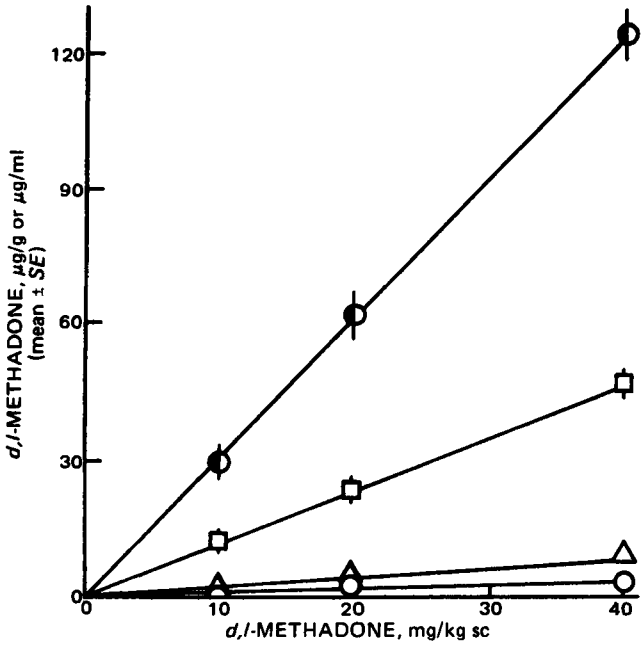

Figure 3—*Tissue* d,l-*methadone levels in the rat 60 min after subcutaneous administration of various* d,l-*methadone doses. Key:* ◐, *lung;* □, *liver;* △, *brain; and* ○, *serum.*

that these metabolites are extracted into the organic phase. However, they do not form fluorophores with paraformaldehyde. Also, morphine, diacetylmorphine (heroin), and codeine do not react with paraformaldehyde to form fluorophores. Cocaine forms a fluorophore but is not extracted from the aqueous phase (pH 9.2) under the conditions employed. Therefore, cocaine probably will not interfere in the methadone assay. Meperidine, amphetamine, and quinine form fluorophores with paraformaldehyde, and they are extracted into the organic phase. To remove the interference from these drugs, separation prior to their extraction into the organic phase is necessary.

Table II gives the levels of *d,l*-methadone in lung, liver, brain, and serum at various time intervals after 20 mg of *d,l*-methadone/kg was administered to rats subcutaneously. Figure 3 shows that the tissue levels were dose dependent.

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Bioavailability of Chlorothiazide Tablets in Humans

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Abstract □ A urinary excretion bioavailability study was conducted in 12 healthy male subjects to evaluate three 250-mg and three 500-mg chlorothiazide tablet products. The study was a crossover design, and urine samples were collected 1, 2, 3, 4, 6, 8, 12, and 24 hr after administration of each dose. The resulting data were statistically analyzed for significant differences in cumulative percent of dose excreted at each sampling time, total drug recovery after 24 hr, maximum excretion rate, and time of maximum excretion rate. No statistically significant differences were found between the three 250-mg tablets tested. The urinary drug recovery after administration of one of the 500-mg products was significantly ($p < 0.05$) lower than that from the other two 500-mg tablets. The total mean recovery from each product ranged from only 11 to 20%, indicating that in general chlorothiazide was not well absorbed following oral administration. Attempts at correlating the urinary excretion data with the dissolution rate determinations were not successful.

Keyphrases □ Chlorothiazide—bioavailability, tablets, humans, urinary recovery □ Diuretics—chlorothiazide, tablets, bioavailability, humans □ Bioavailability—chlorothiazide tablets, humans

The Food and Drug Administration recently implemented a bioequivalence requirement for chlorothiazide tablets (1), and available information indicates that oral chlorothiazide dosage forms might exhibit bioavailability problems. The drug solubility is <1 mg/ml at pH ≤ 7 (2–4), and the usual oral dose is 0.5–1.0 g.

On the basis of urinary excretion studies, chlorothiazide appears to be incompletely absorbed from the GI tract of animals and humans (4–6). These studies reported 10–58% urinary recoveries of the oral dose administered to humans. The low urinary recovery of unchanged drug is not thought to be the result of other elimination routes since no metabolites have been identified and the urinary recovery of intravenously administered chlorothiazide approaches 100% (4, 6, 7).

In view of the potential for oral chlorothiazide dosage

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Table I—*In Vitro* Analysis of Chlorothiazide Tablets

Product[a]	Labeled Dose, mg	Assayed Percent of Label	Mean Disintegration Time, min[b]	Mean Time for Dissolution, min			
				30%	40%	50%	60%
1	250	105.8	1.7 (6)	4	10	34	72
2	500	99.4	0.5 (6)	10	57	110	>120
3	250	98.6	4.6 (12)	3	4	8	21
4	250	101.2	3.1 (6)	9	23	39	63
5	500	101.9	7.7 (6)	10	44	105	>120
6	500	93.5	16.4 (18)	6	19	47	>120

[a] Distributor (manufacturer if different from distributor) and lot numbers are as follows: 1, Merck Sharp & Dohme, S3420; 2, Merck Sharp & Dohme, T0972; 3, Econo-Rx (Bolar), 035437; 4, Columbia Medical Co. (Bolar), 015319; 5, Spencer Mead (Bolar), 065574; and 6, Econo-Rx (Bolar), 035438. [b] Tablets taking >30 min to disintegrate were averaged in as 30 min. Number in parentheses indicates number of tablets tested.

forms to exhibit incomplete or erratic absorption, a study was undertaken to evaluate the relative bioavailability of three lots of 250-mg and three lots of 500-mg chlorothiazide tablets manufactured by two companies. Attempts also were made to relate the *in vivo* data to the *in vitro* tablet disintegration and dissolution characteristics.

EXPERIMENTAL

Product Selection—Six products containing 250 or 500 mg of chlorothiazide were obtained through a local pharmacy. The six products (Table I) were from five different distributors but actually only represent two manufacturers. After the study was completed, it was learned that Products 3–6 had never been the subject of a New Drug Application.

***In Vitro* Studies**—Each product was evaluated for compliance with USP XIX (8) specifications for tablet content and disintegration. Although the USP XIX does not contain a chlorothiazide dissolution rate specification, dissolution testing was undertaken to provide *in vitro* data that might be useful for correlation with data from the *in vivo* studies.

The USP XIX rotating-basket apparatus was employed, using 900 ml of distilled water maintained at 37 ± 0.5° as the dissolution medium. The basket was rotated at 100 rpm, and 0.5-ml aliquots were removed every 5 min and diluted to 25 ml with distilled water. The resulting solutions were analyzed spectrophotometrically at 220 nm. The dissolution data were corrected for drug loss due to sample removal.

Clinical Study Protocol—Twelve adult males, between the ages of 23 and 28 years, volunteered to participate and provided written informed consent. Each subject was screened regarding general health and any known drug allergies. All subjects underwent a urine analysis and a hematologic and blood chemistry[1] analysis to ensure that they were in good health. The subjects ranged in height from 97 to 116 cm and in weight from 61.4 to 95.5 kg. Each subject was instructed to avoid any other medication during the study.

The 12 subjects received one of six different chlorothiazide tablets at weekly intervals for 6 weeks. The administration sequence was based on a crossover matrix to minimize any residual or cumulative effects of the preceding doses (9).

The tablets were administered in the morning following an overnight fast. No food or liquid other than water was permitted until 4 hr following dose ingestion. Just prior to dose administration the subjects voided a urine sample to be used as a blank. Following tablet administration, the subjects collected urine samples at 1, 2, 3, 4, 6, 8, 12, and 24 hr. The subjects were instructed to empty their bladders as completely as possible at each voiding. The sample volume was measured, and a portion was saved and frozen until analysis. Samples voided at other times were also measured and a portion was saved.

Data Analysis—Analysis of variance was used to determine significant differences ($p < 0.05$) between subjects, weeks, and drug products for cumulative percent of drug excreted at each sampling time, maximum excretion rate, time of maximum excretion rate, and cumulative drug excreted at 24 hr. The Newman–Keuls *a posteriori* test (10) was applied to evaluate where statistically significant differences occurred among the various parameters.

Urine Assay Methodology—All urine samples were analyzed in duplicate for chlorothiazide by a previously described spectrophotometric method (6) based on a modification of the procedure developed by Baer *et al.* (3).

[1] SMA 12/60.

RESULTS AND DISCUSSION

***In Vitro* Studies**—Table I summarizes the results of the *in vitro* tests. The analysis of a 20-tablet composite of each lot indicated that each product was within the 93–107% limits specified by the USP XIX for chlorothiazide tablets. Tablet disintegration tests were performed with and without disks in the disintegration chambers, even though USP XIX specifies that disks should be used. With the disks present, the six tablets of each product, except Product 1, disintegrated in less than 1 min; Product 1 disintegrated between 1.5 and 2.8 min. These times are well within the 30-min limit provided for in the USP.

When the disks were removed, there was greater variation in disintegration times among the products. Product 3 had one tablet out of 12 that did not disintegrate within 60 min. Seven of the 18 tablets tested for Product 6 did not disintegrate within 30 min, and two of the tablets did not disintegrate within 60 min. The mean disintegration time for the six products ranged from 0.5 (Product 2) to 16.4 (Product 6) min. When determining the average disintegration time, the maximum time utilized for any tablet was the USP limit of 30 min, even for tablets requiring more than 2 hr to disintegrate.

There was a large range in the tablet dissolution times as indicated in Table I. In view of the limited drug solubility, the 900 ml of water utilized as the dissolution medium probably was not sufficient to permit tablet dissolution under "sink conditions" (11). Therefore, even after 2 hr, the 500-mg tablets had not reached 60% dissolution.

Cumulative Percent of Dose Excreted—The mean cumulative percent of chlorothiazide excreted unchanged at each sampling time for the six products tested is illustrated in Fig. 1.

The mean cumulative 24-hr urinary recovery was quite low, ranging from 10.9% for Product 6 to 19.7% for Product 1. The greatest cumulative recovery observed in any one subject after single-dose administration

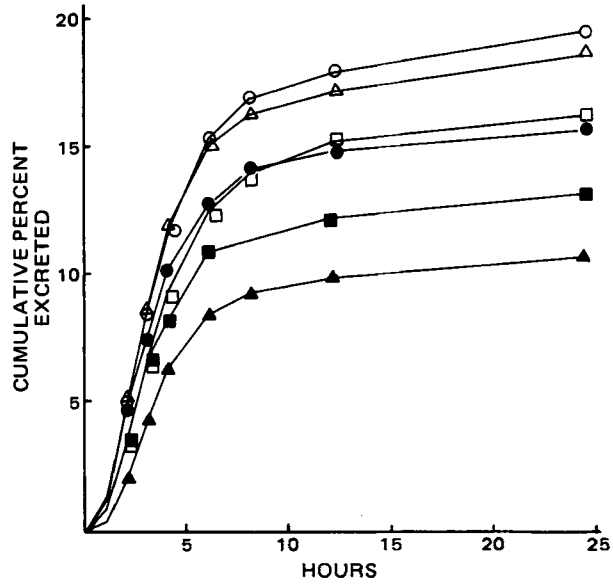

Figure 1—*Mean cumulative percent of chlorothiazide excreted following the oral administration of six tablet products. Each data point is the mean calculated for 12 subjects. Code numbers correspond to the products identified in Table I:* ○, *Product 1;* □, *Product 2;* △, *Product 3;* ●, *Product 4;* ■, *Product 5; and* ▲, *Product 6.*

Table II—Newman–Keuls *a Posteriori* Test for Significant Product Differences in Parameters Studied

Parameter	Product Ranking[a] (Lowest to Highest)					
Cumulative percent of dose excreted at:						
1 hr	6	4	2	5	1	3
2 hr	6	5	2	4	3	1
3 hr	6	5	2	4	3	1
4 hr	6	5	2	4	1	3
6 hr	6	5	2	4	3	1
8 hr	6	5	2	4	3	1
12 hr	6	5	4	2	3	1
24 hr	6	5	4	2	3	1
Total milligrams excreted	4	3	1	6	5	2
Maximum excretion rate, % of dose/hr	6	5	2	4	1	3
Time of maximum excretion rate	5	3	4	1	2	6

[a] Products underlined by a common line did not differ significantly ($p > 0.05$). See Table I for product identification.

was 33.3%, and recovery of more than 30% occurred only one other time. The cumulative 24-hr urinary recoveries also exhibited high coefficients of variation, ranging from 30% for Product 2 to 46% for Product 5. Such variability would be consistent with a poorly and erratically absorbed dosage form. These data may be contrasted to a recently completed study of 25- and 50-mg hydrochlorothiazide tablets in which ~75% of the administered dose was excreted as unchanged drug, and the mean values for the individual products exhibited coefficients of variation between 8 and 16% (12).

Table II summarizes the statistically significant differences among the products at each sampling time. There were differences ($p < 0.05$) at all sampling times in terms of cumulative percent of chlorothiazide excreted. Product 6 exhibited the lowest cumulative percent excreted at each sampling time, and Product 5 exhibited the next lowest recovery at all times except at the 1-hr sampling time.

In general, the three 500-mg chlorothiazide tablets (Products 2, 5, and 6) exhibited lower cumulative percent excretion than the 250-mg tablets at the various sampling times. Product 6 was significantly lower ($p < 0.05$) in cumulative percent excretion than one or more products at each sampling time. At 24 hr, the percent recovery for Products 5 and 6 was significantly lower ($p < 0.05$) than for Product 1, and the percent recovery for Product 6 also was significantly lower than for Products 2 and 3.

Other Urinary Excretion Parameters—Table III summarizes the mean values for maximum excretion rate, time of maximum excretion rate, and total milligrams of drug excreted after 24 hr. The results of the statistical analysis are presented in Table II.

The time of maximum excretion rate did not differ significantly among the six products ($p > 0.05$), although Product 6, which exhibited the lowest urinary recovery of drug, did require the longest time to achieve peak excretion. Since urine samples were collected only hourly during the first 4 hr of the study, the accuracy of the peak excretion time is limited.

As expected, the total chlorothiazide recovered in the urine after 24 hr indicated a greater recovery from the 500-mg tablets than from the 250-mg tablets. The drug recovered from Product 2 was significantly greater ($p < 0.05$) than from any other product, including the two other 500-mg tablets. The recovery from Product 6, a 500-mg tablet, did not differ significantly ($p > 0.05$) from that obtained with the three 250-mg products. On the basis of amount of drug excreted in 24 hr for Products 5 and 6, expressed as a percent relative to Product 2, the bioavailabilities of these two products were 81 and 66%, respectively. Furthermore, the recoveries from Products 5 and 6 did not differ significantly from the recovery from Product 2, which contained 50% as much drug. There was not a significant difference in urinary recovery among the three products containing 250 mg of chlorothiazide. The bioavailabilities of Products 3 and 4, based on the total amount of drug recovered expressed as a percent relative to Product 1, were 95 and 80%, respectively.

When the absorption and disposition processes operative for a drug exhibit linear kinetics, a proportionality between dose administered and amount of drug eliminated is expected. Thus, the percent of dose eliminated and the maximum excretion rate expressed as a percent of dose should be independent of the dose administered. The data obtained in the present study indicate that drug recovery after the 500-mg doses was not twice that after the 250-mg doses. The observed lack of proportionality between dose and urinary recovery could not be attributed to nonlinear elimination kinetics since previously reported studies involving intravenous administration of 500-mg chlorothiazide doses resulted in over 90% urinary recovery of unchanged drug (4, 6, 7).

Furthermore, a preliminary pilot study (6) involving the administration of 250 and 500-mg oral doses as a solution to two subjects resulted in an urinary recovery that was only 30% of the administered dose. Previous investigators (13), using a specific high pressure liquid chromatographic (HPLC) assay, also noted a lack of dose proportionality in the urinary recovery of chlorothiazide administered to dogs. The drug was quantitatively recovered after intravenous administration, but the recoveries declined from 70 to 26% as the oral dose was increased from 125 to 750 mg.

Following completion of the present study, a report (14) appeared which indicated that various modifications of the Bratton–Marshall assay for chlorothiazide may be subject to interferences from urinary constituents, which vary in concentration at each urine sampling time. In a noncrossover study (14) involving oral administration of 250- and 500-mg chlorothiazide tablets to two groups of two subjects, the colorimetric method employed in the present study underestimated by 1% the total 24-hr urinary chlorothiazide recovery in two subjects. In the other two subjects, the recovery was overestimated by 2 and 5.6% compared to recoveries determined using a HPLC assay. However, even with an HPLC assay, the reported 24-hr recoveries were only 5–10% for the 500-mg tablets and 14–20% for the 250-mg tablets. These workers (14) also observed that an additional 4–11% of the administered dose could be accounted for when the urinary collection was extended to 48 hr.

In the present study, less than 2% of the administered dose was recovered in the 12–24-hr collection period. Furthermore, the data shown in Fig. 1 suggest that extending the urine collection time would not have greatly increased the overall percent of administered drug recovered for each dosage form. In general, chlorothiazide apparently is not well absorbed following oral administration.

Subject and Week Differences—Analysis of variance indicated significant subject differences ($p < 0.05$) for each parameter examined, except for the time of maximum excretion rate. There were no significant differences ($p > 0.05$) among weeks.

***In Vitro–In Vivo* Relationships**—Attempts were made to correlate the *in vivo* data with the results of the disintegration time and dissolution rate determinations. Because of the large variability in the urinary excretion data at the early sampling times, only the 24-hr *in vivo* data were employed for correlation purposes. The time for 30% dissolution of the six products ranged from 3 to 10 min. The time for 60% dissolution ranged

Table III—Average Total Cumulative Milligrams, Maximum Excretion Rate, and Time of Maximum Excretion Rate[a]

Product[b]	Dose, mg	Maximum Excretion Rate, % of dose/hr	Time of Maximum Excretion Rate, hr	Total Milligrams Excreted in 24 hr
1	250	4.72 (41.8)	2.9 (46.8)	49.32 (36.45)
2	500	3.79 (31.6)	3.3 (41.4)	81.99 (29.91)
3	250	4.82 (44.5)	2.8 (35.3)	46.81 (42.32)
4	250	4.26 (42.4)	2.8 (31.4)	39.42 (32.15)
5	500	3.18 (55.4)	2.7 (39.3)	66.48 (46.11)
6	500	2.84 (38.3)	3.3 (26.6)	54.30 (31.10)

[a] Data presented as mean values for 12 subjects. Coefficient of variation (percent) is indicated in parentheses. [b] See Table I for product identification.

from 21 to 72 min for the three 250-mg tablets and was >2 hr for all three 500-mg tablets.

Because of the small range in 30% dissolution times and the excessively long 60% dissolution times, only the times for 40 and 50% dissolution were compared to the 24-hr cumulative percent recoveries. The correlation between dissolution time and urinary excretion was poor, although the attempt at correlation may have failed because of the previously cited lack of sink conditions during the dissolution rate determinations. The correlation coefficients, using the times for 40 and 50% dissolution, were only −0.352 and −0.399, respectively.

The disintegration times used for correlation with the urinary excretion data were determined without disks in the disintegration chambers, even though the USP XIX states that disks should be present. The data without disks were utilized because of the small range in disintegration times when the disks were present. In contrast to the correlation between dissolution and urinary excretion at 24 hr, the correlation between disintegration time and urinary excretion was considerably better, with a correlation coefficient of −0.829 ($p = 0.05$). However, the mean disintegration times employed for Products 3 and 6 were somewhat arbitrary because tablets requiring >30 min were averaged in as 30 min.

The results of these studies suggest that the present USP XIX disintegration specification should be revised to omit the use of disks in the apparatus. Moreover, a dissolution rate specification requiring 900 ml of distilled water as the dissolution medium apparently would not be useful in predicting the *in vivo* performance of chlorothiazide tablets.

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Effect of Temperature and an Ion-Exchange Resin on Cation Diffusion through Silicone Polymer Tubing

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Received October 23, 1978, from the *Department of Pharmaceutics, College of Pharmacy, University of Utah, Salt Lake City, UT 84112.* Accepted for publication February 28, 1979.

Abstract □ Permeation of cations through silicone rubber tubing was measured, and the effect of an ion-exchange resin on the cation diffusion was determined. Silicone rubber has been used as a biomedical polymer and shows a very low solubility to ionizable species. Correlations between the calculated diffusion coefficients, with and without the resin, depended on the charge and number of waters of hydration for each cation. These increases ranged from 1.11 for potassium to 3.06 for iron, multiplied by the diffusion coefficient as a result of the resin. Solubilities of each cation in the polymer were temperature dependent. Activation energies were calculated for each cation by measuring the increased permeation with increasing temperature, with and without the resin. Decreasing magnitudes of activation energies ranged from 0.91 for sodium to 0.57 for iron when the resin was present. Correlations were established between the measured activation energies and reported free energy change for the hydration of each cation.

Keyphrases □ Cations—diffusion through silicone polymer tubing, effect of temperature and ion-exchange resin □ Temperature—effect on cation diffusion through silicone polymer tubing □ Ion-exchange resins—effect on cation diffusion through silicone polymer tubing □ Dosage forms, sustained release—silicone polymer tubing, effect of temperature and ion-exchange resin on cation diffusion

Because of the minimal body tissue response and relatively high diffusivities of hydrophobic solutes, polydimethylsilicone is an excellent candidate for sustained-release medication implantation devices. Hydrophobic solute diffusion through this polymer is well documented (1–6), showing high rates of diffusivity and polymer solubility.

BACKGROUND

Little information is available on the permeation of charged or uncharged solutes that show a low solubility in silicone films. In evaluating the function of silicone heart valves, a previous investigator (7) reported that hydrophobic dyes such as rhodamine diffused into the valve, while hydrophilic dyes such as methylene blue did not. Silicone capsules containing normal saline, 5% dextrose in water, sodium citrate, and a calcium-saturated solution of edetic acid showed a lack of permeation of these solutes through the polymer (8).

Permeation of both charged and uncharged solutes through silicone membranes has been measured (9). Silicone was not permeated by the charged organic molecules but was permeated by the uncharged organic molecules, which were lipophilic. Both atropine base and histamine diffused through silicone rubber tubes (10). Histamine is water soluble.

The limited permeability of charged or water-soluble solutes has re-

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