by the proximal tubular active transport mechanism, and drug–drug interactions may result from competition with this system. Since tolazamide and oxyphenbutazone are weakly acidic drugs, they might compete for active secretion by the proximal tubular active transport mechanism. The hypoglycemic action of acetohexamide is enhanced by the simultaneous administration of phenylbutazone by the same mechanics (8). Similarly, the hypoglycemic action of tolbutamide is enhanced by the presence of phenylbutazone (9). The value of β for tolazamide seems to decrease with increasing oxyphenbutazone, which could result in an enhanced hypoglycemic effect of tolazamide.

REFERENCES

(1) M. Rowland and S. B. Martin, *J. Pharmacokinet. Biopharm.*, **1**, 553 (1973).

(2) D. A. Hussar, *J. Am. Pharm. Assoc.*, **NS10**, 619 (1970).

(3) L. K. Christensen, J. M. Hansen, and M. Kristensen, *Lancet*, **2**, 1298 (1963).

(4) A. Sedman, and J. G. Wagner, "Manual for Autoan, A Decision-Making Pharmacokinetic Program," Publication Distribution Service, University of Michigan, Ann Arbor, Mich., 1974.

(5) J. G. Wagner, and M. Pernarowski, "Biopharmaceutics and Relevant Pharmacokinetics," Drug Intelligence, Hamilton, Ill., 1971, p. 257.

(6) L. F. Prescott, P. Roscoe, and J. A. H. Forrest, in "Biological Effects of Drugs in Relation to Their Plasma Concentrations," D. S. Davies and B. H. C. Prichard, Eds., University Park Press, London, England, 1973, p. 51.

(7) S. M. Pond, D. J. Birkett, and D. N. Wade, *Clin. Pharmacol. Ther.*, **22**, 573 (1977).

(8) J. G. Field, M. Ohta, C. Boyle, and A. Remer, *N. Engl. J. Med.*, **277**, 889 (1967).

(9) K. F. Ober, *Eur. Clin. Pharmacol.*, **7**, 291 (1974).

ACKNOWLEDGMENTS

Supported by the Research Institute of Pharmaceutical Sciences.

Influence of Food and Fluid Volume on Chlorothiazide Bioavailability: Comparison of Plasma and Urinary Excretion Methods

PETER G. WELLING ˣ and RASHMI H. BARBHAIYA *

Received February 23, 1981, from the *School of Pharmacy, University of Wisconsin, Madison, WI 53706.* Accepted for publication May 13, 1981.

* Present address: Department of Drug Metabolism and Pharmacokinetics, Bristol Laboratories, Syracuse, NY 13201.

Abstract □ The bioavailability of chlorothiazide from oral tablets was examined under fasting and nonfasting conditions in healthy male volunteers. Bioavailability was determined from urinary excretion data and plasma chlorothiazide concentrations. Two fasting treatments and one nonfasting treatment yielded similar plasma chlorothiazide profiles, characterized by sharply ascending and descending segments until 12–13 hr postdosing, followed by a prolonged period with variable and erratic chlorothiazide levels. A triexponential function that adequately described mean data from each treatment could not be applied to individual plasma curves because of their variable nature. Chlorothiazide absorption was not influenced by different accompanying water volumes in fasted individuals but was doubled when tablets were administered immediately after a standard meal. Urinary excretion of chlorothiazide correlated well with plasma drug concentrations; 48-hr urinary recovery accounted for 24.7% of a 500-mg dose in nonfasted subjects compared to 12.3 and 14.9% in fasted subjects receiving the drug with 20 and 250 ml of water, respectively. Observed relationships between chlorothiazide dosage and absorption efficiency are consistent with previous suggestions that chlorothiazide absorption from the GI tract is saturable and site specific.

Keyphrases □ Chlorothiazide—effect of food and fluid volume on bioavailability, plasma and urinary excretion methods compared □ Bioavailability—chlorothiazide, effect of food and fluid volume, plasma and urinary excretion methods compared □ Diuretics—chlorothiazide, influence of food and fluid volume on bioavailability, plasma and urinary excretion methods compared

Chlorothiazide is poorly absorbed after oral doses. Less than 25% of orally administered compound is recovered in urine, compared to >90% following intravenous injection (1–4). Inefficient GI absorption of chlorothiazide may be partly due to its low aqueous solubility but also may be related to saturable and site-specific absorption (5, 6).

The presence of food and the variation in fluid volumes with which a drug is administered can markedly influence drug bioavailability (7–9) with possible clinical consequences (10). The poor and possibly site-specific absorption characteristics of chlorothiazide make it conducive to a bioavailability study under varying dosage conditions.

This report describes chlorothiazide bioavailability following oral doses of commercial tablets to healthy male volunteers in fasting and nonfasting states and with small and large accompanying water volumes. Plasma concentrations and urinary excretion of chlorothiazide were compared using recently described high-pressure liquid chromatographic (HPLC) procedures (11).

EXPERIMENTAL

Subjects—Nine healthy male volunteers[1], 22–33 years of age (mean 27) and weighing 62–88 kg (mean 74), participated in the study after giving informed consent. No subject had histories of drug allergy.

Protocols—Subjects were instructed to take no drugs for 1 week before the study and no drugs other than chlorothiazide during the study. No caffeine-containing beverages were permitted for 1 day before or during the plasma and urine sampling periods following each chlorothiazide dose.

Chlorothiazide[2] was administered as three oral treatments: Treatment A, two 250-mg tablets with 250 ml of water following an overnight fast; Treatment B, two 250-mg tablets with 20 ml of water following an overnight fast; and Treatment C, two 250-mg tablets with 250 ml of water given immediately after a standard breakfast (cornflakes with milk, 150 ml (5 oz) orange juice, two poached eggs, two slices of toast, and one cup of caffeine-free coffee).

Subjects were randomly divided into three groups of three, and the treatments were administered according to a 3 × 3 Latin square design at 1-week intervals. Each treatment was given after an overnight fast; no food, apart from the standard breakfast for those receiving Treatment

[1] Technical staff and graduate students.

[2] Chlorothiazide tablets USP (250 mg), lot 559-197, Lederle Laboratories, American Cyanamid Co., Pearl River, NY 10965.

0022-3549/82/0100-0032$01.00/0

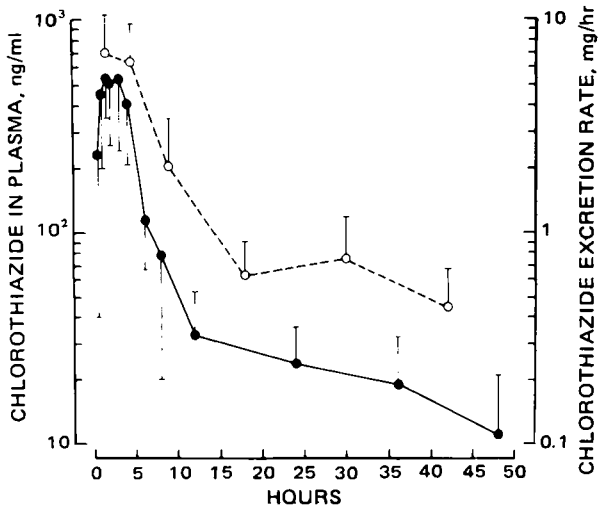

Figure 1—*Mean plasma concentrations (●) and urinary excretion rates (○) of chlorothiazide following Treatment A. Error bars indicate one standard deviation.*

C, was permitted until 4 hr after each chlorothiazide dose, after which time normal eating and drinking were permitted.

On the morning of each treatment, 250 ml of water was ingested on rising, at least 1 hr before dosing. Chlorothiazide was administered at 8 am. Tablets were swallowed whole, without chewing.

Blood samples (10 ml) were taken from a forearm vein into vacuum tubes[3] containing heparin as anticoagulant immediately before and then serially to 48 hr after dosing. Urine was collected immediately before and then quantitatively at intervals up to 48 hr after dosing. Plasma was separated by centrifugation, and plasma and urine samples were stored at −20° until assayed, generally within 2 weeks.

Analytical—Concentrations of chlorothiazide in plasma and in urine were determined by the HPLC methods described previously (11). The methods, both involving extraction steps prior to chromatography, are linearly sensitive to chlorothiazide concentrations of 2–100 μg/ml in urine and 10–750 ng/ml in plasma with coefficients of variation of <10% within these concentration ranges. The occasional plasma samples that contained chlorothiazide concentrations of >750 ng/ml were appropriately diluted with water and reassayed. Dilution with water had no effect on the extraction efficiency of chlorothiazide or the internal standard.

Data Analysis—The irregular nature of plasma chlorothiazide curves in individual subjects precluded data description in terms of a general mathematical function. However, the means of plasma curves obtained from each treatment were fitted to a triexponential function using

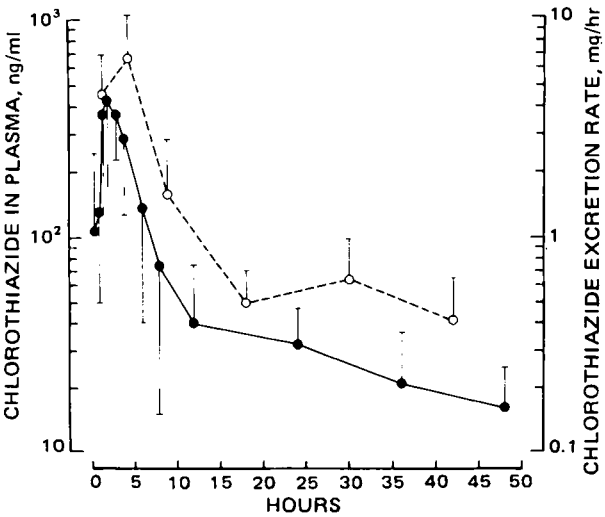

Figure 2—*Mean plasma concentrations (●) and urinary excretion rates (○) of chlorothiazide following Treatment B.*

[3] Vacutainer.

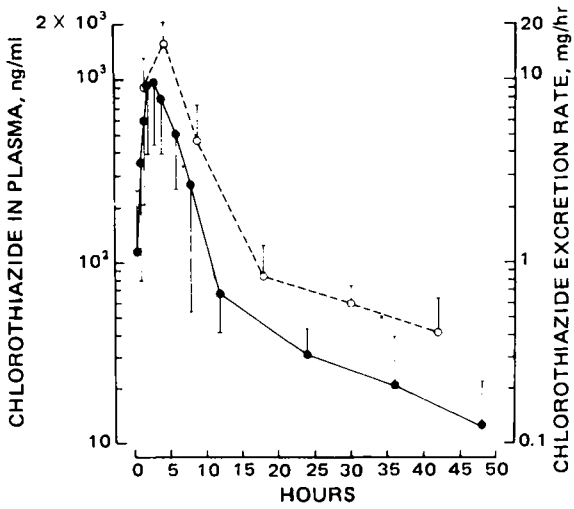

Figure 3—*Mean plasma concentrations (●) and urinary excretion rates (○) of chlorothiazide following Treatment C.*

standard graphical procedures. Improved parameter estimates, together with statistical analysis, were obtained using the computer program NREG (12) on a digital computer[4].

Plasma and urine data from the three treatments were compared by analysis of variance for a crossover design. Differences between individual treatments were examined by Tukey's test (13).

Reagents—Human plasma for assay standardization was purchased[5]. Human drug-free urine was obtained from male donors as required. Chlorothiazide[6], hydrochlorothiazide[6], and hydroflumethiazide[7] of reference standard quality for chromatography and methanol[8], acetonitrile[8], acetic acid[9], sodium perchlorate[10], and perchloric acid[11] of analytical grade quality were used as received.

RESULTS

Plasma Chlorothiazide Levels—The mean plasma chlorothiazide levels resulting from each treatment are shown in Figs. 1–3. For comparison, the mean plasma curves are combined in Fig.4.

The overall characteristics of the chlorothiazide plasma curves were similar for all treatments. Levels reached peak values at 2–3 hr and then

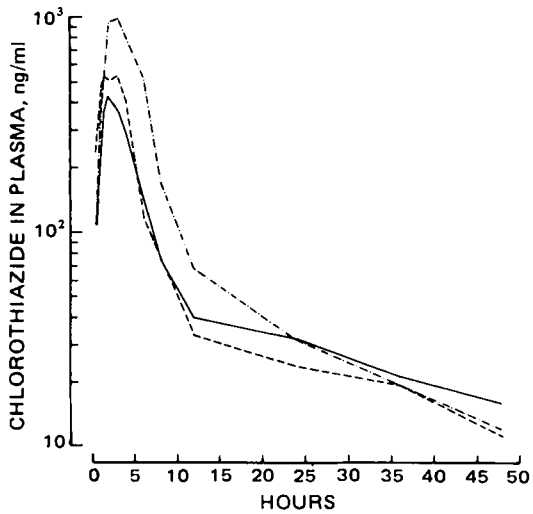

Figure 4—*Mean plasma concentrations of chlorothiazide following Treatments A (- -), B (—), and C (-•-•-).*

[4] Univac model 1110, Madison Academic Computer Center, Madison, Wis.
[5] American Red Cross, Madison, Wis.
[6] Merck Sharp and Dohme, West Point, Pa.
[7] Bristol Laboratories, Syracuse, N.Y.
[8] Burdick & Jackson, Muskegon, Mich.
[9] Allied Chemical Corp., Morristown, N.J.
[10] Fisher Scientific Co., Fair Lawn, N.J.
[11] J. T. Baker Chemical Co., Phillipsburg, N.J.

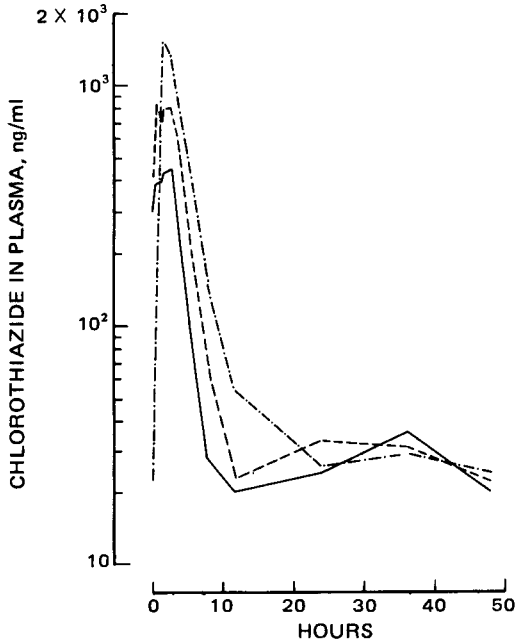

Figure 5—*Plasma concentrations of chlorothiazide in one subject following Treatments A (- -), B (—), and C (- • - •).*

declined rapidly until 12–13 hr. At later sampling times, mean chlorothiazide levels declined more slowly.

Despite the similarity in the plasma chlorothiazide profiles from the treatments, significant differences existed between treatments in the absolute values obtained. Chlorothiazide concentrations at each sampling time were statistically indistinguishable between the two fasting treatments, A and B. However, Treatment C gave rise to drug concentrations that were significantly higher compared to both fasting treatments at 2, 3, 4, 6, and 8 hr and significantly higher than Treatment A alone at 1.5 hr and then Treatment B alone at 12 hr. The mean peak chlorothiazide level from Treatment C (1107 ± 577 ng/ml) was approximately twofold higher than the levels from Treatments A (513 ± 205 ng/ml) and B (681 ± 214 ng/ml); the mean trapezoidal area under the plasma level *versus* time curve from 0 to 48 hr for Treatment C (6.4 ± 2.5 μg/hr/ml) was also twofold larger than the areas for Treatments A (3.0 ± 1.0 μg/hr/ml) and B (3.4 ± 1.1 μg/hr/ml). The mean time of peak levels from Treatment C (3.7 ± 2.1 hr) was significantly longer than those from Treatments A (2.0 ± 0.8 hr) and B (2.1 ± 1.0 hr).

Analysis of the mean chlorothiazide profiles in Figs. 1–4 in terms of a simple, triexponential function yielded the values in Eqs. 1–3 for Treatments A–C, respectively:

$$C' = -1627e^{-0.70t} + 1526e^{-0.38t} + 56.6e^{-0.026t} \quad \text{(Eq. 1)}$$

$$C' = -2626e^{-0.73t} + 2547e^{-0.43t} + 48.7e^{-0.029t} \quad \text{(Eq. 2)}$$

$$C' = -2914e^{-0.58t} + 2658e^{-0.26t} + 108e^{-0.046t} \quad \text{(Eq. 3)}$$

In the equations, C' is the plasma chlorothiazide concentration at time t. The coefficients of determination between mean plasma levels and those predicted from the respective equations were 0.97, 0.98, and 0.95.

The high coefficients of determination imply that chlorothiazide plasma levels may be adequately described by such a function following oral doses and that the mean terminal phase plasma half-life varied from 15 to 27 hr. Examination of individual chlorothiazide curves, however, shows that the apparent slow terminal elimination phase was largely artifactual, resulting from the averaging of individual data. Typical drug level curves for one subject are shown in Fig. 5. The steeply ascending and descending segments are well defined for all treatments, but drug levels during the post 12-hr period are erratic, exhibiting a "saw-tooth" effect. Thus, it was not possible to describe this section of the curve mathematically.

If the sharply descending portion of the chlorothiazide concentration curve is considered separately, the mean half-lives obtained from this segment are 2.2 ± 0.7, 2.2 ± 1.0, and 2.5 ± 0.8 hr from Treatments A, B, and C, respectively.

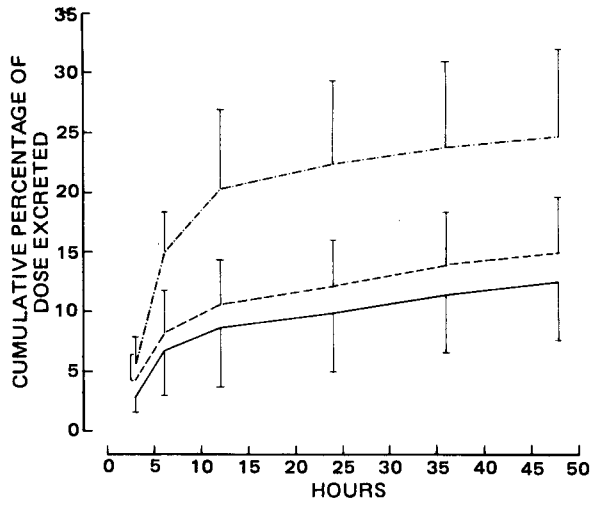

Figure 6—*Mean cumulative percentage of chlorothiazide dose excreted in urine following Treatments A (- -), B (—), and C (- • - •). Error bars indicate one standard deviation.*

Urinary Excretion of Chlorothiazide—The mean cumulative excretion of chlorothiazide during the 48-hr postdosing period is shown in Fig. 6. Following Treatment A, 8.6% of the administered dose was recovered at 12 hr, 9.8% at 24 hr, and 12.3% at 48 hr. Following Treatment B, recoveries at these times were 10.5, 12.1, and 14.9%, respectively. In contrast, the recoveries from Treatment C were 20.3, 22.3, and 24.7% at 12, 24, and 48 hr, respectively. The recovery values from Treatment C were significantly higher than those from both fasted treatments at all urine sampling intervals. The urinary recovery of chlorothiazide from the fasting treatments was similar to values reported previously (3, 4).

The renal clearances of chlorothiazide, calculated by dividing the quantity of drug recovered in 48-hr urine by the area under the chlorothiazide plasma curve during the same time period, were 3.56 ± 1.07, 37.3 ± 1.06, and 3.46 ± 11.0 ml/min from Treatments A, B, and C, respectively. The high renal clearance of chlorothiazide indicate that it is eliminated by both renal filtration and secretion.

DISCUSSION

Until recently, the low circulating levels of chlorothiazide following therapeutic doses prevented accurate description of its pharmacokinetics; bioavailability determinations were based on urinary excretion data (3). The recent development of a sensitive assay for chlorothiazide in plasma (6) has made it possible to examine the pharmacokinetics of chlorothiazide in plasma and to compare quantitatively the plasma profiles and urinary excretion rates resulting from oral chlorothiazide doses.

The plasma profiles obtained in the present study were similar to those reported by Shah et al. (3). In their study, peak chlorothiazide plasma levels of 245 and 500 ng/ml were obtained in two subjects 3 hr after a 500-mg tablet dose. Plasma levels during the 12–48-hr sampling period also exhibited a variable, saw-tooth effect.

The cause of the variable chlorothiazide plasma levels during later sampling times is not clear but may be related to drug release from extravascular storage depots or to an enterohepatic cycling effect. It is a consistent phenomenon and occurred in every subject.

The close similarity of plasma profiles and urinary excretion rates of chlorothiazide following the Treatments A and B indicates that, unlike some therapeutic agents (14–16), chlorothiazide absorption is not influenced by the accompanying fluid volume when taken on an empty stomach. However, chlorothiazide absorption efficiency is doubled when taken immediately following a meal.

The increased but delayed absorption of chlorothiazide in nonfasting individuals can possibly be explained in terms of an altered stomach emptying rate and saturable, site-specific absorption. Solid food delays stomach emptying (7) and is likely to reduce the rate at which chlorothiazide passes the absorption site and the drug concentration at the absorption surface. These combined effects give rise to more efficient but somewhat slower drug absorption into the systemic circulation. Propantheline bromide, a potent inhibitor of stomach emptying and intestinal motility, has been shown to increase GI absorption of chlorothiazide in dogs (5). Increased systemic availability in the presence of food, due

to nonsaturation of specific absorption sites, was demonstrated previously for riboflavin (17).

Increasing the accompanying water volume in fasted subjects might be expected to increase the dissolution rate of chlorothiazide and to accelerate the stomach emptying rate (7). However, neither factor should markedly alter the absorption efficiency of chlorothiazide. Faster stomach emptying would increase the rate at which drug passes the active absorption site and, hence, reduce its bioavailability. Faster dissolution should have little effect since chlorothiazide has been shown to be only 25% bioavailable when dosed as an oral solution (6).

It is instructive to compare chlorothiazide plasma levels and urinary excretion as indicators of chlorothiazide bioavailability. The mean urinary recoveries of chlorothiazide from Treatments A, B, and C were 12.3, 14.9, and 24.7% of the dose, respectively, while the respective areas under the plasma curves to 48 hr were 3.0, 3.4, and 6.4 μg hr/ml, indicating excellent agreement between plasma and urine data. The overall correlation between the percentage of dose excreted and the areas under the plasma level curves was 0.726 ($p < 0.001$), while the correlation between peak drug levels in plasma and percent excretion was somewhat lower at 0.480.

Similarly, the mean ratios of the percentage of dose excreted between Treatments A and B, A and C, and B and C were 0.87, 0.51, and 0.63; the equivalent ratios of areas under the plasma curves between these treatments were 0.92, 0.47, and 0.57.

To compare the kinetics of chlorothiazide recovery in urine with those of drug loss from plasma, the urinary excretion rates following the three treatments were calculated at the midpoint of each urine collection interval and the mean values were plotted along with the plasma levels in Figs. 1–3. Comparison of the curves indicates close similarity between the urinary excretion rates and plasma chlorothiazide levels throughout the entire sampling period.

Chlorothiazide absorption, which is normally poor, is doubled by the presence of food. This fact, together with the insensitivity of chlorothiazide absorption to varying fluid volumes, supports the view that chlorothiazide absorption is saturable and occurs at a particular site in the GI intestinal tract (5, 6). For optimal absorption, chlorothiazide tablets should be taken with or immediately after meals.

REFERENCES

(1) R. E. Kauffman and D. L. Azarnoff, *Clin. Pharmacol. Ther.*, **14**, 886 (1973).

(2) M. C. Meyer and A. B. Straughn, *Curr. Ther. Res.*, **22**, 573 (1977).

(3) V. P. Shah, V. K. Prasad, B. E. Cabana, and P. Sojka, *ibid.*, **24**, 366 (1978).

(4) A. B. Straughn, A. P. Melikian, and M. C. Meyer, *J. Pharm. Sci.*, **68**, 1009 (1979).

(5) D. E. Resetarits and T. E. Bates, *J. Pharmacokinet. Biopharm.*, **7**, 463 (1979).

(6) P. G. Welling, D. M. Walter, R. B. Patel, R. H. Barbhaiya, W. A. Porter, G. L. Amidon, T. S. Foster, V. P. Shah, J. P. Hunt, and V. K. Prasad, *Curr. Ther. Res.*, **29**, 815 (1981).

(7) P. G. Welling, *J. Pharmacokinet. Biopharm.*, **5**, 291 (1977).

(8) A. Melander, *Clin. Pharmacokinet.*, **3**, 337 (1978).

(9) R. D. Toothaker and P. G. Welling, *Ann. Rev. Pharmacol. Toxicol.*, **20**, 173 (1980).

(10) P. G. Welling, *Prog. Drug Metab.*, **4**, 131 (1980).

(11) R. H. Barbhaiya, T. A. Phillips, and P. G. Welling, *J. Pharm. Sci.*, **70**, 291 (1981).

(12) "MACC Nonlinear Regression Routines," Academic Computer Center, University of Wisconsin, Madison, Wis.

(13) J. Neter and W. Wasserman, "Applied Linear Statistical Models," Richard D. Irwin, Inc., Homewood, Ill., 1974, p. 475.

(14) P. A. Koch, C. A. Schultz, R. J. Wills, S. L. Hallquist, and P. G. Welling, *J. Pharm. Sci.*, **67**, 1533 (1978).

(15) P. G. Welling, L. L. Lyons, W. A. Craig, and G. A. Trochta, *Clin. Pharm. Ther.*, **17**, 475 (1975).

(16) P. G. Welling, H. Huang, P. A. Koch, W. A. Craig, and P. O. Madsen, *J. Pharm. Sci.*, **66**, 549 (1977).

(17) G. Levy and W. J. Jusko, *ibid.*, **55**, 285 (1966).

ACKNOWLEDGMENTS

Funds for this study were provided by National Institutes of Health Grant GM 20327.

Tray Drying of Pharmaceutical Wet Granulations

J. T. CARSTENSEN* [x] **and M. A. ZOGLIO**[‡]

Received August 5, 1980, from the *School of Pharmacy, University of Wisconsin, Madison, WI 53706 and [‡]Merrell-National Laboratories, Cincinnati, OH 45201. Accepted for publication May 15, 1981.

Abstract □ It is shown that in tray drying wet granulated materials, the expected log–linear plots give slopes that are inversely proportional to the bed depth, rather than to the depth squared. A model is proposed for this giving diffusion coefficents of the order of magnitude expected for liquid-water diffusion. The temperature dependence also suggests that this is the rate-limiting process rather than vapor diffusion.

Keyphrases □ Tray drying—wet granulated materials, mathematical models □ Models, mathematical—tray drying of wet granulated materials □ Granulations—tray drying, mathematical models

The drying of granulations is an important pharmaceutical operation and tray drying is a frequently used method of water removal. The way in which drying takes place from a tray (1–3) can be visualized in several ways. The drying could be a function of the individual granule rather than of the mass of granules, *i.e.*, the bed. In that case, the bed thickness would not be a factor (in fluid bed drying it is not of great importance). However, bed thickness is important, and the drying is a function of the properties of the bed. In this case there are two possibilities: (*a*) either the movement through the void space between the granules is important (*i.e.*, the vapor diffusion is rate determining), or (*b*) the drying is primarily from the *bed* surface, and liquid movement up through the bed maintains a water concentration profile in the bed.

BACKGROUND

In the following discussion, the nomenclature outlined in Fig. 1 will be used. The bed is l-cm deep, has a porosity of ϵ (*i.e.*, a solids fraction of $(1 - \epsilon)$). It has a cross-sectional area of A cm^2. The density of an anhydrous granule is ρ gm/cm^3. The wet granulation before drying contains C^* g of moisture per g of anhydrous solid, and after drying contains c g of moisture per g of anhydrous solid. If c is the equilibrium concentration, then $C^* - c = C_0$ is the initially removable moisture concentration, and $C' - c = C$ is the moisture concentration which is removable at time t. The latter is the quantity which will be dealt with in the following discussion. Granules containing c g of moisture/g of anhydrous weight will be denoted dry. If x is a distance coordinate measured from the top of the bed (Fig. 1), then the diffusional equation governing the situation is Fick's law, *i.e.*, at time t:

$$\partial C/\partial t = D\partial^2 C/\partial x^2 \qquad \text{(Eq. 1)}$$

where D is the diffusion coefficient of water. Crank (4) solved this equation using the following boundary conditions: $C = 0$ at $x = 0$, for t