Dissolution of Poorly Water-Soluble Drugs II: Excipient Dilution and Force of Compression Effects on Tablets of a Quinazolinone Compound

JEFFREY O. HIRSCHORN and SAUL S. KORNBLUM*

Abstract □ Tablets of three different dilution ratios, comprised of the same excipients with a constant quantity of drug, demonstrated a significant variation of the drug's dissolution behavior. A linear relationship was obtained when plotting $t_{50}\%$ *versus* tablet weight. The relationship appears to have resulted from the fact that the apparent surface area of the ruptured tablet is related to the number of discrete particles formed from disintegration and deaggregation of the tablet. An increase of the compression force for the three tablets (200, 400, and 600 mg.) provided divergent results when comparing the $t_{50}\%$ of each tablet size, and the dissolution behavior appears to be a function of the dilution factor.

Keyphrases □ Dissolution, poorly water-soluble drug—parameters affecting □ Compression force effect—quinazolinone compound, tablet dissolution □ Excipient–drug ratio—tablet dissolution effect □ UV spectrophotometry—analysis

Research reports (1–3) have demonstrated the possible variation of *in vitro* dissolution of drugs when the composition or manufacturing techniques of a dosage form are altered.

Levy *et al.* (4) indicated the significance for both the size and age of granules on the dissolution rate of salicylic acid from compressed tablets. In another report (5), Levy and Gumtow showed where employment of a hydrophobic lubricant substantially interfered with the dissolution rate of salicylic acid tablets.

In another instance, Higuchi *et al.* (6) offered their observations concerning the force of compression as related to *in vitro* dissolution behavior of aspirin. They proposed that the increased dissolution from a greater compression force resulted due to an increase of particle surface area from granule fragmentation.

The authors (7) reported, in a previous paper, that significant variation of dissolution behavior can exist when comparing a drug powder and a compressed tablet of the same. The present communication deals with the effect on dissolution where a constant quantity of drug was diluted with the same excipients to three different tablet weights. The significance of altering the compression force with reference to *in vitro* dissolution was investigated for the tablet sizes considered in this research.

EXPERIMENTAL

Materials—A heterocyclic nitrogen base compound of quinazolinone structure was synthesized in accordance with specific standards of quality control[1]. The drug was twice passed through a laboratory hammer mill[2] equipped with a plate with 1-mm. perforations.

The drug was dissolved in an alcohol–chloroform solvent and subsequently spray dried in the manner outlined previously (7).

[1] Chemical Development Dept., Sandoz Pharmaceuticals, Hanover, N. J.

[2] Raymond Mill Combustion Engineering Co., Chicago, Ill.

Table I—Composition of Tablets Manufactured by Direct Compaction from Spray-Dried Quinazolinone Compound

Materials	Tablet Weight, mg. 200	400	600
Quinazolinone compound	50.0 mg.	50.0 mg.	50.0 mg.
Lactose USP, spray-dried	128.0 mg.	306.0 mg.	484.0 mg.
Microcrystalline cellulose[a]	20.0 mg.	40.0 mg.	60.0 mg.
Stearic acid powder USP	2.0 mg.	4.0 mg.	6.0 mg.

[a] Avicel, FMC Corp., Marcus Hook, Pa.

The spherical, amorphous drug particles of spray-dried drug were microscopically determined to fall into a diameter range from 1–15 μ, and the specific surface area was determined by the Brunauer, Emmett, and Teller technique to be 1.37 $m.^2/g.$

Direct Compaction Tablet Preparation Employing Spray-Dried Quinazolinone Compound—Compressed tablets were prepared by direct compaction in a hydraulic press equipped with a gauge[3] measuring forces from 0 to 5000 lb. and calibrated in 100-lb. increments. A special steel holder held the bottom punch and die in a fixed position during compression. The specific powder formulation was individually weighed and transferred into the die cavity; the top punch was then gently inserted into the die cavity, and the powder was compressed to a predetermined force. Reproducible dwell time was achieved for each tablet by applying the force to a specific load, and at this point the hydraulic valve was immediately released to reduce the force.

The slow compression method was useful in controlling reproducibility of the physical character of each tablet; however, it provided substantially different stresses than those normally obtained with a high-speed rotary tablet machine. Therefore, tablets prepared under production conditions may differ considerably from the test tablets.

The compositions for tablets manufactured by direct compaction employing the spray-dried drug are given in Table I.

The amount of drug was maintained constant while the quantities of binder-disintegrant and lubricant were varied as related to tablet weight, so that their percentages were the same for each tablet size. Lactose was employed to adjust the dilution ratios to 1:4, 1:8, and 1:12 for drug to total tablet weight, respectively.

Direct Compaction Microscale Manufacturing Procedure—The ingredients listed in Table I were accurately weighed and passed through a No. 20-mesh U. S. Standard sieve. The materials were transferred to a glass mortar and gently blended without force so that the drug's particle structure would not be markedly altered. The premixed blend was placed into a 1-pint twin-shell blender[4] and tumbled for 5 min. The blended powders were chemically analyzed to assure content uniformity for the drug. A specific quantity of the blended powder was filled into the die cavity and compressed, using flat-face, beveled-edge punches of the appropriate size.

The tablet thickness for each size tablet was measured using a micrometer with vernier; each tablet employed in the dissolution studies had to adhere to a tolerance of 0.02 mm. This physical measurement assured compliance of each tablet to similar disintegration times for consecutive tablets of the same size. Samples of each tablet size (200, 400, and 600 mg.) were subjected to the USP disintegration test. The tablet formulations were designed to disintegrate rapidly. This eliminated a lag period in the dissolution experiments, thus providing uninhibited dissolution. A compression

[3] Model C, Fred S. Carver, Inc., Summit, N. J.

[4] Patterson-Kelley, Inc., East Stroudsburg, Pa.

Table II—Physical Description and Compression Forces Relating to Tablets Prepared from Spray-Dried Quinazolinone Compound

Tablet weight, mg.	200	400	600
Punch diameter, mm.	8	10	12
Punch surface area, in.^{2}	0.079	0.123	0.177
Force applied (lb.)/ pressure applied (p.s.i.)	950/12,000	1500/12,000	2150/12,000
Force applied (lb.)/ pressure applied (p.s.i.)	1400/18,000	2200/18,000	3200/18,000
Force applied (lb.)/ pressure applied (p.s.i.)	2200/24,000	2950/24,000	4250/24,000

force of 12,000 p.s.i. was initially chosen since it provided all tablets with a 20–30-sec. disintegration time. A significant variation in the dissolution rates for the three tablet weights evaluated was observed. The fast disintegration gave rise to the formation of discrete particles composed of drug–diluents which resulted from rupture of the tablet matrix.

The physical parameters that were determined as controls in the manufacture of the variety of tablets are listed in Table II.

Dissolution-Rate Analysis for Tablets—The unprotonated form of the quinazolinone compound in the pure form formed a saturated solution of 2.7×10^{-4} moles/l. in distilled water. A quantity of 50 mg. of the drug per tablet was utilized in this study, since it provided a concentration well below the aqueous saturation level of 1.21 mg./ml. at pH 1.2. A rotating-bottle technique was employed, since it was found suitable for attaining reasonably precise data for similar consecutive experiments. The apparatus was immersed in a constant-temperature bath, maintained at 37 ± 0.5°, and rotated at a constant speed of 10 r.p.m.

Each tablet was placed into a 120-ml. capacity, amber glass bottle containing 100 ml. of aqueous solvent which had been previously adjusted to a pH of 1.2 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 container was tightly closed with a bakelite cap lined with a polyethylene sealer.

Apparent sink conditions were adhered to in this study since the solubility of the pure drug at 37° and pH 1.2 was determined to be 4.3×10^{-3} moles/l. The concentration of hydrogen ion was calculated to be 6.3×10^{-2} moles/l., which is about 35 times greater than the concentration of the compound (1.8×10^{-3} moles/l.).

Dissolution of the drug from the tablets was conducted for a 30-min. interval inasmuch as two half-lives were encompassed, which permitted valid comparison of the $t_{50\%}$ for each tablet size.

Table III provides all the dissolution data obtained for each tablet size and compression force. The amount dissolved at each time interval represents an average of four runs.

The analytical details for following dissolution involved the withdrawal of a 1-ml. portion at specified time intervals using a pipet with a filter tip. The aliquot was diluted to 50 ml. with aqueous pH 1.2 fluid. The absorption of the diluted solution was measured in a Cary recording spectrophotometer over the UV spectra, and the maximum absorbance at 232 nm. was used to calculate the drug concentration per 100 ml. of pH 1.2 aqueous solution. Beer's law was obeyed with this drug over a range of 0.001 mg./ml. to 0.005 mg./ml.

Table IV—Physical Specifications Determined for Each Tablet Size Prepared from Spray-Dried Quinazolinone Compound at Various Compression Forces

Compression Force, p.s.i.	Average Tablet Thickness, mm.[a]	Average Disintegration Time, sec.[b]
	200-mg. Tablets	
12,000	3.40 ± 0.02	20 ± 5
18,000	3.30 ± 0.02	45 ± 5
24,000	3.20 ± 0.02	85 ± 5
	400-mg. Tablets	
12,000	4.20 ± 0.02	30 ± 5
18,000	4.04 ± 0.02	45 ± 5
24,000	3.96 ± 0.02	65 ± 5
	600-mg. Tablets	
12,000	4.38 ± 0.02	30 ± 5
18,000	4.25 ± 0.02	55 ± 5
24,000	4.12 ± 0.02	105 ± 10

[a] Represents an average of all tablets employed in dissolution experiments. [b] Represents an average of six tablets performed by USP basket method with plastic disk.

A correction factor was calculated for each sequential sampling as a result of the small volume change that occurred since the test solution withdrawn was not replaced after each sampling. At least five, and not more than six, samples were taken for each run.

RESULTS AND DISCUSSION

A typical direct compression tablet formulation was chosen to study the effect on dissolution behavior, where the excipient content was increased in a relationship to a constant quantity (50 mg.) of drug. The three tablet weights investigated, 200, 400, and 600 mg., provided ratios of 1:4, 1:8, and 1:12 of drug to total tablet weight, respectively. The information in Table I indicates the composition and quantities of diluent, binder-disintegrant, and lubricant for the three tablet weights; the only variables introduced were the extent to which the drug particles were diluted and the surface area of the tablets. Upon disintegration, the tablets gave rise to the formation of discrete particles composed of drug–diluent, with a different content of drug to diluent for each discrete particle depending upon the tablet weights. These discrete particles, in turn, deaggregated to provide even smaller particles. The dissolution process then resulted from the solvent action of the gastric fluid on the discrete particles. Lactose, the main component comprising the tablets, was selected for its hydrophilic characteristic, which would lead one to conclude that the larger the tablet, the more probable that it would possess a more rapid dissolution rate for a specific compression force.

The differences existing between the tablet dilution ratio and force of compression at 12,000, 18,000, and 24,000 p.s.i. for the different tablet sizes are revealed in Figs. 1–3. The curves in these figures demonstrate that, at each compression force, the dissolution rate for the larger tablet is greater at the portion of the curve where the dissolution half-life is approached. The tablet's disintegration time and the thickness specifications for each tablet size that was compressed at the various forces are compiled in Table IV. For each tablet size, an increase in the compression force resulted in an in-

Table III—Dissolution Data at pH 1.2 for All Directly Compacted Tablets Prepared from Spray-Dried Quinazolinone Compound

Solution Time, min.	Amount Dissolved[a], mg./100 ml. 200 mg. at 12,000 p.s.i.	200 mg. at 18,000 p.s.i.	200 mg. at 24,000 p.s.i.	400 mg. at 12,000 p.s.i.	400 mg. at 18,000 p.s.i.	400 mg. at 24,000 p.s.i.	600 mg. at 12,000 p.s.i.	600 mg. at 18,000 p.s.i.	600 mg. at 24,000 p.s.i.
2	8.2	6.3	—	17.3	8.6	5.7	23.7	20.6	8.7
5	16.0	15.9	7.2	27.5	21.7	14.6	31.3	29.3	24.9
10	27.6	26.4	17.5	33.3	31.2	24.5	38.0	36.2	35.4
15	—	—	25.1	—	—	32.6	—	—	39.3
20	36.5	37.3	31.1	38.6	39.5	36.8	42.2	42.6	42.6
30	43.2	43.5	37.3	41.2	44.1	42.1	44.8	45.0	47.8

[a] Represents average of four runs for each tablet weight and compression force.

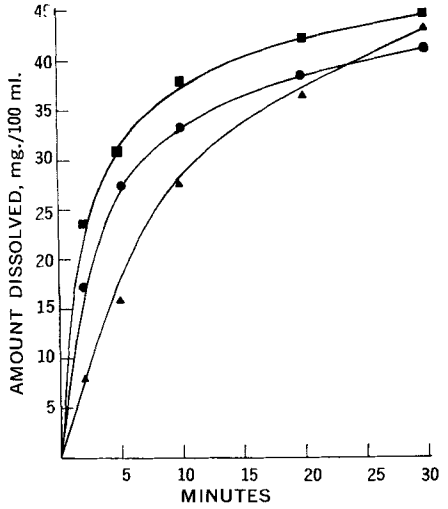

Figure 1—*Dissolution of quinazolinone compound in 100 ml. aqueous solution at pH 1.2 from compressed tablets at 12,000 p.s.i. Key: ▲, 200 mg.; ●, 400 mg.; and ■, 600 mg.*

creased disintegration time. The disintegration time for the three different tablet weights is about the same when compressed at 12,000 and 18,000 p.s.i., and, in all cases, it is under 55 sec. Those tablets compressed at 24,000 p.s.i. had a disintegration time that exceeded 1 min. but was less than 2 min.

The $t_{50\%}$ was determined from Figs. 1–3 for each tablet weight at various compression forces and may be observed in Table V. The half-life data for the 200-, 400-, and 600-mg. tablets indicate that the greater the pressure applied during compression, the longer the period for an equivalent amount of drug to be available in solution. The dissolution half-lives for the different tablet sizes supported the fact that the greater the drug's dilution, the more rapid was the dissolution rate. The apparent surface area, as a result of the number of discrete particles in contact with gastric fluid, appears to be the limiting factor. The greater the tablet weight, the less effect the force of compression exerts on the $t_{50\%}$. This phenomenon most likely relates to the significant increase that exists between the ratio of hydrophilic to hydrophobic materials as the tablet becomes greater in weight.

Figure 4 was prepared to determine the relationship of the half-life ($t_{50\%}$) to the specific tablet weight. When the pressure applied was maintained constant for the three different tablet sizes, a linearity existed for $t_{50\%}$ *versus* tablet weight. The smaller the tablet, the greater was the interference when varying the pressure applied in relation to the drug found in solution.

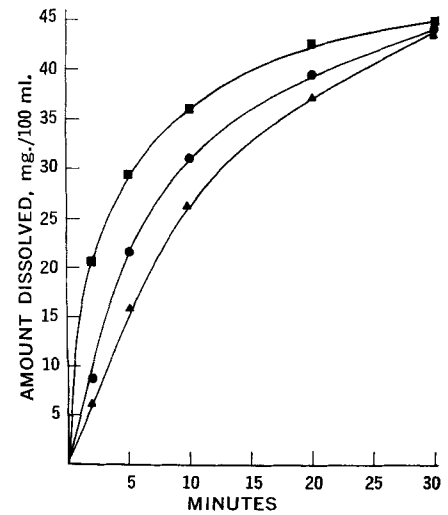

Figure 2—*Dissolution of quinazolinone compound in 100 ml. aqueous solution at pH 1.2 from compressed tablets at 18,000 p.s.i. Key: ▲, 200 mg.; ●, 400 mg.; and ■, 600 mg.*

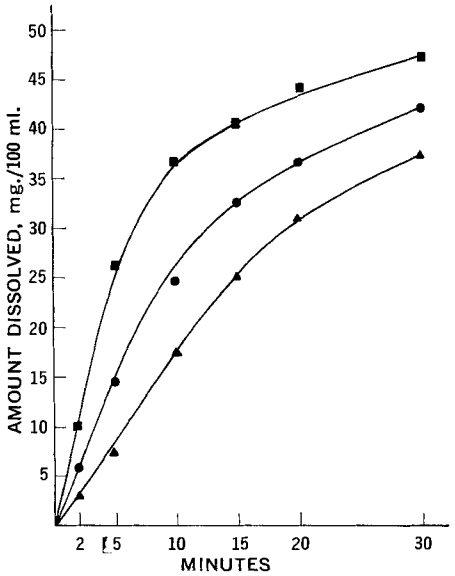

Figure 3—*Dissolution of quinazolinone compound in 100 ml. aqueous solution at pH 1.2 from compressed tablets at 24,000 p.s.i. Key: ▲, 200 mg.; ●, 400 mg.; and ■, 600 mg.*

The linear relationship for tablet weight *versus* dissolution rate at a specific compression force appears to indicate a physical similarity of the various tablet dilutions. This possibly points to a difference in number of the discrete particles as related to their apparent surface area which depends upon the tablet weight. Upon disintegration, the 600-mg. tablet provides relatively three times the number of discrete particles as the 200-mg. tablet. Each discrete particle for the 600-mg. tablet would possibly have one-third the amount of water-insoluble drug in combination with the hydrophilic tablet excipients as compared to the 200-mg. tablet. Therefore, the dissolution rate for various tablet sizes in this study could be dependent upon the aqueous fluid that was in contact with the greater number of discrete particles. A greater dilution of an equivalent amount of drug to be tableted proved to promote a corresponding enhancement of the dissolution rate.

SUMMARY AND CONCLUSIONS

The ratio of tablet diluent to drug has a pronounced effect on the dissolution behavior of this quinazolinone compound at pH 1.2. When a tablet disintegrates, it ruptures into discrete particles which are composed of the drug and diluents. The greater the quantity of diluent to drug in the directly compacted tablet, the larger is the surface area of the discrete particles in contact with alimentary fluid. This particular relationship makes the following assumption: the discrete particle-size distribution is similar for each tablet weight at the same compression force. The dissolution rate increase that occurred when increasing the excipient-to-drug ratio from 3:1 to 7:1 to 11:1 is directly related to the dilution factor.

The diluents selected for this study, with the exception of the lubricant, were hydrophilic, which provided an important capillary effect to the discrete particles in the simulated gastric fluid. Therefore, the greater the dilution of the hydrophobic drug with hydrophilic excipient, it would appear the more readily the solvent would be able to wet and dissolve the drug.

Table V—Half-Lives[a] (in Minutes) of Quinazolinone Compound in 100 ml. Aqueous Solution at pH 1.2 for Tablets of 200, 400, and 600 mg. at Various Compression Forces

Tablet Weight Half-Life Pressure Applied, p.s.i.	200 mg. $t_{50\%}$	400 mg. $t_{50\%}$	600 mg. $t_{50\%}$
12,000	6.8	4.2	2.5
18,000	9.4	6.4	3.4
24,000	14.8	9.4	4.8

[a] Each time interval was obtained from Figs. 1–3.

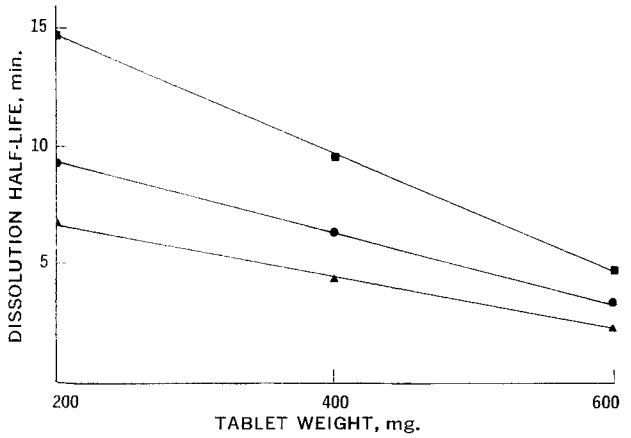

Figure 4—*Relationship of dissolution half-life* ($t_{50\%}$) versus *different tablet sizes compressed at the same pressure. Key:* ▲, $t_{50\%}$, *12,000 p.s.i.;* ●, $t_{50\%}$, *18,000 p.s.i.; and* ■, $t_{50\%}$, *24,000 p.s.i.*

When fabricating a tablet formulation, the research pharmacist many times will select the smallest tablet for a specific quantity of drug. This criterion is both economical and convenient from an oral administration viewpoint. In most cases, if the drug is poorly water soluble, micronization of the drug is utilized to maximize dissolution behavior. The data obtained in this study would recommend a larger tablet than is generally considered appropriate for a 50-mg. quantity of drug. The lesson taught with this poorly water-soluble drug indicates the necessity to consider the ratio of tablet excipient to drug in order to accomplish an optimum dissolution rate.

The force with which the tablet was compressed was also shown to affect dissolution behavior substantially. Figure 4 demonstrates that the larger the tablet size, the less effect compression force has on the dissolution rate.

The linear relationship which existed for tablet size *versus* $t_{50\%}$, when plotted for tablets compressed at 12,000, 18,000, and 24,000 p.s.i., was a good indication of the discrete particle-surface area's dependency on the dissolution characteristics. The discrete particle's total surface area possibly is related as a function of the ratio of diluent to drug when compressed at the same pressure.

The $t_{50\%}$ values reveal that a marked change in dissolution behavior occurs with the smaller tablet when the compression force is changed. This phenomenon is less pronounced as the dilution factor is increased. The dilution of the drug with excipient within each of the discrete particles from disintegration should provide for enhanced *in vivo* dissolution.

In conclusion, it is important to emphasize that when formulating a tablet of a poorly water-soluble drug, the following should be considered: optimum tablet size, hydrophilic nature of diluents, and optimum force of compression.

REFERENCES

(1) A. Morrison and J. Campbell, *J. Pharm. Sci.*, **54,** 1(1965).

(2) J. G. Wagner, *ibid.*, **50,** 359(1961).

(3) J. G. Wagner, *Drug Intel.*, **3,** 198(1969).

(4) G. Levy, J. M. Antkowiak, J. A. Procknal, and D. C. White, *J. Pharm. Sci.*, **52,** 1047(1963).

(5) G. Levy and R. Gumtow, *ibid.*, **52,** 1139(1963).

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

(7) S. S. Kornblum and J. O. Hirschorn, *J. Pharm. Sci.*, **59,** 606(1970).

ACKNOWLEDGMENTS AND ADDRESSES

Received September 4, 1970, from the *Pharmacy Research and Development Department, Sandoz Pharmaceuticals, Hanover, NJ 07936*

Accepted for publication October 27, 1970.

The technical assistance of C. Kenworthy and F. Darling is gratefully acknowledged.

* To whom all correspondence should be addressed.

DRUG STANDARDS

TLC Identification of Sulfonamides

HANNAH R. KLEIN and WILLIAM J. MADER

Abstract □ An improved identification procedure for the official sulfonamides is presented. The method described uses TLC for separation; identification is accomplished on the plates using a specific detection reagent and suitable reference standards. By the use of three developing systems, the identity of any individual sulfonamide or the components of a mixture of sulfonamides may be established with certainty.

Keyphrases □ Sulfonamides, individual, mixed—identification procedure □ Chromatographic systems (TLC)—sulfonamide identification □ TLC—separation, identification

The USP and NF monograph procedures for identification of the official sulfonamides rely principally on the classical methods of organic chemistry for the recognition of a particular material. While used as identity tests, these procedures are extremely difficult and time consuming and often do not provide absolute proof in distinguishing individual substances of a class of compounds such as the sulfonamides.

The identity tests used in both compendia illustrate the difficulty in using these methods to identify and distinguish the sulfonamides. Roughly 80% of the methods used for official identity tests are based on visual observation of one of the following: heat decomposition, diazotization and coupling with β-naphthol, color or precipitate formed with cupric sulfate, color or fluorescence with resorcinol or phenol, ferric chloride, sodium bicarbonate solubility, or reduction. All of these procedures are subject to interferences, and none of them effectively distinguishes individual sulfonamides. The UV spectra of some compounds are used; and while they may be of considerable quantita-