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Absorption of Triazolam from Pelleted Drug–Diet Mixtures by the Mouse: Quantitation of α-Hydroxytriazolam in Urine

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Abstract ☐ The absorption of triazolam from pelleted drug–diet mixtures by mice under steady-state conditions was determined for doses up to 150 mg/kg/day by measuring α-hydroxytriazolam, the principal urinary metabolite of triazolam in the mouse, in urine samples collected over a 24-hour period. Following β-glucuronide glucuronosohydrolase hydrolysis of the urine, quantitation of α-hydroxytriazolam was accomplished using a specific reverse-phase liquid chromatographic method which utilized UV detection at 214 nm. Assay precision was >2.7% (*CV*) over the concentration range of interest. Statistical analysis of the excretion data indicated that the mathematical relationship between the triazolam dose and the quantity of α-hydroxytriazolam excreted was linear for female mice and nonlinear for male mice. Triazolam absorption, as reflected by α-hydroxytriazolam urinary excretion data, increased with triazolam dose.

Keyphrases ☐ Triazolam—absorption from drug–diet mixtures by mice, determination by metabolite excretion in urine, α-hydroxytriazolam ☐ α-Hydroxytriazolam—urinary excretion, use to measure triazolam absorption in mice, drug–diet mixtures ☐ Absorption—triazolam in mice, drug–diet mixtures, measurement by α-hydroxytriazolam excretion in urine

The incorporation of drugs into the laboratory diet of mice and rats is a convenient and commonly used method of administering drugs in chronic toxicology studies since it eliminates the need for time-consuming daily administration of aqueous solutions or suspensions by gavage. In addition to its convenience, this mode of administration also eliminates the daily trauma and danger of pulmonary complications associated with dosing by gavage. As is well known, however, the administration of a drug in a carrier, such as laboratory diet, may affect drug absorption. Information concerning the absorption of a drug from the carrier over the range of dosages administered in toxicological studies may be useful, if not essential, in assessing the significance of study results. It should also be noted that the Food and Drug Administration's recently instituted Good Laboratory Practice regulations may require that the degree of absorption of a drug from a carrier be determined (1).

Several methods have been reported for determining the relative absorption of drugs following administration of pulverized drug–diet mixtures. Van Harken and Hottendorf (2) determined the exposure of rats to cefatrizine, under steady-state conditions, by comparing the area

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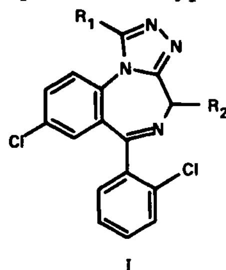
under the 24-hr plasma concentration–time curves of the antibiotic after feeding a pulverized cefatrizine–diet mixture *ad libitum* and administering a suspension of the drug once daily. Although satisfactory results were obtained, the authors indicated that it was a very laborious procedure that required a team of technicians working overnight to collect the blood samples. This procedure also places the animals under a great deal of stress, particularly if a sufficient number of blood samples are collected to characterize the blood level profile adequately, and the analysis of a large number of samples is required. To overcome these problems, Smyth *et al.* (3) studied the absorption of several drugs in rats by comparing the urinary excretion of radioactivity after feeding radiolabeled drug–diet mixtures and administering a solution/suspension of each drug. Difficulties may be encountered using this procedure also, since incorporation of radiolabeled drug into the diet using the same techniques that were used to prepare drug–diet mixtures for the corresponding toxicological study may not be possible. In addition, adequate quantities of radiolabeled drug must be available.

The present report describes a study of the absorption of triazolam[1] (I), a potent new hypnotic with a short du-



I

I: R_1=CH_3, R_2=H; triazolam

I-a: R_1=CH_2OH, R_2=H; α-hydroxytriazolam

I-b: R_1=CH_2OH; R_2=OH; α, 4-dihydroxytriazolam

I-c: R_1=H, R_2=H; 1-demethyltriazolam

I-d: R_1=CH_3, R_2=OH; 4-hydroxytriazolam

ration of action (4), from pelleted drug–diet mixtures by mice under steady-state conditions. The extent of triazolam absorption was determined by quantitating α-hydroxytriazolam, 8-chloro-6-(2-chlorophenyl)-1-(hydroxymethyl) - 4*H*-*s*-triazolo[4,3 - *a*][1,4]benzodiazepine (I-a), the principal urinary metabolite of triazolam in the mouse[2], in 0 to 24-hr urine samples following β-glucuronide glucuronosohydrolase hydrolysis.

EXPERIMENTAL

Study Protocol—One week prior to the termination of a 24-month carcinogenicity study of triazolam in $B_6C_3F_1$ mice, three male and three female mice were randomly selected from among surviving mice in each dosage group of the study and placed in individual stainless steel metabolism cages equipped with urine and feces separators. As in the carcinogenicity study, water and pelleted food[3] containing sufficient drug to provide approximately 0-, 10-, 30-, and 100-mg/kg/day triazolam doses were provided *ad libitum* to mice in each dosage group. The potency, content uniformity, and stability of the pelleted triazolam–diet mixtures were determined using a high-performance liquid chromatographic (HPLC) assay[4]. Food consumption was measured daily by weighing tared feed cups. Following a 2-day acclimatization period, urine samples were collected over two consecutive 24-hr periods in screw-capped vials fitted with aluminum-lined caps. Any urine remaining in the cages was rinsed into the containers with deionized water. The samples were stored at −20°.

Reagents—The solvents used in the study were distilled-in-glass UV grade[5]. Analytical reagent-grade inorganic chemicals[6] were prepared in distilled, deionized water. The reference standard, α-hydroxytriazolam, and the internal standard, alprazolam (8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine), were used without further purification[7]. The β-D-glucuronide glucuronosohydrolase preparation[8] (E.C. 3.2.1.31) was used as received.

Standards—A 20-μg/ml stock solution of α-hydroxytriazolam was prepared by dissolving an accurately weighed sample of the reference standard in acetonitrile. Calibration curve standards containing 20, 14, 10, 7, 5, 3, 2, 1, and 0.5 μg/ml of α-hydroxytriazolam were prepared by making appropriate dilutions of the stock solution with acetonitrile. A 1-μg/ml working internal standard solution was prepared by dissolving the reference standard, alprazolam, in acetonitrile.

Calibration Curves—Calibration curves were prepared each day of sample analysis to establish the linearity and reproducibility of the method. One-milliliter aliquots of the internal standard and the appropriate calibration curve standard were added to 16 × 125-mm screw-capped culture tubes fitted with polytef-lined caps, and the acetonitrile was evaporated to dryness at 50° under a gentle stream of dry nitrogen[9]. A 500-μl aliquot of blank mouse urine was added to each tube prior to enzymatic hydrolysis.

Sample Preparation—One milliliter of internal standard was added to 16 × 125-mm screw-capped culture tubes fitted with polytef-lined caps, and the acetonitrile was evaporated to dryness at 50° under a gentle stream of dry nitrogen. The urine samples were thoroughly mixed, and 500-, 175-, and 50-μl aliquots of the samples collected from animals administered 0 and ∼10, ∼30, and ∼100 mg/kg/day of triazolam, respectively, were transferred to the sample tubes for analysis. The 175- and 50-μl samples were diluted to 500-μl with 0.05 *M* acetate buffer (pH 4.5) prior to enzymatic hydrolysis.

Enzymatic Hydrolysis—The calibration curve standards and unknowns were hydrolyzed in a water bath[10] at 37° for 24 hr following addition of 100 μl of 2 *M* acetate buffer (pH 4.5) and 400 μl of 0.05 *M* acetate buffer (pH 4.5) containing 30,000 Fishman units of β-D-glucuronide glucuronosohydrolase.

Extraction—The hydrolyzed samples were buffered with 2 ml of 4 *M* NaOH and extracted twice with 5-ml aliquots of methylene chloride–toluene (1:1, v/v) for 15 min at 280 cpm on a two-speed reciprocating shaker[11]. Following centrifugation for 10 min at 2000 rpm, the organic phase was transferred to 15-ml conical tubes and evaporated to dryness at 50° under a gentle stream of dry nitrogen. The resulting residues were reconstituted in 4 ml of chromatographic mobile phase, thoroughly mixed on a high-speed vortex mixer[12], and chromatographed (250-μl samples).

Chromatographic Analysis—A constant-flow liquid chromatograph[13] equipped with a loop injection valve[14] and a 214-nm UV detector[15] was used for the analysis. The samples were chromatographed on a commercially prepared reverse-phase column[16], thermostated[17] at 50°, using a mobile phase containing water–acetonitrile (7:3, v/v) at a flow rate of 2.0 ml/min. Under these chromatographic conditions the retention times of the α-hydroxytriazolam and internal standard were ∼9.5 and 14 min, respectively.

Mass Spectrometry—Chromatographic fractions collected at the retention times of major peaks in chromatograms of enzymatically hydrolyzed urine extracts were lyophilized, and electron-impact mass spectra (EI/MS) (70 eV) were recorded using a magnetic sector mass spectrometer[18].

[1] Halcion; The Upjohn Co., Kalamazoo, MI 49001.
[2] E. G. Daniels, R. L. VanEyk, and J. E. Stafford, unpublished data.
[3] 5003M Purina Laboratory Chow; Ralston Purina Co., St. Louis, Mo.
[4] W. J. Adams and P. A. Bombardt, unpublished data.
[5] Burdick & Jackson Laboratories, Muskegon, Mich.
[6] Mallinckrodt, St. Louis, Mo.
[7] Pharmaceutical Research & Development Laboratories, The Upjohn Co., Kalamazoo, Mich.
[8] Sigma Chemical Co., St. Louis, MO 63178.
[9] Multivap Analytical Evaporator; Organomation Associates, Shrewsbury, Mass.
[10] Model 3005-7 Sample Thermostat; Chicago Apparatus Co., Chicago, Ill.
[11] Eberbach and Sons, Ann Arbor, Mich.
[12] Lab-Line Instruments, Melrose Park, Ill.
[13] Model 6000A; Waters Associates, Milford, Mass.
[14] Model CV-6-HP_{ax}; Valco Instruments, Houston, Tex.
[15] Model 1203 UV Monitor; Laboratory Data Control, Riviera Beach, Fla.
[16] Brownlee Labs RP-5A; Rheodyne, Inc., Berkeley, Calif.
[17] LAUDA K-2/R Circulating Water Bath; Brinkmann Instruments, Westbury, NY 11590
[18] Model CH7A; Varian MAT, Bremen, W. Germany.

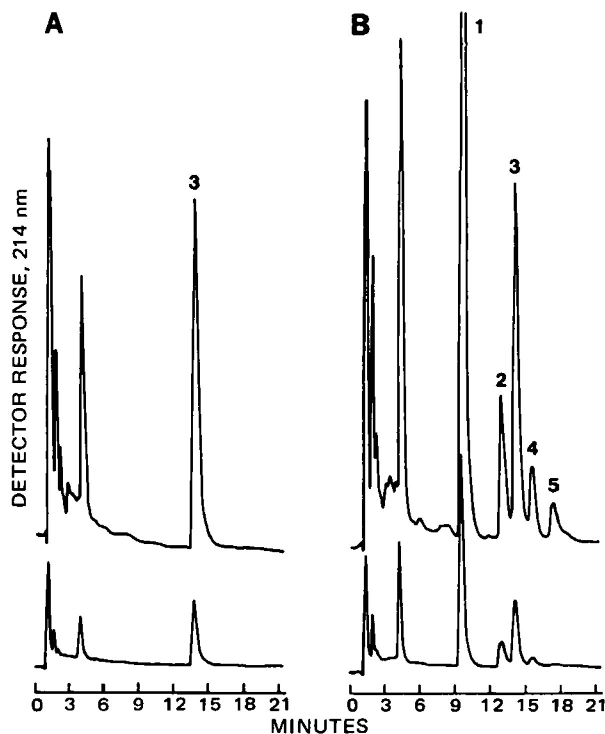


Figure 1—*Chromatograms of extracts of hydrolyzed mouse urine from (A) a control mouse and (B) a mouse administered ~10 mg/kg triazolam. Key: (1) α-hydroxytriazolam; (2) 1-demethyltriazolam; (3) internal standard; (4) triazolam; and (5) 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)-2′-chlorobenzophenone.*

Calculations—The α-hydroxytriazolam concentrations of the unknown samples were calculated from peak height ratios using the slope computed by linear regression analysis of the unweighted calibration curve data. Peak height ratios were calculated by dividing the α-hydroxytriazolam peak heights by the internal standard peak heights. The quantity of α-hydroxytriazolam excreted over a 24-hr period, expressed as milligrams of α-hydroxytriazolam per kilogram of body weight, was calculated from the α-hydroxytriazolam concentration, the volume of urine collected over the 24-hr period, and the mean body weight.

The triazolam dose received by each animal, expressed as milligrams of triazolam per kilogram of body weight, was calculated from the quantity of food consumed over the 24-hr period in which the urines were collected and the mean body weight. No attempt was made to correct the diet consumption data for the amount of food dropped through the bottom of the cage. The quantity of food dropped into the urine appeared to be small and evenly distributed among the dosage groups.

Statistical Analysis—Statistical analyses of the experimental data were performed using the SAS statistical analysis programs (5) and NONLIN (6), a computer program for parameter estimation in nonlinear situations.

RESULTS AND DISCUSSION

The measurement of drug levels in the blood following single- or multiple-dose administration of drugs is the experimental approach most frequently used in relative bioavailability studies in humans and large animals, where sequential sampling at precisely known times is possible. This approach is also feasible for bolus drug administration to mice, but has the disadvantage of requiring the sacrifice of several mice at each time point for which data are needed. In the case of *ad libitum* administration of drug–diet mixtures to mice or rats, however, drug ingestion occurs over an extended period instead of precisely known times; therefore, it is difficult and extremely laborious to obtain reliable estimates of relative bioavailability by analysis of blood samples.

An alternative to the determination of relative bioavailability from drug levels in the blood is the measurement of the urinary excretion of intact drug or of a principal drug metabolite (7). A recent single-dose metabolism study of [^{14}C]triazolam in $B_6C_3F_1$ mice established that although there is no urinary excretion of intact drug, ~17% of the orally administered dose of triazolam is excreted in the urine as α-hydroxytriazolam[2]. Excretion of all drug-related materials was complete within 72 hr. Under the chronic-dosing conditions of this study, α-hydroxytriazolam was the major extractable metabolite. Therefore, quantitation of α-hydroxytriazolam in 24-hr urine samples under steady-state conditions was the logical experimental approach for the determination of the relative bioavailability of triazolam in mice. An HPLC method utilizing UV detection was developed for the quantitation of α-hydroxytriazolam in mouse urine.

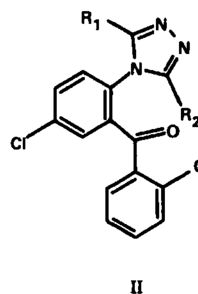
Table I—Chromatographic Retention Times of Triazolam and Selected Triazolam Metabolites [a]

Compound	Retention Time, min [b]
I	15.5
I-a	9.5
I-b	6.0
I-c	12.8
I-d	10.6
II	11.9
II-a	17.4
II-b	10.0

[a] Samples chromatographed on a 5-μm LiChrosorb RP-8 reverse-phase column thermostated at 50° using a mobile phase containing water-acetonitrile (7:3, v/v): at a flow rate of 2.0 ml/min. [b] The void volume of the column was 1.2 ml.

Chromatographic Analysis—Resolution of α-hydroxytriazolam and the internal standard from coextracted endogenous interferences was accomplished using a 5-μm LiChrosorb RP-8 reverse-phase column thermostated at 50° and a mobile phase containing water–acetonitrile (7:3, v/v) at a flow rate of 2.0 ml/min. Thermostating the column at 50° reduced column back-pressure and shortened the retention times of the compounds of interest. Typical chromatograms of extracts of urine from a control mouse and from a mouse administered ~10 mg/kg/day of triazolam are shown in Fig. 1. The internal standard was added to both samples. The α-hydroxytriazolam and internal standard eluted at ~9.5 and 14.0 min, respectively.

Comparison of chromatograms of urine extracts from control and triazolam-dosed mice indicated that significant quantities of triazolam and several metabolites in addition to α-hydroxytriazolam had been extracted from the urine of the triazolam-dosed mice. Although triazolam was not detected in the urine of mice in the recently conducted metabolism study[2], its presence in the urine samples collected in this study was not unexpected, since it was apparent that all collected urine samples had been contaminated with small pieces of pelleted food which had dropped through the bottom of the cage. The triazolam eluted at ~15.5 min and did not interfere in the analysis. Chromatography of authentic samples of triazolam metabolites that had been identified in mice[2], rats[2,19], dogs (8), or humans (9) provided tentative evidence that the metabolites eluting at ~6.0, 11.9, 12.8, and 17.4 min were α,4-dihydroxytriazolam (I-b), 5-chloro-2-(3-hydroxymethyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-2′-chlorobenzophenone (II), 1-demethyltriazolam (I-c), and 5-chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)-2′-chlorobenzophenone (II-a), respectively (Table I). Direct-inlet MS characterization of chromatographic



II

II: R_1=CH_3, R_2=CH_2OH; 5-chloro-2-(3-hydroxymethyl-5-methyl-4H-1,2,4-triazol-4-yl)-2′-chlorobenzophenone

II-a: R_1=CH_3, R_2=H; 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)-2′-chlorobenzophenone

II-b: R_1=CH_2OH, R_2=H; 5-chloro-2-(3-hydroxymethyl-4H-1,2,4-triazol-4-yl)-2′-chlorobenzophenone

[19] F. S. Eberts and R. C. Meeks, unpublished data.

Table II—Abbreviated Electron-Impact Mass Spectra of Triazolam, Selected Triazolam Metabolites, and Lyophilized Chromatographic Fractions

Compound	$M^{+\cdot}$	Six Most Intense Ions for $m/z > 100$, % Relative Abundance
Peak 1[a]	—	360(66), 358(100), 330(35), 328(50), 323(32), 318(33)
I-a	358(100)	360(65), 330(39), 329(32), 328(58), 323(27), 239(33)
II-b	347(13)	320(65), 318(100), 312(54), 284(41), 139(55), 111(50)
Peak 2[b]	—	328(52), 293(30), 265(20), 236(29), 137(18), 111(33)
I-c	328(100)	330(66), 329(30), 293(62), 265(28), 239(20), 137(27)
Peak 4[c]	—	344(66), 342(100), 315(61), 314(31), 313(87), 238(67)
I	342(81)	344(55), 315(69), 314(34), 313(100), 239(34), 238(84)
Peak 5[d]	—	331(19), 296(63), 268(19), 236(16), 183(19), 139(31)
II-a	331(31)	298(35), 296(100), 268(32), 139(47), 127(27), 111(41)

[a] Figure 1, peak 1; 9–11 min fraction. [b] Figure 1, peak 2; 12.5–13.8 min fraction. [c] Figure 1, peak 4; 15.3–16.6 min fraction. [d] Figure 1, peak 5; 17.0–19.0 min fraction.

fractions collected at the retention times of major peaks in the chromatograms confirmed the presence of α-hydroxytriazolam (Table II, peak 1), 1-demethyltriazolam (Table II, peak 2), triazolam (Table II, peak 4), and 5-chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)-2′-chlorobenzophenone (Table II, peak 5) in extracts of the enzymatically hydrolyzed urine. No attempt was made to confirm the identity of minor metabolites. However, a minor metabolite that eluted as a shoulder on the trailing edge of the α-hydroxytriazolam peak in some chromatograms was collected in the same chromatographic fraction as α-hydroxytriazolam (Fig. 1; peak 1, 9–11 min) and was tentatively identified as 5-chloro-2-(3-hydroxymethyl-4*H*-1,2,4-triazol-4-yl)-2′-chlorobenzophenone (II-b). In addition to α-hydroxytriazolam, 4-hydroxytriazolam (I-d) and α,4-dihydroxytriazolam were also isolated from urine and identified by GC/MS in the recently conducted metabolism study of triazolam in the mouse[2]; 5-chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)-2′-chlorobenzophenone was tentatively identified. The low extraction efficiencies of 4-hydroxytriazolam and α,4-dihydroxytriazolam in toluene–methylene chloride (1:1, v/v) precluded isolation of sufficient quantities of these metabolites to allow confirmation by MS in the present study.

Assay Recovery—The absolute recovery of α-hydroxytriazolam from hydrolyzed urine was determined by comparing the slopes of standard curves for which the α-hydroxytriazolam standards were added prior to and following the extraction step in the sample preparation procedure. Alprazolam was added as an external standard in the recovery experiments.

Extraction of the hydrolyzed urine with toluene provided excellent recoveries of triazolam, as had been found in previously developed analytical methods for triazolam in serum (10, 11); however, the recovery of α-hydroxytriazolam was <30%. Addition of methylene chloride to the toluene (1:1, v/v) increased the recovery to 94.5 ± 2.7% and provided an extract that was free of endogenous interferences. Furthermore, the recoveries of the internal standard, triazolam, 5-chloro-2-(3-hydroxymethyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-2′-chlorobenzophenone, and 5-chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)-2′-chlorobenzophenone were all >90%. However, the recoveries of α,4-dihydroxytriazolam and 4-hydroxytriazolam were <3 and 45%, respectively.

Assay Linearity and Precision—The linearity and precision of the method were established by analyzing standard curve samples on each day that unknowns were analyzed. Linear regression analysis of calibration curve data indicated no significant deviations from linearity ($r^2 \geq 0.9962$, $n = 3$) for α-hydroxytriazolam concentrations ranging from 0.5 to 20 μg/ml. The standard curve intercepts were not significantly different from zero ($p > 0.05$) for all three curves.

An estimate of the interassay reproducibility and precision was obtained by comparison of standard curves prepared over a 3-day period. The slopes of the three curves ranged from 1.0703 to 1.2145 ml/μg with a mean slope ± percent relative standard deviation of 1.1563 ± 0.0097 ml/μg and a mean correlation coefficient (r^2) of 0.9994. The percent relative standard deviations of the interassay ordinate values for the three curves were ± 3.3, 3.4, 3.2, 4.9, 8.4, 3.6, 6.3, 10.8, and 5.7 for concentrations (abscissa) of 0.5, 1.0, 2.0, 3.0, 5.1, 7.1, 10.2, 14.3, and 20.4 μg/ml, respectively. The limit of detection of the method was ~6 ng/ml (0.5 ng on-column; signal/noise, 3/1).

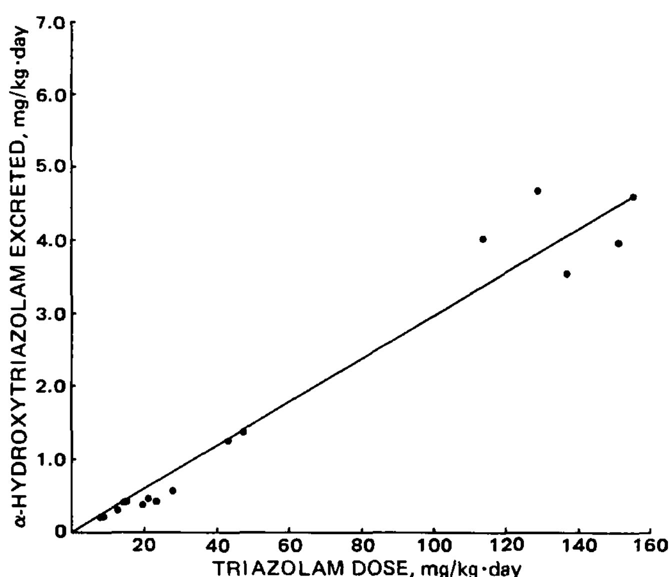


Figure 2—*Plot of the α-hydroxytriazolam excretion data for female mice. The solid line is a plot of the theoretical model which gave the best fit of the experimental data;* $E = C_1(dose)$, *where* E *represents the milligrams of α-hydroxytriazolam excreted per kilogram body weight per day and* $C_1 = 0.0298 \pm 0.0011$ *(ESD) mg of α-hydroxytriazolam/mg of triazolam.*

Triazolam Absorption—Plots of the quantity of α-hydroxytriazolam excreted in urine over a 24-hr period *versus* triazolam dose for the female and male mice are shown in Figs. 2 and 3, respectively. Regression analysis of the female excretion data (5) indicated that the quantity of α-hydroxytriazolam excreted (E) was proportional to the triazolam dose. That is, coefficients for the $n = 0, 2, 3, 4$, *etc.* terms in the polynomial expression, $E = \sum_{n=0}^{N} C_n \cdot (\text{dose})^n$, were not statistically significant ($p > 0.05$). The root-mean-square (RMS) deviation for the linear function, $E = C_1 \cdot (\text{dose})$, was 0.301 mg of α-hydroxytriazolam/kg-day, with $C_1 = 0.0298 \pm 0.0011$ (*ESD*) mg of α-hydroxytriazolam/mg of triazolam. Regression analysis of the male α-hydroxytriazolam excretion data (5), assuming dose proportionality, indicated that the slope of the line, 0.0428 ± 0.0047 (*ESD*) mg of α-hydroxytriazolam/mg of triazolam, was greater than that found for the female excretion data. More important, however, a distinct

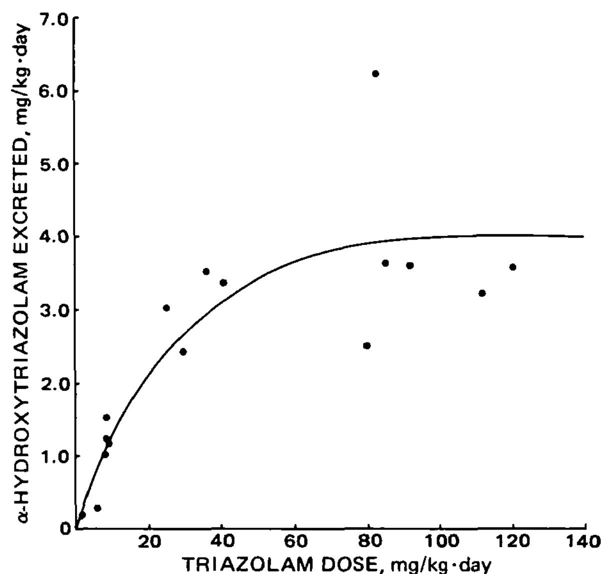


Figure 3—*Plot of the α-hydroxytriazolam excretion data for male mice. The solid line represents the theoretical model which gave the best fit of the experimental data:* $E = A[1 - e^{-B(\text{dose})}]$, *where* E *represents the milligrams of α-hydroxytriazolam excreted per kg body weight per day,* $A = 4.02 \pm 0.40$ *(ESD) mg of α-hydroxytriazolam/kg-day, and* $B = 0.038 \pm 0.010$ *(ESD) kg-day/mg.*

nonlinear trend in the male excretion data was apparent, reflected in the RMS deviation (1.162 mg of α-hydroxytriazolam/kg·day) which was nearly four times greater than that for the female data. A plausible nonlinear model of the male excretion data is one in which the quantity of α-hydroxytriazolam excreted approaches an asymptotic value with increasing doses of triazolam. An exponential function of the dose was adopted, $E = A[1 - e^{-B\cdot(\text{dose})}]$, where A and B are adjustable parameters. The best fit parameters for the male excretion data, estimated using NONLIN (6), were $A = 4.02 \pm 0.40$ mg of α-hydroxytriazolam/kg·day and $B = 0.038 \pm 0.010$ kg·day/mg; the associated RMS deviation was 0.70 mg of α-hydroxytriazolam/kg·day, a significantly better fit of the experimental data than that afforded by the one-parameter linear model ($F_{\text{statistic}} = 34.6$; $n = 22$).

In conclusion, triazolam absorption, as reflected by α-hydroxytriazolam urinary excretion data for female and male mice, increased with triazolam dose. The quantity of α-hydroxytriazolam excreted by female mice was proportional to the triazolam dose, while the male excretion data were adequately represented by a model which predicts that the quantity of α-hydroxytriazolam excreted approaches an asymptotic value with increasing doses of triazolam.

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Mechanisms of Potassium Chloride Release from Compressed, Hydrophilic, Polymeric Matrices: Effect of Entrapped Air

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Abstract □ The release of potassium chloride from hydroxypropyl methylcellulose matrices was investigated for tablets prepared with several different compression forces. It was determined that the release kinetics for these systems deviates significantly from the classical $t^{1/2}$ dependence. This behavior was attributed to air entrapped in the matrix during preparation. Removal of the air prior to release restored the traditional $t^{1/2}$ behavior.

Keyphrases □ Potassium chloride—release from hydroxypropyl methylcellulose matrices, effect of entrapped air, kinetics □ Matrices, hydroxypropyl methylcellulose—release of potassium chloride, effect of entrapped air, kinetics □ Kinetics—release of potassium chloride from hydroxypropyl methylcellulose matrices, effects of entrapped air

Compressed, hydrophilic, polymeric matrices provide a convenient method for achieving sustained release of highly water-soluble drugs (1, 2). Release profiles are usually analyzed using equations derived by T. Higuchi (3) and W. Higuchi (4) and adapted by Lapidus and Lordi (5, 6). However, such systems often exhibit complex kinetics (7, 8) that are poorly explained by these traditional models of drug release. Modeling efforts in this area may be assisted by better understanding of the physical factors that contribute to (a) the swelling of the polymeric matrix due to transport of the penetrating species into the porous system and (b) the initial dissolution and release of the incorporated drug.

The goal of this work was to investigate some of the factors affecting the overall release behavior, especially the importance of entrapped air in the porous structure. The model system chosen consisted of potassium chloride as the water-soluble drug and hydroxypropyl methylcellulose as the hydrophilic polymer. Some of the technological factors influencing the overall potassium chloride release profile in this system have been analyzed by Salomon *et al.* (9–11). Their studies revealed that the release deviates significantly from the traditional $t^{1/2}$ dependence called for by the Higuchi and Lapidus–Lordi models during the early stages of the experiments. Even improved mathematical models especially developed for this system (12) could not fully describe the release behavior. To investigate this physical phenomenon more thoroughly, the experimental procedure of Salomon *et al.* (9–11) was followed with improved time resolution.

EXPERIMENTAL

Materials—The materials used were potassium chloride[1] (water solubility, 332 mg/cm^3 at 37°) and hydroxypropyl methylcellulose[2]. This polymer had the following characteristics according to the manufacturer:

[1] Ph. Helv./Ph. Eur. grade; Siegfried, Zofingen, Switzerland.
[2] Methocel K 15M Premium; Dow Chemical Co., Midland, MI 48640.

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