diffusion-dissolution-diffusion processes required for dissolution of a drug from the discrete particles resulting from tablet disintegration. Water-insoluble components in the tablet matrix would tend to retard the overall dissolution process of a poorly water-soluble drug. This aspect has been utilized in the design of sustained-release dosage forms by employing a water-insoluble material to reduce dissolution rate. When a tablet disintegrates, the discrete particles formed should be as hydrophilic in property as possible in order to assist the dissolution process.

The variation of dissolution behavior shown in this paper for the pure drug, and tablets of same, underline the fallacy of performing dissolution rate analysis with various physical forms of the pure drug without inclusion of a proposed solid dosage form in such studies. The early initiation of preformulation kinetic studies for new drugs quite often incorrectly forces one to select the supposed best physical form of a drug prior to the consideration of dosage form research. The physical form and its dissolution behavior must be considered by the research pharmacist in organizing the development protocol for new drugs which fall into the category of poorly water soluble.

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