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* Present address: The Alexandria Co. for Pharmaceuticals, Alexandria, Egypt.

[x] To whom inquiries should be directed.

In Vitro and *In Vivo* Availability of Spironolactone from Oral Dosage Forms

ALLEN Y. CHAO, DILIP R. SANVORDEKER [x], JUDY ZAGARELLA, KIRK MATTES, BILIANA NICHOLOVA, and AZIZ KARIM

Abstract □ Tablet formulations of spironolactone with hydrochlorothiazide were studied *in vitro* and *in vivo* to evaluate the effect of formulation parameters on the bioavailability of spironolactone. The time required for 50% tablet dissolution (T_{50}) in simulated gastric fluid was linearly correlated with the disintegration times of four experimental formulations and one commercial tablet of spironolactone and hydrochlorothiazide. Bioavailability studies were conducted in four healthy, female beagle dogs. The mean time to peak concentration of canrenone, the major metabolite of spironolactone, was proportional to the T_{50} dissolution parameter. A study of spironolactone administered orally with and without hydrochlorothiazide showed that the bioavailability of spironolactone is not affected by hydrochlorothiazide. No significant differences in the bioavailability of spironolactone from one 100-mg and four 25-mg tablets were observed. Estimates of some pharmacokinetic parameters for canrenone closely agreed with those previously reported.

Keyphrases □ Spironolactone—dissolution and bioavailability, tablet formulations with and without hydrochlorothiazide, effect of formulation parameters □ Dissolution—spironolactone tablet formulations with and without hydrochlorothiazide, effect of formulation parameters □ Bioavailability—spironolactone, tablet formulations with and without hydrochlorothiazide, effect of formulation parameters □ Hydrochlorothiazide—effect on dissolution and bioavailability of spironolactone in tablet formulations □ Dosage forms—tablets, spironolactone with and without hydrochlorothiazide, dissolution and bioavailability, effect of formulation parameters □ Diuretic agents—spironolactone, dissolution and bioavailability, tablet formulations with and without hydrochlorothiazide

Bioavailability of a drug from a dosage form is of public health interest (1–4). Several investigations have documented the importance of formulation factors affecting drug bioavailability (4–7). Consequently, it has become increasingly important to recognize and evaluate the *in vitro* availability of existing drug products and to determine the influence of formulation on *in vivo* availability from oral dosage formulations. With this approach, effective *in vitro–in vivo* correlations can be established so that improvements in the drug bioavailability from a given drug combination can be achieved (6–10).

Spironolactone (I), a potent aldosterone antagonist, in combination with hydrochlorothiazide (II) is an effective antihypertensive agent. It is also used for the treatment of edema and ascites of congestive heart failure (11–13).

The objectives of this study were: (*a*) to test whether differences exist in the bioavailability of tablet formulations of I given orally with and without II, (*b*) to assess the *in vitro–in vivo* relationship for four experimental and one commercial tablet preparations of I and II, and (*c*) to determine the pharmacokinetics of canrenone (III), a major metabolite of I, with and without II.

EXPERIMENTAL

Materials—Starch USP[1], microcrystalline cellulose[2], povidone NF[3], calcium sulfate dihydrate NF[4], spironolactone USP[5] (I), hydrochlorothiazide USP[6] (II), magnesium stearate USP[4], polyethylene glycol 400[7], and methanol, analytical reagent grade, were used.

Methods—*Tablet Preparation*—Batches (2 kg) of each formulation, except the commercial tablets[8] containing 25 mg each of I and II, were processed. The drugs and excipients, except magnesium stearate, were mixed and wet granulated with distilled water.

The granulations were oven dried, comminuted, and then lubricated with 0.5% magnesium stearate. Each batch was compressed on a rotary tablet press[9] equipped with 16 sets of 0.95-cm (0.375-in.) standard concave tablet punches. Each batch was analyzed for the content of I per tablet (discussed later).

[1] Anheuser-Busch Inc., St. Louis, Mo.
[2] FMC Corp., Newark, N.J.
[3] Plasdone, GAF Corp., New York, N.Y.
[4] Mallinckrodt Chemical Works, St. Louis, Mo.
[5] Searle & Co., San Juan, Puerto Rico.
[6] Ciba-Geigy Corp., Summit, N.J.
[7] Matheson, Coleman & Bell, Norwood, Ohio.
[8] Aldactone, 25-mg tablets (Lot 273-438), and Aldactazide, 25-mg tablets (Lot 21).
[9] Stokes B-2, Pennwalt Corp., Philadelphia, Pa.

Table I—Formulation Parameters of Tablet Preparations of Spironolactone (I) and Hydrochlorothiazide (II)

Formulation	Excipient[a], %			*In Vitro* Parameter		
	Starch USP	Microcrystalline Cellulose	Calcium Sulfate Dihydrate	Potency, %	Hardness, kg	Disintegration Time, min
1	20	2	60.5	100.8	4.8	3.0
2	5	2	75.5	100.4	5.5	13.5
3	5	10	67.5	99.6	8.3	15.4
4	20	10	52.5	103.5	7.6	5.8
5	—	—	—	100.3	4.0	2.5

[a] Povidone and magnesium stearate made up the rest of the excipients.

Disintegration Test—The disintegration times for six randomly sampled tablets of each formulation were measured in simulated gastric fluid without pepsin using the USP test apparatus. Disintegration tests were run without disks, and the mean disintegration time was recorded.

Hardness Test—Tablet hardness[10] was measured using 20 randomly sampled tablets from each formulation, and the mean was recorded.

Dissolution Test—The dissolution of four randomly selected tablets from each formulation was determined on an individual basis in the following manner.

Due to solubility limitations of I, one tablet was dropped in 1500 ml of simulated gastric fluid (without pepsin) maintained at 37 ± 0.5° in a constant-temperature bath and stirred at 100 rpm. A 20-ml aliquot of the dissolution fluid was withdrawn at 5, 10, 20, 40, 60, 90, and 120 min. The sample was filtered through a glass wool filter[11] fitted in a filtration unit[12]. Upon appropriate dilution, the filtrate was assayed spectrophotometrically at 241 nm on a dual-beam spectrophotometer[13].

Analysis of Spironolactone in Tablets—Twenty tablets were ground to a fine powder in a mortar and pestle. A weighed amount of this powder, equivalent to one tablet, was dissolved in 100 ml of methanol. After filtering and appropriate dilution, the sample was assayed spectrophotometrically as already described.

Bioavailability Studies in Dogs—Bioavailability studies were conducted in four healthy, female beagle dogs. A 2-week washout period was allowed prior to administration of each preparation. The animals were dosed orally with either one 100-mg[14] or four 25-mg tablets of each formulation of I with or without II. A 100-mg dose of I with and without II in 15 ml of polyethylene glycol 400 solution was administered intragastrically to each dog. An additional 15 ml of the vehicle was then administered to ensure total delivery of the dose.

Approximately 3 ml of blood was collected in heparinized tubes *via* a butterfly catheter[15] implanted securely into the saphenous vein of the right leg. Blood samples were collected at 0.25, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, and 24 hr after dosing of each preparation. Sterile normal saline solution[16] was infused in the animals at approximately 20 ml/hr prior to and after blood sampling. The blood samples were centrifuged immediately, and the plasma was stored frozen until analysis.

Assay of Canrenone in Dog Plasma—The fluorometric[17] method of Gochman and Gantt (14) was used to quantify the concentration of canrenone (III) in the dog plasma. Due to limitations on the sample size, levels of III below 50 ng/ml were not considered reliable.

RESULTS AND DISCUSSION

Formulation Characteristics *In Vitro*—The composition and characteristics of four experimental tablet formulations are shown in Table I. In these formulations, magnesium stearate and povidone were kept constant at 0.5 and 3%, respectively, to eliminate their influence as variables in drug release and dissolution. Comparison of Formulation 1 with 2 and of Formulation 3 with 4 (Table I) shows that increasing the amount of corn starch with a constant level of microcrystalline cellulose in the formulations resulted in a shorter disintegration time while maintaining the hardness in a relatively close range. This finding agrees with the reported results on improved disintegration properties due to starch (15, 16). Comparison of Formulation 1 with 4 and of Formulation 2 with 3 shows that increasing the amount of microcrystalline cellulose from 2 to 10%, while maintaining a constant starch level, resulted in improved tablet hardness. However, the disintegration time was not affected significantly.

The dissolution profiles of I from four experimental formulations and one commercial tablet are illustrated in Fig. 1. Each point on the graph is a mean of four separate determinations. The T_{50} value, defined as the time required for 50% of I to dissolve in the dissolution medium, was estimated for each formulation from these data.

When the T_{50} value for each formulation was plotted against the corresponding disintegration time, a linear relationship (Fig. 2) was

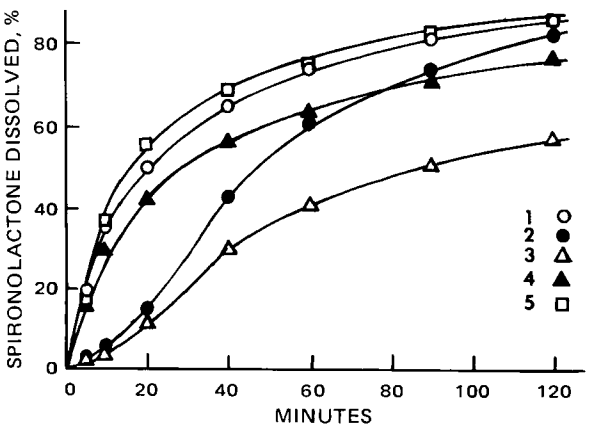

Figure 1—*Dissolution profile of I from four experimental (1–4) and one commercial (5) tablet formulations of I and II.*

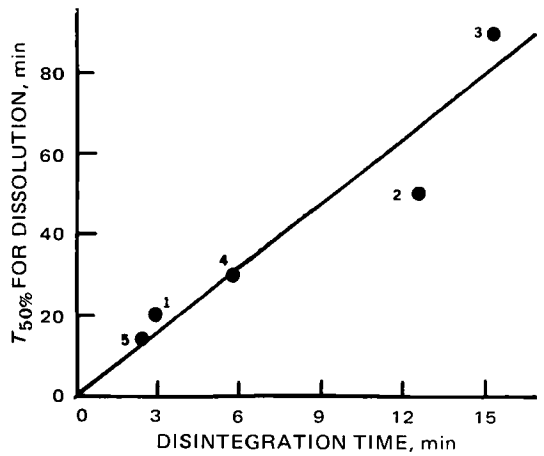

Figure 2—*Linear relationship between tablet disintegration time and $T_{50\%}$ for dissolution of I from four experimental (1–4) and one commercial (5) tablet formulations of I and II.*

[10] Heberlein, Vector Corp., Hiawatha, Iowa.
[11] Reeve-Angel Co., Clifton, N.J.
[12] Millipore Corp., Bedford, Mass.
[13] Model 124-D, Coleman, Perkin-Elmer Corp., Maywood, Ill.
[14] Aldactone, 100-mg tablets (Lot 912-1068), prepared for clinical trials, Searle Laboratories, Chicago, Ill.
[15] Butterfly-19 infusion catheter, Abbott Laboratories, North Chicago, Ill.
[16] Baxter Laboratories, Morton Grove, Ill.
[17] All fluorometric measurements were performed on an Aminco-Bowman spectrophotofluorometer, American Instrument Co., Silver Spring, Md.

Table II—*In Vivo* and *In Vitro* Parameters for Five Tablet Formulations of Spironolactone (I) and Hydrochlorothiazide (II)

Formulation	Dog	Observed Maximum		Smoothed Maximum		Disintegration Time, min	T_{50}, min
		Time, hr	Concentration, ng/ml	Time, hr	Concentration, ng/ml		
1	1	2.0	190	2.36	175		
	2	1.5	190	1.86	182		
	3	1.25	150	1.34	150		
	4	1.5	390	1.75	422		
	Mean:	1.56	230	1.83	232	3.0	21.0
2	1	2.0	100	—	—		
	2	2.5	210	2.77	204		
	3	2.5	120	2.34	111		
	4	3.0	150	2.78	152		
	Mean:	2.5	145	2.63	156	13.5	46.8
3	1	2.5	250	2.07	222		
	2	3.0	240	3.41	233		
	3	1.5	170	1.75	162		
	4	7.0	520	10.75	599		
	Mean:	3.5	295	4.50	304	15.4	89.2
4	1	1.5	300	1.92	286		
	2	2.25	160	2.07	158		
	3	2.0	170	1.86	138		
	4	5.0	410	4.72	276		
	Mean:	2.69	260	2.64	215	5.8	30.8
5	1	2.0	330	2.17	319		
	2	2.0	210	2.22	194		
	3	2.0	190	2.27	181		
	4	1.0	500	1.37	590		
	Mean:	1.75	308	2.01	321	2.5	15.0

observed. Since the dissolution process of a drug from a tablet is dependent on its disintegration into dispersed aggregates, it is reasonable to expect that a longer disintegration time for a given tablet formulation would give a longer T_{50} value.

Bioavailability Studies in Dogs—Previous studies (17–21) demonstrated that the bioavailability of I can be measured by the appearance of III, a major fluorogenic metabolite in the plasma. In a series of investigations, Sadée *et al.* (20–22) showed that I was rapidly metabolized to III and nonfluorogenic metabolites in dog plasma.

In Vitro–In Vivo *Correlation for Tablet Formulations of I and II*—Figure 3 is a semilogarithmic plot of the plasma concentration of III *persus* time and illustrates the comparative bioavailability of I from the five tablet formulations of I and II. It is apparent that the bioavailability of the commercial preparation (Formulation 5), as reflected by the plasma levels of III, was optimal compared to the other four experimental formulations. The plasma levels of III achieved from Formulations 1 and 4 during the absorption phase (0–1 hr) were higher, while those achieved from 2 and 3 were below the detectable level of 50 ng/ml. Whereas Formulations 2 and 3 exhibited a lag phase in the dissolution profile (Fig. 2), Formulations 1, 4, and 5 did not. These differences in the dissolution profiles were reflected in the plasma levels of III monitored during the absorption phase. It was deemed important to evaluate whether there was a correlation between the T_{50} parameter and mean time to peak concentration of III in the plasma.

Table II illustrates the individual dog data and the observed *in vitro* parameters for the five tablet preparations of I and II. The mean time

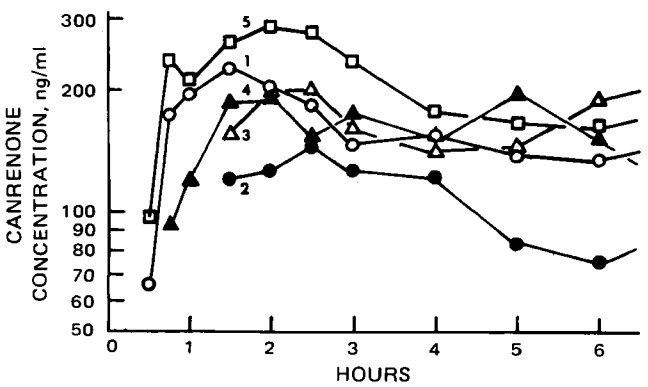

Figure 3—*Semilogarithmic plots of mean plasma levels of III monitored as a function of time after oral dosing of four experimental (1–4) and one commercial (5) tablet formulations of I and II to four dogs.*

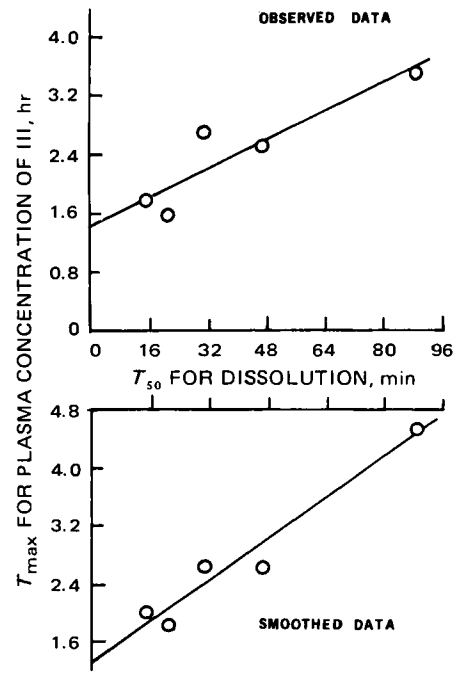

Figure 4—*Linear relationship between time for maximum concentration of III in dog plasma (T_{max}) and T_{50} value for dissolution of I from four experimental and one commercial tablet formulations of I and II.*

Table III—Pharmacokinetic Parameters of Canrenone (III) in Dog Plasma after Oral Dosing of Spironolactone

Mode of Oral Administration of I	Apparent Pharmacokinetic Parameter: Half-Life for Appearance in Plasma, hr	Half-Life for Distribution from Plasma, hr	Half-Life for Elimination from Plasma, hr (Mean ± *SE*)	*AUC* (0.25–8 hr), ng/ml × hr (Mean ± *SE*)
100 mg in polyethylene glycol 400	0.40[a]	0.82[a]	13.5 ± 2.9[b]	5042 ± 599[c]
Four 25-mg tablets	—	—	15.5 ± 1.3[b]	1582 ± 612[d]
One 100-mg tablet	—	—	20.4 ± 4.8[b]	958 ± 70

[a] Determined on the basis of the mean plasma concentration–time profile of III in four dogs. [b] Determined on the basis of the slope of the terminal portion (4–24 hr) of the plasma concentration–time profile of III in each dog. Difference was not statistically significant at $p < 0.05$ level. [c] The difference between polyethylene glycol and both tablet formulations was statistically significant at the $p < 0.05$ level. [d] The difference between the two tablet formulations was not statistically significant at the $p < 0.05$ level.

to peak and the peak plasma concentration of III were estimated by a quadratic spline "smoothening" technique (23) (Table II). The Pearson product moment correlation coefficients (r) were calculated to correlate both the observed and "smoothed" *in vivo* data with the *in vitro* dissolution times, *i.e.*, T_{50} value (Table II).

The correlation of mean time to peak with T_{50} value for the five formulations was statistically significant ($p < 0.05$) based on the observed *in vivo* data ($r = 0.91$) and confirmed by the smoothed *in vivo* data ($r = 0.97$). This correlation indicated that there was a significant linear relationship between the *in vitro* and *in vivo* parameters established for the five tablet preparations of I and II (Fig. 4).

Bioavailability of 100- and 25-mg Tablets of I—Figure 5 is a semilogarithmic plot of the mean plasma concentration of III achieved after oral administration of one 100[14]- or four 25-mg tablets[8] of I and four 25-mg tablets[8] of I and II to the four dogs used in the previous studies. The mean time to peak plasma concentration of III fell in the 1.5–2-hr range after dosing, regardless of the dose distribution of I in the three different tablet types. This finding suggests that the drug release from these tablet preparations of I and/or I and II (4 × 25 mg) during the absorptive phase was virtually equivalent. The plasma elimination profile of III observed for these tablet preparations indicates that the presence of II did not affect the pharmacokinetic disposition of III.

Bioavailability of I with and without II in Polyethylene Glycol 400 Solution—Figure 6 is a semilogarithmic plot of the mean plasma concentration of III *versus* time following oral administration of a 100-mg dose of I and II in 15 ml of polyethylene glycol 400 solution. The peak plasma concentration of III occurred at about 1.5 hr after drug administration. The half-life for the biological disposition of III, $(t/2)_\beta$, as estimated from the terminal portion of the plasma concentration–time profile, was about 8 hr. These observations are consistent with reported results (20–22).

To test whether coadministration of II in solution had any significant effect on the bioavailability of I, an additional study with a 100-mg dose of only I in 15 ml of polyethylene glycol 400 solution was conducted in the same dogs. Statistical analysis of the area under the plasma concentration–time curve (*AUC*) of III for the four dogs revealed no significant difference ($p < 0.05$) in the bioavailability of I with and without coadministration of II.

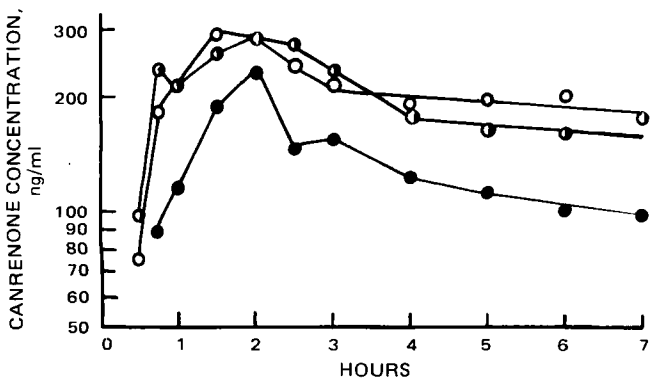

Figure 5—*Semilogarithmic plots of mean plasma levels of III. Key: ◑, tablets of I and II; ○, four 25-mg tablets of I; and ●, one 100-mg tablet of I.*

Pharmacokinetic Analysis—Since I is rapidly metabolized to III in the dog (21), it is reasonable to assume that biotransformation of I by a first-order process during the absorptive phase results in a first-order appearance or input of III and other metabolities in the plasma. An equation that describes the first-order input (or appearance) of III and its subsequent distribution and elimination from the plasma (central) compartment of a two-compartment open model is:

$$C_{p(t)} = -C'e^{-k_{III}(t)} + A'e^{-\alpha(t)} + B'e^{-\beta(t)} \qquad \text{(Eq. 1)}$$

where A', B', and C' are the zero-time plasma concentration intercepts, in nanograms per milliliter, derived from a graphical analysis of the plasma concentration–time profile by the method of residuals (24). As illustrated in Fig. 6, such an analysis was performed; the apparent rate constants k_{III} (input rate constant for III) and the hybrid rate constants α and β (for distribution and elimination of III) were obtained.

Table III illustrates some biopharmaceutical parameters estimated for III following oral dosing of I in polyethylene glycol solution and tablet dosage forms to four beagle dogs. The biological half-life, $(t/2)_\beta$, for the elimination of III for the plasma did not show any statistical difference ($p < 0.05$) regardless of the mode of administration of I. Moreover, no difference ($p < 0.05$) was observed for the *AUC* parameter of four 25-mg and one 100-mg tablets of I.

The apparent differences observed in the plasma concentration–time profile (Fig. 5) of III after oral dosing of one 100-mg and four 25-mg tablets of I may be attributed to the surface area of tablets and their aggregates exposed for dissolution and then absorption of I from the GI tract. The *AUC* parameter indicates that administration of polyethylene glycol 400 solutions of I resulted in significantly ($p <$

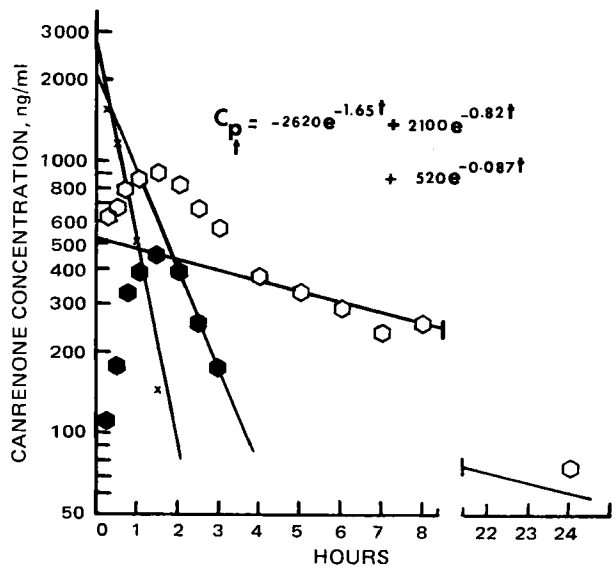

Figure 6—*Graphical analysis of mean plasma levels of III achieved in four dogs after oral dosing of I and II in polyethylene glycol 400 solution. Key: ○, mean plasma levels of III; ●, first residual plot; and ×, second residual plot.*

0.05) higher levels of III in the plasma than those achieved from tablet dosage forms.

Although such differences have not been observed in humans (25), it is possible that the presence of a cosolvent, such as polyethylene glycol, in the dog gut provided an effective dissolution medium for I, thus allowing increased amounts of the drug to be absorbed over a given period of the drug transit in the GI tract. This could explain the observed differences in the relative bioavailability of I in the plasma from a solution and tablet dosage forms.

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[x] To whom inquiries should be directed.

Dissolution Rate Equations in Column-Confined Dissolution

J. T. CARSTENSEN [x] and KAILASH DHUPAR

Abstract □ Equations are derived for the dissolution of a soluble solid in a column into a liquid stream. The equations are substantiated by experiments using oxalic acid dihydrate as a test substance. The dissolution rate constant, k, of oxalic acid dihydrate depends on linear velocity, $\bar{v}$ (centimeters per second), by the following equation: $k = (2.54 \pm 0.76) \times 10^{-4}\ \bar{v}$, where k is measured in centimeters per second.

Keyphrases □ Dissolution—soluble solid in a column into a liquid stream, equations derived □ Column-confined dissolution—soluble solid into a liquid stream, equations derived □ Solids, soluble—dissolution in a column into a liquid stream, equations derived

Numerous recent publications have discussed dissolution testing[1]. Pernarowski (1) cited 100 different published methods. LeHir (2) also described the technology in depth.

Some reported work relates to the use (or potential use) of column apparatuses for dissolution of dosage forms (3–13). The scope of this article is the experimental probing of an actual monodisperse system dissolving in a column at low liquid velocities[2]. Oxalic acid was used because it was tested previously under other conditions (14) and found to be easy to reproduce by controlled recrystallization from water.

EXPERIMENTAL

Oxalic acid[3] was recrystallized as the dihydrate and classified by sieving as described previously (14). The dissolution experiments were performed in a column such as the one shown in Fig. 1. A female ground joint (A_1) was fused[4] onto the top of a 50-ml buret. A male ground joint (A_2) was fused onto a sintered-glass filter in a 1-cm i.d. Pyrex tube. A stopcock (C), Pyrex tubing, and a female joint were fused onto the other end of the sintered-glass filter tube, and the tube was bent beyond C at the angle shown. The female joint fit the outlet

[1] There was no attempt here to make a complete bibliography; only articles directly relevant to the particular arguments in this study are cited. For a bibliography of methodology, the reader is referred to Ref. 1.

[2] Reynolds numbers between 10 and 100.

[3] Mallinckrodt analytical reagent oxalic acid dihydrate, Mallinckrodt Chemical Works, Saint Louis, Mo.

[4] All fusing was done by glass blowing using Pyrex glass and a gas–oxygen flame.