Influence of Dispersion Method on Dissolution Rate and Bioavailability of Digoxin from Triturations and Compressed Tablets II

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Abstract □ Ball milling or muller milling digoxin with a 20-fold excess of lactose, sucrose, calcium phosphate dibasic, or microcrystalline cellulose significantly enhanced its dissolution rate. Tablets prepared with such triturations also exhibited superior rates of dissolution. Those prepared with the digoxin-lactose trituration gave plasma levels in rats that were 89.6% of the values from an oral solution of digoxin. A simple blend of unmilled digoxin with lactose yielded tablets producing plasma levels only 80% as high. Excellent content uniformity was characteristic for all triturations and tablets prepared by ball or muller milling.

Keyphrases □ Digoxin—effects of ball milling and muller milling on dissolution and bioavailability from triturations and compressed tablets □ Dissolution rates—digoxin triturations and compressed tablets prepared by ball milling or muller milling □ Bioavailability—digoxin triturations and compressed tablets prepared by ball milling or muller milling □ Dispersion methods—effects of ball milling and muller milling on dissolution and bioavailability of digoxin triturations and compressed tablets □ Milling—effects on dissolution and bioavailability of digoxin triturations and compressed tablets

The variation in bioavailability of digoxin from tablet dosage forms was recently reported (1–5). Such variations were also found in different lots of the formulated product made by the same manufacturer (1, 6, 7). Several poorly absorbed preparations were reported (1–4) to be therapeutically ineffective or associated with digoxin levels below the therapeutic range. The hydrophobicity and poor aqueous solubility of digoxin account to a significant degree for these variations.

Excellent correlation of digoxin tablet dissolution rate with biological availability in humans was demonstrated by Lindenbaum *et al.* (8). These authors recommended that a lower limit of acceptability for the dissolution rate be established for digoxin to be used in patients.

In an earlier report (9), it was shown that the application of frictional force to digoxin–lactose or hydrocortisone–lactose blends produced 1:20 triturations with markedly improved dissolution rates. Thus, for example, at the end of 60 min, 91.7 ± 3.5% of digoxin had dissolved in simulated gastric fluid whereas a simple blend of 325-mesh digoxin and powdered lactose exhibited 65.4 ± 5.2% dissolution at the end of 120 min. The application of frictional force was carried out with a mortar and pestle.

This paper describes the use of a ball mill and a muller to prepare 1:20 lactose, sucrose, calcium phosphate dibasic, and microcrystalline cellulose triturations possessing excellent dissolution rates. Tablets prepared from the four triturations by wet and dry methods also exhibited rapid rates of digoxin dissolution. Excellent correlation of digoxin dissolution from the tablet dosage form and bioavailability is demonstrated. Plasma digoxin levels of fasting rats after oral administration of tablets and a solution were used as the basis for comparison.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: digoxin[1,2] USP; lactose[3] USP; lactose[4], spray-dried; sucrose[3] USP; calcium phosphate[5] NF, dibasic, anhydrous; microcrystalline cellulose[6] NF; sodium chloride[7] USP; hydrochloric acid[5], reagent grade; ethanol[5], absolute; acetone[5], reagent grade; chloroform[3], reagent grade; potato starch[8]; sodium lauryl sulfate[8]; magnesium stearate[7] USP; digoxin radioimmunoassay kit[9]; and ion-free serum[10].

Equipment—The following pieces of equipment were used: USP XVIII dissolution test basket assembly[11]; temperature-controlled water bath[12]; jarmill, 10.16-cm (4-in.) diameter with 1.27-cm (0.5-in.) diameter porcelain balls[13]; muller, laboratory model[14]; double-beam spectrophotometer[15]; immersion filter, 1.57 × 5.08 cm (0.62 × 2 in.), medium porosity[16]; Swinny adapter (13 mm)[17]; filter paper, 0.45-μm porosity[17]; tablet press, single punch[18]; Carver press[19]; tablet hardness tester[20]; gyrotory shaker[21]; and U.S. standard sieves[22].

Preparation of Drug Triturations—Powdered digoxin[23] had a particle-size range of 40–180 μm (microscopic examination, average of 10 determinations). A portion of the powdered digoxin was reduced in particle size using a mortar and pestle to a 3–45-μm range (microscopic examination).

Manual bottle tumbling of the unmilled digoxin with a 20-fold excess of diluent for 15 min was carried out in preparing the simple blend. The diluents used were: powdered lactose; powdered sucrose; calcium phosphate dibasic, anhydrous; and microcrystalline cellulose. A simple blend of micronized digoxin[24] with powdered lactose was also prepared. The micronized digoxin had a particle-size range of 1–25 μm (microscopic examination).

Solvent deposition consisted of dissolving the digoxin in sufficient 80% ethanol and uniformly wetting a 20-fold excess of powdered diluent contained in a beaker. The mixture was stirred with a magnetic stirrer, and the solvent was evaporated in a stream of air. The powder was then dried at 37° for 24 hr. Passage through a 60-mesh screen to break up any agglomerates and bottle blending to ensure homogeneity completed the operation.

[1] Barrows Pharmacal Co., Inwood, N.Y.
[2] Roussel Corp., New York, N.Y.
[3] Matheson, Coleman and Bell, Norwood, Ohio.
[4] McKesson Foremost, Inc., Bridgeport, Conn.
[5] J. T. Baker Chemical Co., Phillipsburg, N.J.
[6] Avicel, F. M. C. Corp., Newark, Del.
[7] Mallinckrodt Chemical Works, St. Louis, Mo.
[8] Fisher Scientific Co., Fairlawn, N.J.
[9] Schwarz/Mann, Orangeburg, N.Y.
[10] Chem-Varion, Los Angeles, Calif.
[11] Hanson Research Corp., Northridge, Calif.
[12] Precision Scientific Co., Chicago, Ill.
[13] Paul O. Abbe, Inc., Little Falls, N.J.
[14] Science Machine Shop, St. John's University, Jamaica, N.Y.
[15] Coleman Hitachi 124, Coleman Instrument Corp., Maywood, Ill.
[16] Arthur H. Thomas Co., Philadelphia, Pa.
[17] Millipore Corp., Bedford, Mass.
[18] Stokes, Pennsalt Chemicals Corp., Union, N.J.
[19] Fred S. Carver Inc., Summit, N.J.
[20] Strong Cobb Arner Inc., Cleveland, Ohio.
[21] New Brunswick Scientific Co., New Brunswick, N.J.
[22] Dual Manufacturing Co., Chicago, Ill.
[23] Barrows.
[24] Roussel.

Table I—Dissolution of Digoxin and Digoxin Triturations in Simulated Gastric Fluid at 37°

Minutes	Sample (Processing Method)	Percentage Dissolved				
		No Diluent	Lactose	Sucrose	Calcium Phosphate Dibasic	Microcrystalline Cellulose
15	Pure drug, unmilled	26.6	—	—	—	—
	Pure drug, pestle ground	28.5	—	—	—	—
	Pure drug, micronized (simple blend)	—	50.0	—	—	—
	Trituration (simple blend)	—	32.0	30.0	29.3	26.6
	Trituration (solvent deposited)	—	45.8	42.8	40.1	40.1
	Trituration (ball milled)	—	85.0	67.5	66.5	60.5
	Trituration (muller milled)	—	72.0	64.0	58.5	45.5
30	Pure drug, unmilled	31.8				
	Pure drug, pestle ground	35.3	—	—	—	—
	Pure drug, micronized (simple blend)	—	59.0	—	—	—
	Trituration (simple blend)	—	38.3	43.0	35.2	32.6
	Trituration (solvent deposited)	—	49.2	48.0	43.3	43.3
	Trituration (ball milled)	—	90.0	78.8	73.0	70.8
	Trituration (muller milled)	—	86.5	72.0	70.7	59.5
45	Pure drug, unmilled	34.4	—	—	—	—
	Pure drug, pestle ground	41.5	—	—	—	—
	Pure drug, micronized (simple blend)	—	64.0	—	—	—
	Trituration (simple blend)	—	44.0	47.0	38.7	36.0
	Trituration (solvent deposited)	—	58.1	52.9	50.0	50.0
	Trituration (ball milled)	—	94.5	86.0	82.0	75.0
	Trituration (muller milled)	—	92.0	81.0	75.0	69.5
60	Pure drug, unmilled	39.4	—	—	—	—
	Pure drug, pestle ground	45.3	—	—	—	—
	Pure drug, micronized (simple blend)	—	66.0	—	—	—
	Trituration (simple blend)	—	50.5	51.0	44.9	42.2
	Trituration (solvent deposited)	—	62.3	59.6	56.6	54.0
	Trituration (ball milled)	—	97.0	90.9	87.5	81.0
	Trituration (muller milled)	—	95.0	85.5	85.0	76.0
90	Pure drug, unmilled	44.5	—	—	—	—
	Pure drug, pestle ground	59.5	—	—	—	—
	Pure drug, micronized (simple blend)	—	68.0	—	—	—
	Trituration (simple blend)	—	56.0	54.8	51.3	50.8
	Trituration (solvent deposited)	—	66.6	66.3	63.3	58.0
	Trituration (ball milled)	—	99.0	95.7	92.0	88.7
	Trituration (muller milled)	—	98.5	92.5	90.0	89.0
120	Pure drug, unmilled	52.0	—	—	—	—
	Pure drug, pestle ground	66.0	—	—	—	—
	Pure drug, micronized (simple blend)	—	68.0	—	—	—
	Trituration (simple blend)	—	62.5	58.5	58.0	57.7
	Trituration (solvent deposited)	—	70.9	70.5	67.3	67.3

Table I—(*Continued*)

Minutes	Sample (Processing Method)	Percentage Dissolved				
		No Diluent	Lactose	Sucrose	Calcium Phosphate Dibasic	Microcrystalline Cellulose
	Trituration (ball milled)	—	100.3	100.3	97.5	95.0
	Trituration (muller milled)	—	99.5	97.0	94.5	93.5

Ball-milled triturations were prepared as follows. Digoxin powder and a 20-fold excess of the various diluents were blended and transferred to a ball mill jar. The jar was half filled with 1.27-cm (0.5-in.) porcelain balls. The sealed jar was set in motion on motor-driven rollers. Samples were removed at various time intervals to establish the optimal grinding time. Ball milling for 48 hr was found to be ideal, since no improvement in digoxin dissolution rate was obtained after an additional 12 hr of milling.

Muller-milled triturations were prepared in a similar manner. The laboratory muller was more efficient than the ball mill, since only 6 hr of muller milling was required to duplicate the dissolution rate of digoxin–lactose triturations ball milled for 48 hr.

Preparation of Digoxin Tablets (0.25 mg) Using Various Triturations—Wet and dry methods were used in preparing the following tablet (quantities for one tablet): *(a)* digoxin trituration, 5.25 mg; *(b)* spray-dried lactose, 55 mg; *(c)* sucrose powder, 55 mg; *(d)* potato starch, 8.5 mg; *(e)* magnesium stearate, 1.125 mg; and *(f)* sodium lauryl sulfate, 0.125 mg. The weight of one tablet was 125 mg.

The triturations (5.25 mg) were prepared by simple blending, solvent deposition, ball milling, and muller milling. They consisted of 0.25 mg of digoxin and 5 mg of diluent (lactose; sucrose; calcium phosphate dibasic, anhydrous; or microcrystalline cellulose). By the dry method, a blend of *(b)*, *(c)*, and *(d)* was prepared; *(a)* was diluted with the blend by geometric dilution. A mixture of *(e)* and *(f)* was separately prepared, and an appropriate quantity was added to the remaining ingredients. After blending to ensure homogeneity, the powder mixture was compressed on a single-punch tablet machine using 0.48-cm (0.19-in.) square punches.

Chloroform was used as the granulating solvent in converting the entire series of triturations into tablets by the wet method. Ingredients *(b)*, *(c)*, and *(d)* were blended; *(a)* was then incorporated by geometric dilution. Sufficient chloroform was added to wet the mixture of powders. The wet mass was passed through a 10-mesh sieve to form granules, and the granules were dried at 37° for 24 hr. The dried granules were passed through a 40-mesh sieve, and the mixed lubricant [blend of *(e)* and *(f)*] was added. After manual bottle tumbling the mixture for 10 min, the blend of powders was compressed into tablets.

Absolute ethanol was also used as a granulating solvent in converting the ball-milled lactose trituration into tablets using the standard formula already described.

Tablet hardness, by the wet or dry methods, ranged from 4 to 6. The disintegration rates were less than 5 min.

Preparation of Digoxin Tablets (0.067 mg) for Blood Level Studies in Rats—Smaller digoxin tablets, weighing 0.0283 ± 0.002 g [0.32-cm (0.125-in.) diameter], were prepared to facilitate oral administration to rats. They were prepared with a Carver press by direct compression at a force of 509.4 kg (1100 lb). These tablets represented an aliquot of the blend for the 125-mg tablet. Their content uniformity did not deviate outside the range of 100 ± 5%.

One batch of tablets used the 48-hr ball-milled digoxin–lactose trituration. The second batch used a trituration prepared as a simple blend of powdered digoxin and lactose. Tablet hardness for either batch ranged from 4 to 7. Their disintegration rates were uniformly less than 3 min.

Spectrophotometric Absorption and Calibration Curves for Digoxin in Simulated Gastric Fluid—Twenty milligrams of digoxin was dissolved in 10 ml of hot 80% ethanol. Sufficient simulated gastric fluid without pepsin was added to make 1 liter. This solution was used to determine absorption spectral and calibration curves. The concentrations of digoxin in the dissolution study obey Beer's law at 224 nm. Incorporation of a 20-fold excess of the four diluents did not alter the absorbance values for digoxin.

Dissolution Studies—A modification of the procedure of Monkhouse and Lach (10) was used to determine the dissolution rates of the various samples of digoxin and its triturations. This procedure was described in an earlier publication (9). It was established that a saturated solution of digoxin in simulated gastric fluid contained 188.8 mg/200 ml (shaking for 13 days at 37°). Sink conditions were maintained throughout the dissolution test since only 4 mg of digoxin was added to 200 ml of simulated gastric fluid.

The procedure for determining the dissolution rate of digoxin from the various tablet formulas was identical to that used for the triturations with two exceptions. First, accurately weighed tablets equivalent to 4 mg of digoxin were placed into the USP dissolution basket at zero time. Second, it was not always possible to use simulated gastric fluid as the blank, since the large excess (greater than 20-fold) of inert ingredients affected the digoxin absorbance values. In such instances, placebo tablets containing an identical quantity of inert ingredients were added to simulated gastric fluid. The filtrate was used as the blank.

The dissolution data are summarized in Tables I and II.

Plasma Levels of Digoxin in Sprague-Dawley Rats—Three groups of six 10-week-old, female Sprague-Dawley rats (weight range 214 ± 8.4 g) were fasted overnight and orally dosed with 0.067 mg of digoxin. The drug was administered as an aqueous solution (1 ml) or as compressed tablets. One milliliter of water was administered after each tablet.

Blood samples were drawn into heparinized glass capillaries from the rats' tails after 0.25, 0.50, 1, and 2 hr. A 4-hr sample was drawn into a heparinized syringe after cardiac puncture. After centrifugation to remove the red blood cells, the samples were diluted with ion-free serum to ensure that the readings would be in the linear portion of the standard curve. Digoxin plasma levels were determined by a radioimmunoassay procedure using ^{125}I as the marker (11). The assay data are summarized in Table III.

RESULTS AND DISCUSSION

In Table I, the digoxin dissolution from triturations is summarized. After 120 min, the extent of dissolution of milled and unmilled digoxin is 66 and 52%, respectively. A simple blend of micronized digoxin and lactose shows 68% dissolution after 120 min. The poor performance of the milled and micronized drug is not unexpected. Lin *et al.* (12) demonstrated that the *in vitro* dissolution of micronized griseofulvin and glutethimide was slower than that of coarser particles. Poor wettability and the aggregation of fine particles most likely account for these observations.

The dissolution of digoxin from solvent-deposited triturations was not much faster. Thus, the digoxin–lactose trituration prepared by solvent deposition was only 70.9% dissolved at 120 min. The superiority of ball-milled or muller-milled triturations is clearly evident. All four diluents exhibit greater than 93.5% drug dissolution within 120 min. The soluble diluents, lactose and sucrose, release the digoxin more rapidly than the insoluble ones. Of the four, powdered lactose proved to be the best. Within 15 min, 85% of the digoxin from the ball-milled lactose trituration had dissolved.

From the data in Table II, a number of generalizations can be made on the dissolution of digoxin from tablets prepared from the various triturations.

Tablets Prepared from Triturations Made by Simple Blending—The dissolution rates of digoxin from tablets prepared by di-

Table II—Dissolution Rate of Digoxin in Simulated Gastric Fluid at 37° from Tablet Dosage Forms

Minutes	Trituration Sample and Processing Method	Percentage Dissolved			
		Lactose	Sucrose	Calcium Phosphate Dibasic	Microcrystalline Cellulose
15	Simple blend, dry	32.0	37.2	32.1	29.3
	Solvent deposition, dry	48.1	44.2	40.1	40.1
	Ball milled, dry	77.5	72.1	69.5	62.0
	Muller milled, dry	64.1	58.8	48.1	42.7
	Simple blend, wet (chloroform)	37.4	34.7	40.1	32.1
	Solvent deposition, wet (chloroform)	53.4	48.2	45.7	42.7
	Ball milled, wet (chloroform)	64.2	63.6	53.4	53.4
	Ball milled, wet (ethanol)	64.0	61.0	53.4	53.4
	Muller milled, wet (chloroform)	64.0	58.8	48.1	42.7
30	Simple blend, dry	35.2	40.9	35.2	35.2
	Solvent deposition, dry	54.5	46.5	46.5	43.2
	Ball milled, dry	87.4	84.2	79.1	74.0
	Muller milled, dry	78.6	70.1	56.9	67.0
	Simple blend, wet (chloroform)	43.5	40.9	41.5	35.5
	Solvent deposition, wet (chloroform)	60.2	49.1	49.1	46.5
	Ball milled, wet (chloroform)	73.7	76.4	78.8	62.8
	Ball milled, wet (ethanol)	79.2	76.2	76.2	76.0
	Muller milled, wet (chloroform)	79.0	68.1	67.9	65.5
45	Simple blend, dry	41.7	44.6	41.5	38.7
	Solvent deposition, dry	58.5	50.0	50.0	47.2
	Ball milled, dry	92.4	90.0	86.2	80.4
	Muller milled, dry	85.7	80.2	69.2	74.8
	Simple blend, wet (chloroform)	47.3	44.6	46.3	39.0
	Solvent deposition, wet (chloroform)	64.2	58.2	58.1	50.0
	Ball milled, wet (chloroform)	78.1	81.0	83.4	77.5
	Ball milled, wet (ethanol)	83.6	83.4	80.7	83.2
	Muller milled, wet (chloroform)	83.5	80.5	74.8	72.4
60	Simple blend, dry	50.8	48.3	45.2	44.9
	Solvent deposition, dry	65.5	54.0	53.7	54.0
	Ball milled, dry	96.2	94.1	91.1	85.2
	Muller milled, dry	93.0	85.0	73.5	81.8
	Simple blend, wet (chloroform)	51.5	48.3	48.6	42.5
	Solvent deposition, wet (chloroform)	68.4	64.9	62.2	56.6
	Ball milled, wet (chloroform)	85.6	90.0	87.9	82.1
	Ball milled, wet (ethanol)	85.5	85.5	85.2	85.2
	Muller milled, wet (chloroform)	84.9	95.2	82.1	79.6
90	Simple blend, dry	54.5	52.1	49.3	51.3
	Solvent deposition, dry	69.2	62.5	60.9	60.5
	Ball milled, dry	97.5	96.5	95.9	92.7
	Muller milled, dry	98.0	92.4	80.4	86.6
	Simple blend, wet (chloroform)	52.4	52.1	49.7	46.2
	Solvent deposition, wet (chloroform)	72.7	71.8	66.5	60.6
	Ball milled, wet (chloroform)	92.7	90.1	92.7	86.6
	Ball milled, wet (ethanol)	87.4	87.4	87.1	87.0
	Muller milled, wet (chloroform)	90.3	89.8	86.6	84.2
120	Simple blend, dry	58.5	58.5	50.0	51.6
	Solvent deposition, dry	72.7	70.1	67.5	67.5

Table II—(*Continued*)

Minutes	Trituration Sample and Processing Method	Percentage Dissolved			
		Lactose	Sucrose	Calcium Phosphate Dibasic	Microcrystalline Cellulose
	Ball milled, dry	100.8	98.5	97.5	95.0
	Muller milled, dry	98.0	94.5	91.5	91.1
	Simple blend, wet (chloroform)	53.5	53.2	50.8	47.2
	Solvent deposition, wet (chloroform)	74.0	72.0	70.8	66.3
	Ball milled, wet (chloroform)	97.5	95.1	94.9	91.5
	Ball milled, wet (ethanol)	89.5	89.5	89.4	89.3
	Muller milled, wet (chloroform)	98.0	94.6	91.4	91.4

Table III—Digoxin Plasma Levels in Sprague–Dawley Rats after Oral Administration of an Aqueous Solution and Tablets[a]

Hours	Concentration, ng/ml		
	Aqueous Solution (1 ml)	Tablet Prepared from Simple Blend Trituration	Tablet Prepared from Ball-Milled Tritur tion
0.25	34.8 ± 2.2	22.6 ± 2.3	25.1 ± 2.2
0.50	46.2 ± 3.1	37.1 ± 0.6	41.4 ± 3.1
1	29.4 ± 2.0	20.9 ± 2.1	25.5 ± 2.1
2	25.4 ± 2.9	18.2 ± 1.2	20.9 ± 1.7
4	21.9 ± 2.2	16.5 ± 1.0	19.5 ± 1.2

[a] Dose administered was 0.067 mg.

rect compression were slightly faster than from triturations prepared by simple blending. Digoxin tablets prepared by the wet method exhibited faster dissolution of drug than those prepared by the dry procedure.

Tablets Prepared from Solvent-Deposited Triturations—Tablets prepared by the wet or dry procedures exhibited digoxin dissolution rates as good as those for the four solvent-deposited triturations used in their preparation. Within 120 min, the percentage of digoxin dissolved was similar for the four triturations and the eight tablets.

Tablets Prepared from Ball-Milled and Muller-Milled Triturations—Digoxin tablets prepared from ball-milled and muller-milled triturations were clearly superior to those using triturations prepared by simple blending or solvent deposition. At each time interval, tablets prepared with ball-milled or muller-milled triturations exhibited greater dissolution of drug. As might be expected, the soluble diluents, lactose and sucrose, yielded ball-milled and muller-milled triturations and compressed tablets with the fastest dissolution rates.

The content uniformity of the various tablets and triturations was never a problem. Replicate assays rarely fell outside the range of 100 ± 5%.

The drug plasma levels attained in fasting rats after oral administration of 0.067 mg of digoxin as an aqueous solution or as compressed tablets are summarized in Table III. Figure 1 presents a logarithmic plot of the data in Table I. The points are experimental, whereas the lines are drawn from predicted values obtained by the least-squares method. Peak plasma levels for the aqueous solution and the two tablet formulas occurred at 0.5 hr. In addition, the slopes of the lines are similar: solution, −0.041; tablet prepared from a trituration prepared by simple blending, −0.032; and tablet prepared from a ball-milled trituration, −0.035. As a consequence of these similarities, oral absorption efficiency of the tablets can be determined from peak plasma levels with a fair degree of accuracy (9). Thus, the oral absorption efficiency of the digoxin tablet containing the simple blend trituration is only 80% that of the aqueous solution, whereas the oral absorption efficiency of the tablet employing the ball-milled trituration is 89.6%. These differences in peak plasma levels were significant in the analyses of variance (solution *versus* tablet with ball-milled trituration, $p < 0.02$; tablet with ball-milled trituration *versus* tablet with simple blend trituration, $p < 0.01$).

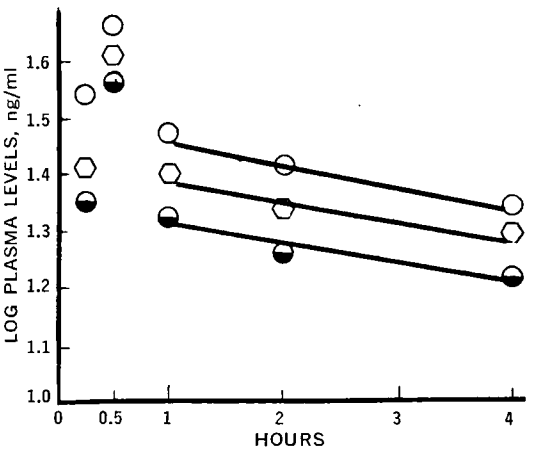

Figure 1—*Digoxin plasma levels in Sprague–Dawley rats after oral administration of an aqueous solution* (○), *tablet prepared from a simple blend of digoxin* (◒), *and tablet prepared from ball-milled digoxin–lactose (1:20)* (○).

Thus, it has been demonstrated in rats that oral absorption efficiency follows *in vitro* dissolution for the two digoxin tablet preparations. The concept of compressing an aliquot of a blend designed for a larger tablet in assessing bioavailability in animals deserves wider application. The excellent content uniformity of triturations and tablets prepared by ball milling a 1:20 blend of digoxin and lactose should simplify the manufacture of digoxin tablets.

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Dissolution Profile of Log-Normal Powders II: Dissolution before Critical Time

DANA BROOKE

Abstract □ The dissolution of log-normal powders, particularly in that period before the smallest particles disappear, was examined. An approximation for the slope of a cube-root law plot was developed for the dissolution before the critical time of ideally distributed powders. Such an approximation does not hold, however, for severely truncated log-normal distributions. The work of previous investigators in this area appears to be incorrect and is discussed.

Keyphrases □ Dissolution profiles—log-normal powders, dissolution before critical time, cube-root law plot approximation □ Powders, dissolution—log-normal distribution profile, dissolution before critical time, cube-root law plot approximation □ Particle dissolution—log-normally distributed powders, dissolution before critical time, cube-root law plot approximation

In their paper on the dissolution of powders that follow the log-normal distribution, Carstensen and Musa (1) attempted to find correlations between the well-known "cube-root law" (2) and their computer-generated dissolution patterns. They offered two approximations to the cube-root law wherein the slopes were stated as functions of the means and standard deviations of the log-normal distributions. One equation dealt with dissolution before the time when the smallest particles disappeared, *i.e.*, before the "critical time." Another equation dealt with dissolution after the critical time.

Brooke (3), in a discussion of exactly calculated dissolution profiles for log-normally distributed powders, reported that the Carstensen and Musa approximation for dissolution before the critical time gave excellent results. Further examination of this subject, however, shows that the approximation is incorrect. The test of the approximation (3) was, in fact, inconclusive.

The present paper examines the time course of dissolution, particularly in that period before a significant number of particles disappear, for log-normally distributed powders varying in standard deviation and extent of truncation. As expected, for narrow distributions the cube-root law holds for dissolution before the critical time. However, one approximation of the cube-root law slope will not apply for all log-normal distributions. An approximation is offered that does hold for powders obeying the ideal log-normal distribution.

THEORETICAL AND CALCULATIONS

The complete derivation of an expression that exactly describes the dissolution of log-normal powders was given by Brooke (3). Briefly, if there is a powder containing spherical particles of diameters a_0 which are distributed, on a numbers basis, so that $\ln a_0$ is normal with mean μ and standard deviation σ, then the probability frequency f of log diameters is:

$$f = (1/\sigma\sqrt{2\pi})e^{-(\ln a_0 - \mu)^2/2\sigma^2} \qquad \text{(Eq. 1)}$$

If such particles dissolve isotropically under sink conditions and if the solubility C_s is independent of particle size, then the diameters a_τ of particles at some function τ of time can be written (1) as:

$$a_\tau = a_0 - \tau \qquad \text{(Eq. 2)}$$

Here τ is $2kC_st/\rho$, where k is a proportionality constant, ρ is particle density, and t is time. The weight w_τ of a powder remaining at any τ is found by the integration:

$$w_\tau = \int(\pi\rho N/6)(a_0 - \tau)^3 f \, d \ln a_0 \qquad \text{(Eq. 3)}$$

where N is the number of particles at time zero. This is somewhat different from the integral in Eq. 6 of the Carstensen and Musa (1) paper.

The limits of integration in Eq. 3 depend on τ and on the original powder distribution. Let i and j be numbers that reflect the extent of truncation at the small particle end and the large particle end, respectively. If the powder is such that all $\ln a_0$ are found between $\mu - i\sigma$ and $\mu + j\sigma$, then for $\ln \tau \leq \mu - i\sigma$, the integration would be from $\mu - i\sigma$ to $\mu + j\sigma$. For $\ln \tau > \mu - i\sigma$, the integration would be from $\ln \tau$ to $\mu + j\sigma$. If $i = j = \infty$, the solution to Eq. 3 becomes Eq. 13 of the previous paper (3).