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Effects of Amorphous Silicon Dioxides on Drug Dissolution

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Abstract □ The dissolution profiles of prednisone, digoxin, and griseofulvin in simulated GI fluids were determined after solvent deposition or ball milling with three commercially available grades of amorphous silicon dioxide. The former procedure resulted in adsorbates showing evidence of drug entrapment by the two grades with larger average pore diameters. Ball milling the drugs with the grade possessing the largest average particle diameter produced triturations with the slowest dissolution rates. A relationship between drug dissolution and extent of dilution with the amorphous silicon dioxides was shown. Particle-size measurements revealed that the ball milling procedure was more apt to broaden the size distribution as compared with the solvent-deposition method of drug incorporation.

Keyphrases □ Dissolution rate—effects of amorphous silicon dioxides on prednisone, digoxin, griseofulvin, simulated GI fluids, solvent deposition compared to ball milling □ Silicon dioxide, amorphous—effect on dissolution rates of prednisone, digoxin, griseofulvin in simulated GI fluids, solvent deposition compared to ball milling □ Dispersions, solid—effect of amorphous silicon dioxides on prednisone, digoxin, griseofulvin, simulated GI fluids, solvent deposition compared to ball milling

Various water-insoluble drugs, solvent deposited on fumed silicon dioxide, have been reported to have more rapid dissolution rates than the pure micronized drugs. Surface area of the acidified and basified silica gel adsorbents was a controlling factor for the increased dissolution rate of these adsorbate samples (1).

This study evaluated the effects of three commercial grades of amorphous silicon dioxide on the dissolution rates of digoxin, griseofulvin, and prednisone. The micrometer-sized, synthetic, amorphous silicon dioxides possess a unique combination of properties. Purity, nontoxicity, uniformity, chemical inertness, large surface area and porosity, controlled particle size, and a high adsorptive capacity for both oil and water characterize these versatile products. The three grades selected differ from one another in surface pH, particle size, surface area, and pore volume and diameter (Table I).

In addition to the customary procedure of solvent deposition, ball milling was used to spread each drug on the amorphous silicon dioxide surfaces. Earlier studies had shown that ball milling was superior to solvent deposition for preparing drug–lactose triturations (2, 3). Besides comparison of these two methods, the effect of pore diameter on the dissolution rate of entrapped drug molecules was studied.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: amorphous silicon dioxides[1], digoxin[2] USP, griseofulvin[3] USP, prednisone[4] USP, sodium hydroxide[5] USP, monobasic sodium phosphate[6] USP, sodium chloride[7] USP, reagent grade hydrochloric acid[5], and absolute ethanol[8].

Equipment—The following were used: the USP XIX dissolution test basket assembly[9]; a constant-temperature shaker bath[10]; a grating spectrophotometer with digital display[11]; a jar mill, 10.16-cm (4-in.) diameter with 1.27-cm (0.5-in.) diameter porcelain balls[12]; a pH meter[11]; a particle-size counter[13]; a U.S. standard sieve, 60 mesh[14]; a Swinny adapter[15], 13 mm; and filter paper, 0.45-μm porosity[15].

Preparation of Drug–Amorphous Silicon Dioxide Triturations—The drug–amorphous silicon dioxide triturations were prepared in a weight ratio of 1:20. Simple blends were prepared by manual bottle tumbling for 15 min. Ball milled triturations were prepared from homogeneous simple blends. Ball milling was carried out for 48 hr in a jar mill half-filled with porcelain balls.

Solvent deposition consisted of dissolving prednisone or griseofulvin in sufficient absolute ethanol (80% ethanol was used for digoxin) and uniformly wetting the various silicas contained in a beaker. The mixture was stirred with a magnetic stirrer while the solvent was evaporated in an air stream. The residues were dried at 37° for 24 hr and passed through a 60-mesh screen to break up any agglomerates. The sieved material was bottle blended to ensure homogeneity.

[1] Syloid 63, 72, and 266, Davison Chemical Division, W. R. Grace & Co., Baltimore, Md.
[2] Roussel Corp., New York, N.Y.
[3] Ayerst Laboratories, New York, N.Y.
[4] The Upjohn Co., Kalamazoo, Mich.
[5] J. T. Baker Chemical Co., Phillipsburg, N.J.
[6] Fisher Scientific Co., Fair Lawn, N.J.
[7] Apache Chemicals, Seward, Ill.
[8] U.S. Industrial Chemicals Co., New York, N.Y.
[9] Hanson Research Corp., Northridge, Calif.
[10] Model WBR, New Brunswick Scientific Co., New Brunswick, N.J.
[11] Model DB-GT, Beckman Instruments, Fullerton, Calif.
[12] Paul O. Abbe Inc., Little Falls, N.J.
[13] Model T, Coulter Electronics Inc., Hialeah, Fla.
[14] Dual Manufacturing Co., Chicago, Ill.
[15] Millipore Corp., Bedford, Mass.

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Table I—Physicochemical Analyses of Amorphous Silicon Dioxides

Property	Silica 63[a]	Silica 72[b]	Silica 266[c]
Total volatiles (1750° F), %	5.9	5.5	7.7
pH (5% slurry)	3.8	6.8	8.0
Na_2O, %	0.035	0.062	0.09
Sulfate, %	0.07	0.065	0.05
Al_2O_3, %	0.03	0.074	0.05
CaO, %	0.034	0.13	0.09
Fe, ppm	50	70	70
NH_3, %	—	0.02	0.02
Oil adsorption, lb/100 lb	75	195	315
Through 325 mesh, %	99.95	100	100
Bulk density, g/c^3	0.34	0.145	0.08
Centrifuge density, g/cm^3	0.57	0.28	0.15
Surface area, m^2/g	760	290	295
Pore volume, ml/g	0.43	1.08	—
Average pore diameter, Å	20	150	210
Average particle size, μm	11.1	4.85	2

[a] Lot 334. [b] Lot 4072. [c] Lot 189; typical analysis.

Table II—Wavelengths of UV Light Used in Development of Calibration Curves for the Three Drugs in Various Solvents

Solvent	Wavelength of Light, nm		
	Digoxin	Griseofulvin	Prednisone
Simulated gastric fluid (without pepsin)	222	296	242
Simulated intestinal fluid (without pancreatin)	222	296	245
Absolute ethanol	—	290	240
80% Ethanol	220	—	—

Triturations were assayed spectrophotometrically for content uniformity. Only samples containing 100 ± 5% of the required amount of drug were used in the dissolution studies.

Spectrophotometric Absorption and Calibration Curves—Stock solutions were prepared by dissolving 100 mg of each drug in 50 ml of absolute ethanol or 80% ethanol (digoxin). Aliquots were diluted with appropriate solvents to develop absorption spectral and calibration curves. The following solution concentrations were employed: prednisone, 20 μg/ml; griseofulvin, 10 μg/ml; and digoxin, 40 μg/ml.

To blank out interference of colloidal silica particles on the UV measurements, stock suspensions of the silicas were prepared. Aliquots were added 20:1 (w/w) to the drug solutions. The suspensions were filtered through a 0.45-μm membrane filter before determination of the absorption spectral and calibration curves. Only in the case of digoxin was an interference found. An absorption spectral curve of one amorphous silicon dioxide (silica 63) in 80% ethanol showed a maximum absorbance at 228 nm. The maximum absorbance values for digoxin ranged from 220 to 222 nm. Thus, the blanks used for the spectrophotometric measurements of digoxin solutions were the corresponding solvents plus the appropriate silica. For the measurements of prednisone and griseofulvin, the appropriate solvent without silica addition was adequate.

All calibration curves determined at the wavelength of maximum absorbance obeyed Beer's law. The wavelengths employed for calibration curves are summarized in Table II.

Assay of the Drug–Silica Triturations—The various drug-silica triturations were extracted with absolute or 80% ethanol. The extracts were passed through a 0.45-μm membrane filter. After dilution with solvent, the absorbance was determined spectrophotometrically and the concentration was ascertained from the calibration curves.

Dissolution Studies—The dissolution studies were conducted in simulated gastric fluid (without pepsin) and simulated intestinal fluid (without pancreatin) (4). The stability of the three drugs was satisfactory in these dissolution media after 2 hr of exposure at 37°. An insignificant change in absorbance occurred after addition of 20-fold excesses of either silica 63 or 266. On the basis of these observations, the possibility of drug adsorption by the silicas during the dissolution rate determinations was discounted (Fig. 1).

A modification of the procedure of Monkhouse and Lach (1) was used to determine the dissolution rates of the three drugs and the various triturations. Simulated gastric fluid, 200 ml, was brought to 37° in a constant-temperature bath. The dissolution medium was stirred with the basket used in the USP dissolution test. The stirrer was vertically centered at a depth 2 cm from the beaker bottom and was maintained at 60 rpm.

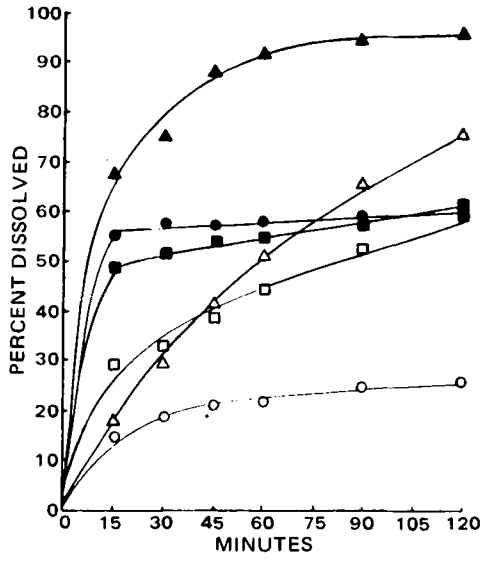

Figure 1—*Dissolution rate in simulated gastric fluids of selected samples of griseofulvin, digoxin, and prednisone solvent deposited on amorphous silicon dioxide (drug–silica 63 ratio, 1:20) compared with the pure drugs. Key: ○, griseofulvin (simulated intestinal fluid); ●, griseofulvin–silica 63 (simulated intestinal fluid); □, digoxin (simulated gastric fluid); ■, digoxin–silica 63 (simulated gastric fluid); △, prednisone (simulated gastric fluid); and ▲, prednisone–silica 63 (simulated gastric fluid).*

Accurately weighed samples, equivalent to a quantity of drug to ensure sink conditions, were spread over the medium surface (digoxin, 9.44 mg; grisofulvin, 1.45 mg; and prednisone, 8 mg). Any large aggregates that formed at this stage were lightly broken up within 10 sec after sample addition. Aliquots of the dissolution medium were withdrawn periodically and passed through a 0.45-μm membrane filter. After appropriate dilution, the absorbance was determined spectrophotometrically.

Immediately after withdrawing an aliquot, an equal quantity of dissolution medium was added to the beaker to maintain a constant volume. Cumulative corrections were made for the previously withdrawn aliquots in calculating the total amount of drug dissolved. Each point on the dissolution curves represents at least two determinations.

In another series of experiments, 500 ml of dissolution medium was used. The quantity of sample added was 2.5-fold greater than that used in the experiments with 200 ml. The dissolution rate data are summarized in Tables III and IV.

Initial screening experiments showed that the dissolution rates were not significantly altered when 0.02% polysorbate 80 was present in the media, so it was not used.

Particle-Size Measurement—Pure drug, each of the three silica grades, and the drug–silica triturations were ultrasonically dispersed in an aqueous medium buffered at pH 2. The concentrations of the resulting aqueous dispersions were less than 0.01%. Aperture diameters ranged from 30 to 280 μm, and two apertures were routinely used. Each particle-size determination was completed in less than 10 min. The particle-size data are summarized in Table V.

RESULTS AND DISCUSSION

A significant drop in digoxin potency resulted from 48-hr ball milling, making dissolution rate determination impossible. This potency drop was unexpected, since such ball milling operations were conducted at room temperature with ingredients previously dried at 37°[16].

Digoxin (4.8%), solvent deposited on the three grades of silica, did not show a significant improvement in dissolution rate in simulated gastric fluids (Samples 4–6 and 10–12) compared with the pure drug. However, the best of the three proved to be silica 63 (Samples 4 and 10) due to its larger surface area (Table I). Indications of digoxin instability were encountered with the digoxin–silica 63 trituration but not with either of the other two[17].

The data in Table IV clearly show that the dissolution rate of digoxin in simulated gastric fluid increased as the quantity of silica 63 increased

[16] Details of these observations will be presented in a future publication.
[17] The stability studies will be described in a future publication.

Table III—Dissolution of Digoxin, Griseofulvin, Prednisone, and Their 1:20 Drug–Silica Triturations in Simulated Gastric Fluids at 37° (Volume of Solvent, 200 ml)

Sample	Solvent		Method of Preparation			Grade of Silica			Percentage Dissolved					
	Simulated Gastric	Simulated Intestinal	Solvent Deposition	Simple Blend	Ball Milling	63	72	266	15 min	30 min	45 min	60 min	90 min	120 min
1. Digoxin	+								28.9	32.8	37.7	43.8	52.4	59.2
2. Digoxin[a]	+		+						37.0	43.2	46.9	51.6	59.7	67.8
3. Digoxin	+			+		+			20.4	22.2	24.8	27.1	30.5	34.9
4. Digoxin	+		+			+			48.8	51.7	54.6	55.4	58.5	61.2
5. Digoxin	+		+				+		33.3	37.3	39.0	42.7	46.0	49.2
6. Digoxin	+		+					+	32.6	33.3	35.1	36.7	39.8	44.3
7. Digoxin		+							17.6	19.1	21.2	22.9	26.9	29.0
8. Digoxin		+	+						30.3	34.3	38.3	40.3	41.5	42.2
9. Digoxin		+		+		+			12.5	14.0	16.5	17.8	20.1	22.0
10. Digoxin		+	+			+			55.3	57.1	59.2	61.1	62.8	63.7
11. Digoxin		+	+				+		48.9	46.9	47.4	47.9	48.5	50.8
12. Digoxin		+	+					+	43.0	44.4	46.2	46.4	47.2	50.5
13. Griseofulvin	+								19.1	29.7	35.3	41.6	47.7	53.4
14. Griseofulvin[a]	+		+						8.7	10.5	13.2	16.6	19.9	22.9
15. Griseofulvin	+			+		+			51.6	55.6	56.6	61.8	65.8	69.2
16. Griseofulvin	+		+			+			32.0	34.2	35.3	36.9	36.8	37.7
17. Griseofulvin	+		+				+		31.0	35.3	37.7	39.4	42.6	45.3
18. Griseofulvin	+		+					+	31.0	34.8	37.5	39.6	42.6	45.3
19. Griseofulvin	+				+	+			19.7	22.6	24.0	25.5	26.6	28.3
20. Griseofulvin	+				+		+		23.2	45.0	48.1	50.8	54.0	56.8
21. Griseofulvin	+				+			+	46.6	50.8	54.7	57.1	60.5	63.6
22. Griseofulvin		+							14.0	18.2	20.5	21.4	24.4	25.7
23. Griseofulvin[a]		+	+						10.0	11.9	13.0	16.1	20.4	23.5
24. Griseofulvin		+		+		+			33.8	36.9	42.6	46.0	49.2	52.6
25. Griseofulvin		+	+			+			54.5	57.0	56.5	57.7	59.0	58.7
26. Griseofulvin		+	+				+		30.5	33.1	36.1	37.9	38.8	40.5
27. Griseofulvin		+	+					+	33.1	36.8	38.2	40.4	42.2	44.3
28. Griseofulvin		+			+	+			30.9	38.4	43.5	47.4	51.7	55.2
29. Griseofulvin		+			+		+		49.9	53.1	55.2	56.8	59.6	62.2
30. Griseofulvin		+			+			+	50.0	53.2	56.8	59.0	63.4	65.2
31. Prednisone	+								16.9	29.9	40.9	50.8	65.8	75.4
32. Prednisone[a]	+		+						16.0	29.0	40.0	51.6	66.2	73.6
33. Prednisone	+			+		+			32.2	40.6	46.2	51.4	59.1	65.1
34. Prednisone	+		+			+			67.6	75.1	87.7	91.7	94.7	96.4
35. Prednisone	+		+				+		29.4	43.0	50.1	55.0	60.2	65.0
36. Prednisone	+		+					+	44.5	52.6	55.8	56.8	58.8	59.5
37. Prednisone	+				+	+			15.6	17.4	19.5	20.8	21.4	21.8
38. Prednisone	+				+		+		40.0	49.0	53.9	55.7	57.3	57.4
39. Prednisone	+				+			+	43.9	54.3	58.9	61.2	63.6	64.7
40. Prednisone		+							23.0	35.1	45.7	59.3	69.4	82.0
41. Prednisone[a]		+	+						22.8	34.9	45.0	58.9	68.2	80.4
42. Prednisone		+		+		+			22.3	29.1	37.2	43.1	52.3	58.5
43. Prednisone		+	+			+			38.8	46.3	51.0	54.4	59.4	64.6
44. Prednisone		+	+				+		65.5	75.7	76.4	76.6	76.9	78.1
45. Prednisone		+	+					+	58.6	63.9	66.4	67.5	68.3	69.1
46. Prednisone		+			+	+			16.1	22.1	26.9	29.1	34.4	37.1
47. Prednisone		+			+		+		42.6	49.6	50.4	50.5	51.2	51.6
48. Prednisone		+			+			+	55.0	59.0	60.4	61.2	62.1	63.6

[a] Each drug was dissolved in absolute or 80% ethanol (digoxin). The solvent was evaporated in the absence of silica in an air stream and then dried at 37° for 24 hr. The crystalline residue was passed through a 60-mesh screen.

(Samples 49–56). Minimal improvement in the dissolution rates of drugs with the addition of fumed silicon dioxide above 10% was reported (1). The dissolution profiles in Table IV reveal that increased dilutions of the amorphous silicon dioxides favor a more rapid digoxin dissolution rate. The increased dissolution rate became apparent only in the 120-min study, which is why it was missed by previous researchers using a 14-min experimental design (1). The 120-min dissolution study clearly shows the advantage of adding additional adsorbent.

Significant portions of the total drug went into solution within the first 15 min (Table III). Thus, while 55.5% (Sample 55) of the digoxin had dissolved within the first 15 min, only 12.4% more dissolved after an additional 105 min. The dissolution profiles reported previously (1) also are indicative of a reduction in rate after 14 min. Increased dissolution of solvent-deposited phenylbutazone with increased silicon dioxide concentration has been reported (5). In agreement with our findings, these authors also showed that incomplete recovery of the solvent-deposited phenylbutazone occurred with the more concentrated triturations.

Whereas the simple blend was not of value for digoxin (Sample 3), it enhanced the griseofulvin dissolution rate in simulated gastric fluid (Sample 15). Solvent deposition of 4.8% griseofulvin on each of the three silicas produced equally inefficient triturations as measured in simulated gastric fluid (Samples 16–18). In simulated intestinal fluid, the dissolution rate of pure griseofulvin was much slower (Samples 22 and 23). In this dissolution medium, the simple blend (Sample 24) and the three silica triturations prepared by solvent deposition (Samples 25–27) all showed significant improvement over micronized griseofulvin (Sample 22).

Solvent deposition of 4.8% griseofulvin on silica 63 showed the expected rapid dissolution rate in simulated intestinal fluid (Sample 25).

Griseofulvin, 4.8%, with silica 266 unexpectedly yielded the best dissolution rate after 48 hr of ball milling (Sample 30), followed by silica 72 (Sample 29). This order is exactly the rank order in average particle size (Tables I and V). Thus, silica 266, with the finest particle size (2.05 μm) significantly increased in particle size when ball milled (15.3 μm) or when treated with solvent (22.4 μm). Such increases probably result from an aggregation of particles with little further reduction in size of individual silica 266 particles.

Silica 63 has the largest particle size (9.2 μm), and one would expect the generation of more fines from its ball milling. Ball milling silica 63[18] with griseofulvin yielded a trituration with smaller particle size and a very broad cumulative particle-size distribution (7.8 μm; $V = 2.6$). Thus, an increase in the production of fines and a decrease in particle size might possibly favor the trapping of drug particles beneath and between the fine particles of silica 63. With silica 266, the large increase in average particle size may be due primarily to the buildup of large, softer agglomerates from which the drug particles can be expected to dissolve more readily. Silica 72[19] had an intermediate average particle size (3.4 μm). It yielded an intermediate particle-size increase on ball milling with griseofulvin (10.3 μm). Solvent treatment of silica 63[20] led to an insig-

[18] Lot 22288.
[19] Lot 3580.
[20] Lot 334.

Table IV—Dissolution of Digoxin, Griseofulvin, Prednisone, and Various Drug–Silica 63 Triturations Prepared by Solvent Deposition (Volume of Simulated Gastric Fluid, 500 ml)

Sample	Concentration of Drug in Sample, %	Percentage Dissolved					
		15 min	30 min	45 min	60 min	90 min	120 min
49. Digoxin	100	19.5	22.0	24.3	30.4	35.9	42.3
50. Digoxin[a]	100	26.5	33.3	37.8	41.2	47.3	51.0
51. Digoxin	90	19.1	18.8	20.2	21.1	22.6	24.2
52. Digoxin	80	23.8	24.4	26.5	29.4	31.1	34.6
53. Digoxin	50	36.5	43.1	47.1	48.6	49.3	52.8
54. Digoxin	25	47.5	52.9	57.1	57.7	59.5	62.4
55. Digoxin	10	55.5	57.7	61.4	63.8	65.2	67.9
56. Digoxin	4.8	56.8	59.9	61.0	62.7	66.7	68.6
57. Griseofulvin	100	18.2	25.5	33.4	43.5	51.4	53.8
58. Griseofulvin[a]	100	7.3	9.7	12.7	15.2	17.9	21.7
59. Griseofulvin	90	9.2	12.1	15.3	16.8	20.6	23.4
60. Griseofulvin	80	6.9	11.6	13.8	13.9	17.0	19.9
61. Griseofulvin	50	22.1	26.5	32.1	38.7	38.2	41.0
62. Griseofulvin	25	20.5	24.5	27.0	29.5	33.1	37.7
63. Griseofulvin	10	33.4	36.8	39.2	41.9	46.4	50.5
64. Griseofulvin	4.8	28.4	32.2	34.5	36.1	37.7	39.4
65. Prednisone	100	15.2	27.1	41.1	49.6	62.3	74.9
66. Prednisone[a]	100	17.0	26.0	39.5	50.6	68.7	75.8
67. Prednisone	90	22.2	39.6	51.4	58.7	72.1	83.4
68. Prednisone	80	41.8	50.9	60.2	68.3	76.2	84.2
69. Prednisone	50	64.5	68.8	75.2	78.8	85.0	86.5
70. Prednisone	25	57.7	63.6	65.6	68.7	73.4	74.4
71. Prednisone	10	34.0	40.2	46.4	50.6	57.2	61.6
72. Prednisone	4.8	46.5	52.3	59.8	62.0	67.4	69.3

[a] Each drug was dissolved in absolute or 80% ethanol (digoxin). The solvent was evaporated in the absence of silica 63 in an air steam and then dried at 37° for 24 hr. The crystalline residue was passed through a 60-mesh screen.

Table V—Particle-Size Data of Griseofulvin, Prednisone, and Selected Drug–Silica Triturations

Sample	Method of Preparation		Dual Aperture Diameters, μm	Average Particle Size, μm	Width[a], V
	Solvent Deposition	Ball Milling			
Silica 63, lot 22288					
Silica 63			50 + 140	9.2	1.15
Silica 63		+	50 + 140	12.0	2.4
Silica 63 + griseofulvin 4.8%		+	50 + 140	7.8	2.6
Silica 63 + prednisone 4.8%		+	50 + 140	8.6	2.5
Silica 63[b]	+		50 + 140	9.9	1.15
Silica 63 + griseofulvin 4.8%	+		50 + 140	9.5	1.15
Silica 63 + prednisone 4.8%	+		50 + 140	9.6	1.15
Silica 63, lot 334					
Silica 63			50 + 140	11.1	1.15
Silica 63 + prednisone 4.8%	+		50 + 140	12.2	1.15
Silica 63 + prednisone 9%	+		50 + 140	13.4	1.15
Silica 63 + prednisone 25%	+		140 + 280	13.5	1.15
Silica 63 + prednisone 50%	+		140 + 280	15.3	1.3
Silica 63 + prednisone 80%	+		140 + 280	23	1.3
Silica 63 + prednisone 90%	+		140 + 280	21	1.15
Silica 72, lot 4072					
Silica 72			30 + 100	4.85	1.15
Silica 72, lot 3580					
Silica 72			30 + 100	3.4	1.15
Silica 72		+		9.7	2.15
Silica 72 + griseofulvin 4.8%		+		10.3	2.1
Silica 72 + prednisone 4.8%		+	50 + 100	9.4	2.05
Silica 72[b]	+			6–8	—[c]
Silica 72 + griseofulvin 4.8%	+			4.0	0.9
Silica 72 + prednisone 4.8%	+			4.3	1.4
Silica 266, lot 158					
Silica 266			30 + 70	2.05	1.15
Silica 266		+	100 + 200	15.3	2.15
Silica 266 + griseofulvin 4.8%		+		13.7	2.2
Silica 266 + prednisone 4.8%		+		11.0	1.7
Silica 266[b]	+			22.4	3.4
Silica 266 + griseofulvin 4.8%	+			19.9	3.2
Silica 266 + prednisone 4.8%	+			15.8	2.4
Pure drugs					
Prednisone				59	0.85
Prednisone	+			28	0.95
Griseofulvin	+			31	0.85
Griseofulvin				7.7	0.95

[a] The parameter V is a measure of the width of a particle-size distribution. Mathematically such width corresponds to dispersion around a central measure such as the average, mean, median, or mode. V is dimensionless and is calculated from the 84% (D_1) and 16% (D_2) points of the cumulative curve: $V = \sqrt{D_2/D_1} - 1$. For a true log normal distribution, $V = \sigma_g - 1$, where σ_g is the geometric standard deviation. In practice, most distributions are skewed, and $V + 1$ is then only an approximation to σ_g. Since relative, rather than absolute, measures of width of nonsymmetrical distributions were of interest, the tedious calculations associated with σ_g were avoided by using V as a basis for comparison. For disperse systems, the range of V is as follows: $V = 0$, monosize particles; $V = 0.5$, narrow distribution; $V = 1.5$, broad distribution; and $V \geq 2.0$, very broad distribution. The Coulter reproducibility of V is ±0.05% at $V = 1$ and ±10% at V above 1.5. [b] The pure silica was wet with ethanol. The solvent was evaporated in the absence of drug in an air stream and then dried at 37° for 24 hr. The residue was passed through a 60-mesh screen. Alternatively, the drug was dissolved in ethanol and the solution was evaporated to dryness in an air stream and then dried at 37° for 24 hr. The crystalline residue was passed through a 60-mesh screen. [c] Full distribution could not be determined because of the failure of agglomerates to pass through the 50-μm aperture.

Table VI—Dissolution Rates of Selected Samples in Simulated Gastric Fluids at 37° Plotted in First-Order Fashion (Ratio of Drug to Amorphous Silicon Dioxide, 1:20)

Number and Description of Sample	Simulated Gastric Fluid			Simulated Intestinal Fluid		
	K_1, min^{-1} (×0.0001)	K_2, min^{-1} (×0.0001)	t_{50}[a], min	K_1, min^{-1} (×0.0001)	K_2, min^{-1} (×0.0001)	t_{50}, min
1 and 7. Digoxin	—	54.4	127	—	14.9	465
4 and 10. Digoxin (solvent deposited on silica 63)	—	25.3	274	—	2.0	3500
13 and 22. Griseofulvin	—	50.5	137	—	12.9	537
16 and 25. Griseofulvin (solvent deposited on silica 63)	—	7.7	902	—	12.2	568
19 and 28. Griseofulvin (ball milled with silica 63)	—	9.8	704	—	39.7	175
31 and 40. Prednisone	118	115	60	140	134	52
34 and 43. Prednisone (solvent deposited on silica 63)	139	138	50	66	42	165
37 and 46. Prednisone (ball milled with silica 63)	14.1	2.3	3000	38	20	347
39 and 48. Prednisone (ball milled with silica 266)	80.8	15.7	441	31.8	10.7	648

[a] Some first-order plots exhibited steeper slopes from 15 to 60 min (Figs. 4 and 5). The t_{50} values were calculated from the less steep slopes generated from the dissolution data beyond 60 min.

nificant increase in particle size, whereas silica 72[19] and 266 increased particle size significantly.

The dissolution profiles (Table IV) demonstrated that griseofulvin solvent deposited on silica 63 in concentrations greater than 50% inefficiently dissolved in simulated gastric fluid (Samples 59 and 60). Micronized griseofulvin attained the highest percentage in solution after 120 min (Sample 57). Solvent deposition of griseofulvin in the absence of silica 63 exhibited a poor dissolution rate (Sample 58). This difference can be explained on the basis of particle size. Thus, the average particle size of the solvent-deposited griseofulvin was fourfold greater than the micronized material (Table V).

Solvent deposition of 4.8% prednisone on silica 63 showed the fastest dissolution rate in simulated gastric fluid (Table III, Sample 34). Solvent deposition of a similar quantity on silica 72 produced a trituration with the fastest dissolution rate in simulated intestinal fluid (Sample 45). On the other hand, ball milled triturations containing 4.8% drug showed silica 266 to give the best dissolution in both simulated gastric media (Fig. 2, Samples 39 and 48).

Solvent deposition of prednisone on silica 63 at various drug concentrations produced triturations exhibiting unusual dissolution profiles in simulated gastric fluid (Table IV, Samples 65–72). Triturations with drug concentrations of 50% exhibit dissolution rates faster than 80 or 90% triturations. After 120 min, the three triturations achieved virtually the same extent of dissolution. However, further dilution with silica 63 resulted in less efficiently dissolving triturations (Samples 70–72).

During the dissolution experiments, the three grades of amorphous silicon dioxides did not tend to adsorb dissolved drug under the sink conditions employed. However, there was an indication of drug entrapment within the pores of silicas 72 and 266 in samples prepared by solvent deposition. Thus, silica 63, which has the smallest average pore diameter (20 Å), usually showed the most rapid drug release when compared with silicas 72 (150 Å) and 266 (210 Å). Digoxin (Table III, Sample 4) dissolved most rapidly in simulated gastric fluid after solvent deposition on silica 63. Griseofulvin (Sample 25) dissolved most rapidly in simulated intestinal fluid after solvent deposition on silica 63, whereas prednisone, after solvent deposition on silica 63, showed the most rapid dissolution in simulated gastric fluid (Sample 34).

The selected samples exhibited in Figs. 1 and 2 highlight some key points. The significance of the data presented in Table V may be more quickly grasped by inspection of Fig. 3. Ball milling silica 63, which had the largest average particle size of the three amorphous silicon dioxides used, significantly broadened the particle-size distribution. Solvent

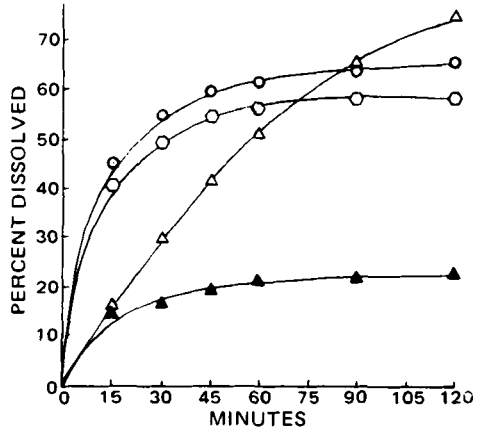

Figure 2—*Dissolution rate in simulated gastric fluid at 37° of selected samples of prednisone ball milled with various amorphous silicon dioxides (ratio of drug–silica, 1:20). Key: △, prednisone; ▲, prednisone–silica 63; ○, prednisone–silica 72; and ○, prednisone–silica 266.*

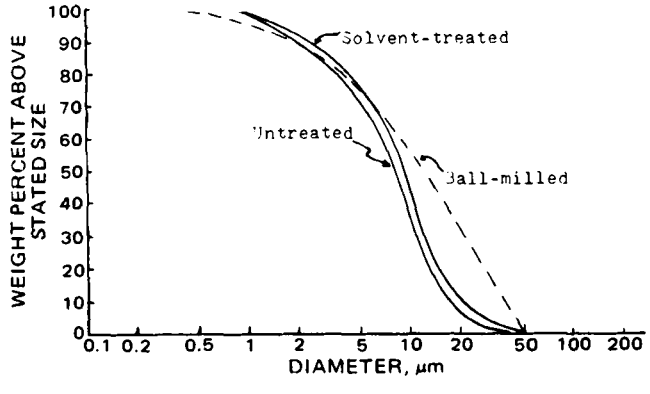

Figure 3—*Particle-size analysis (dual aperture, 50 and 140 μm) of amorphous silicon dioxide (silica 63, lot 22288) in pH 2 buffer before and after treatment with solvent or ball milled for 48 hr.*

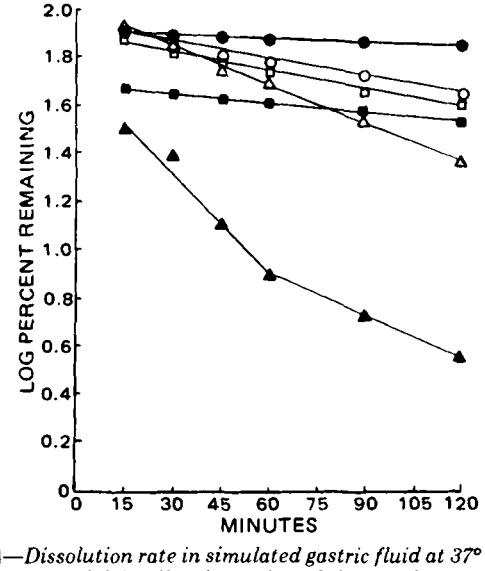

Figure 4—*Dissolution rate in simulated gastric fluid at 37° of selected samples of griseofulvin, digoxin, and prednisone solvent deposited or ball milled with amorphous silicon dioxide (drug–silica 63 ratio, 1:20). Key: △, prednisone; ▲, prednisone–silica 63 (solvent deposited); ○, griseofulvin; ●, griseofulvin–silica 63 (ball milled); □, digoxin; and ■, digoxin–silica 63 (solvent deposited).*

treatment of silica 63, however, resulted in an insignificant change in the particle-size distribution.

In Table VI and Fig. 4, the data gathered on selected samples are plotted in first-order fashion. The values for K_1 and K_2 were determined from the slopes of the lines, and the dissolution half-lives were calculated from the K_2 values. Where two first-order processes were evident, K_2 represented the slower process that occurred 60 min after dissolution had commenced (Fig. 4, prednisone–silica 63, solvent deposited). The data in Table VI clearly show that a significant change in dissolution half-life can be affected by solvent deposition on, or ball milling with, the amorphous silicon dioxides.

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Fusion of Disubstituted Benzenes

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Abstract □ The entropy of fusion of 84 disubstituted benzenes was essentially constant and independent of the participation of the compounds in intramolecular or intermolecular hydrogen bonding. It was also independent of the shapes, sizes, and dipole moments of the rigid molecules studied. While the entropy of fusion was independent of these parameters, the melting point and the heat of fusion showed a direct dependence on molecular properties.

Keyphrases □ Entropy of fusion—disubstituted benzenes, independent of hydrogen bonding, shape, size, dipole moment of rigid molecules, structure-activity relationships □ Melting point—analysis, disubstituted benzenes, structure-activity relationships □ Benzenes, disubstituted—entropy of fusion, melting point, heat of fusion, structure-activity relationships

The ability to predict the melting point, entropy of fusion, and heat of fusion from chemical structure would make possible the design of compounds having a specified physical state or even a specified melting range. The aqueous solubility of many organic compounds can be predicted from their melting points, entropies of fusion, and octanol–water partition coefficients (1). Since partition coefficients can be predicted by several group contribution methods (2, 3), the estimation of fusion properties makes possible the estimation of aqueous solubility. This possibility has direct implications for drug delivery.

BACKGROUND

In 1908, Walden (4) proposed that entropy of fusion is constant for many classes of compounds. Most elements have entropies of fusion of 2–3 entropy units (eu = cal/deg/mole); salts and small organic molecules usually have entropies of fusion of 5–7 eu; most organic molecules have entropies around 13 eu.

The entropy of fusion rule for organic compounds was later refined to account for molecular geometry (5). If heat of fusion is plotted *versus* melting point, molecules fall into groups according to molecular shape. The data for the chain-like, disk-like, and spherical molecules fall into regions (6) characterized by:

$$\frac{\Delta H_f}{T_m - a} = K \qquad \text{(Eq. 1)}$$

where ΔH_f is the heat of fusion, T_m is the melting point, and the constants K and a are characteristic of the spatial form of the molecules. Since at the melting point:

$$\Delta S_f = \frac{\Delta H_f}{T_m} \qquad \text{(Eq. 2)}$$

the entropy of fusion is dependent on the melting point for each class of compounds:

$$\Delta S_f = K - \frac{Ka}{T_m} \qquad \text{(Eq. 3)}$$

The entropy of fusion of flexible chain-like molecules increases as R ln 3 for the addition of each CH_2 group to a chain because there are three potential minima for rotation about a carbon–carbon bond (7). This theory explains the apparent dependencies of ΔS_f on area and volume (8, 9).

The entropy of fusion of rigid molecules does not vary directly with surface area (10, 11) or with molecular volume. The entropy of fusion of rigid hydrocarbons varies according to their moments of inertia and symmetry. Strong dipoles and hydrogen bonding have also been assumed to lower the entropy of fusion by hindering rotation in the liquid.

The purposes of this report are to determine the effect of molecular shape, hydrogen bonding, and dipole moment on ΔS_f for rigid nonspherical organic molecules and to consider the effects of these parameters on heat of fusion and melting point.

EXPERIMENTAL

Data Set—The compounds studied were all disubstituted benzene molecules. They included all 84 combinations of the substituents CH_3, Cl, Br, NO_2, OH, NH_2, and COOH in the *ortho*, *meta*, and *para* positions. The entropy of fusion was either determined experimentally or found in the literature for all compounds solid at room temperature as well as for many that are liquid. These compounds were chosen because of their similar size, shape and symmetry, but the substituents cover a wide range of dipole strengths and hydrogen bonding sites. Entropy of fusion differences due to symmetry and shape should have been minimal, while those due to dipole interactions and hydrogen bonding should have been readily apparent.

Determination of Entropy of Fusion—All entropies of fusion were calculated from the heats of fusion and melting points. These quantities were either obtained from the literature (12) or determined experimentally on a differential thermal analyzer[1] with a high-pressure differential scanning calorimeter cell. The literature values were obtained at atmospheric pressure. The experimental values were obtained at 500 psi to inhibit sublimation of the more volatile compounds. This pressure had little or no effect on the entropy of fusion of nonvolatile compounds and was assumed to have no effect on the entropy of fusion of the volatile crystals.

Reliable values for the entropy of fusion of three solids could not be determined experimentally. *p*-Aminophenol decomposed before melting, even under 1000 psi of nitrogen. Phthalic acid dehydrated to phthalic anhydride upon melting. Terephthalic acid sublimed, even under 1000 psi of nitrogen, as shown by a coating of compound around the inside of the calorimeter cell. This coating was insoluble in dilute sodium hydroxide and had the texture of a polymer, suggesting that some chemical

[1] Dupont model 900.

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