XIII) and dimethyl analogs (XX *versus* XIV) generally produced a small increase in binding affinity. *p*-Methoxy groups increased activity in the dehalogenated cyclopropyl analogs (XIX *versus* XVII and XX *versus* XVIII) with the greatest receptor binding affinity found in compound XVIII. The *cis*-isomer XXI displayed greater receptor affinity than the *trans*-isomer XIX, but there were no apparent differences in the *gem*-dichloro analogs (XV *versus* XIII and XVI *versus* XIV).

When the receptor binding activities of these analogs were compared to the present compounds (1), it was found that the monomethyl and dimethyl substituents at R_2 and R_3 (Table III) in the hydrophobic cyclopropyl skeleton led to a reduction in receptor binding affinity of the derivatives, while diethyl substitution increased receptor binding ability.

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Abstracted in part from a thesis submitted by John F. Stobaugh to the University of Oklahoma in partial fulfillment of the Master of Science degree requirement.

Moment Analysis for the Separation of Mean *In Vivo* Disintegration, Dissolution, Absorption, and Disposition Time of Ampicillin Products

YUSUKE TANIGAWARA ˣ, KIYOSHI YAMAOKA, TERUMICHI NAKAGAWA, and TOYOZO UNO

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Abstract □ The *in vivo* disintegration, dissolution, absorption, and disposition processes of ampicillin products are separated by means of moment analysis. This method is model-independent, that is, any specific model is not assumed. The mean residence time (MRT), mean absorption time (MAT), mean dissolution time (MDT), and mean disintegration time (MDIT) are calculated for several dosage forms of ampicillin. The fraction of dose absorbed (F) is also separated into several fractions corresponding to these *in vivo* processes. Bioavailability and bioequivalence are discussed in terms of the zero and first moments. The flip-flop behavior of ampicillin is proved by the fact that the MRT following intravenous injection is less than the MAT of any oral dosage form. Absorption of released ampicillin is proved to be a rate-determining step, since the MRT of released ampicillin in the GI tract is the greatest of all MRT corresponding to the *in vivo* processes. Moment analysis is compared with classical compartment theory, and a new component concept is introduced.

Keyphrases □ Ampicillin—moment analysis, *in vivo* disintegration, dissolution, absorption, disposition time □ Disintegration—ampicillin, moment analysis, *in vivo* dissolution, absorption, disposition time □ Dissolution—ampicillin, moment analysis, *in vivo* disintegration, absorption, disposition time □ Absorption—ampicillin, moment analysis, *in vivo* disintegration, dissolution, disposition time

In recent years moment analysis has been developed in the pharmacokinetic field as a method to comprehend drug behavior in the body, that is, absorption, distribution, metabolism, and excretion (1–10)[1]. Since statistical moments are characteristic of the shape of the statistical distribution curves such as plasma concentration–time curve or urinary excretion rate–time curve, they are only dependent on the observed time course data and are independent of the pharmacokinetic compartment model. Zero moment represents the area under the plasma concentration–time curve (AUC) or the total amount of drug excreted in urine, which is widely used as a model-independent parameter. The first moment, which is defined as the mean residence time (MRT), gives significant information with respect to kinetic features of the process which a drug undergoes in the GI tract and the body (1).

The absorption of a drug from its oral preparation involves a process too complex to be described by a simple mathematical equation. Therefore, a model-independent approach has been undertaken to evaluate the absorption rate (1–3, 11–13). These methods are based on deconvolution. The mean absorption time (MAT) is the useful index of the rate of bioavailability (1–3). The *in vivo* drug absorption involves disintegration and dissolution steps

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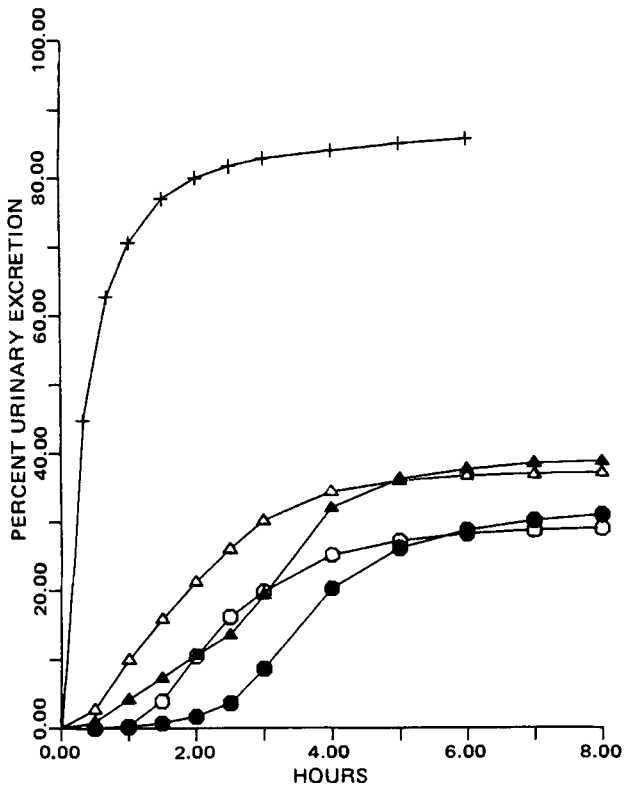


Figure 1—*Cumulative urinary excretion of ampicillin after intravenous and oral administrations to Subject 2. Key: (+) intravenous injection; (△) solution; (▲) Powder A; (●) Capsule A; (○) Capsule B.*

prior to absorption of released drug. The evaluation of *in vivo* disintegration and dissolution of a drug product is necessary for the development of a drug delivery system. It is also necessary to know the rate-determining step in these *in vivo* processes.

Recently the mean dissolution time (MDT) was defined as the magnitude of *in vivo* dissolution rate (3). In this article, moment analysis using urinary excretion data is carried out to separate four *in vivo* steps from administration of an ampicillin product through urinary excretion, that is, disintegration, dissolution, absorption, and disposition steps. The rate-determining step is specified by comparing the mean residence time intrinsic to each step. The extent and rate of bioavailability of the anhydrate and trihydrate forms of ampicillin are estimated in terms of the zero and first moments. Bioequivalence is discussed from the results for the urinary recovery and the mean residence time.

EXPERIMENTAL

Procedure—Four healthy male volunteers, 25–32 years of age, weighing 62–76 kg participated in this study. The subjects were fasted overnight before each dosage and were permitted to eat no food until 3 hr after dosing except for intravenous administration. No other drugs were taken for at least 1 week prior to and during the study. All subjects received single doses of ampicillin in five different dosage forms (*a–e*). Each dosage was separated by at least 1 week:

(a) *Intravenous injection*—A 2.5-ml injectable ampicillin[2] solution containing 125 mg (as potency) was intravenously administered in 1 min.

(b) *Solution*—A solution of 500-mg (as potency) of ampicillin sodium[2] dissolved in 100 ml of water was orally administered.

(c) *Powder* A—The contents of a 500-mg (as potency) ampicillin trihydrate capsule[3] were removed and orally administered with 100 ml of water.

(d) *Capsule* A—One 500-mg (as potency) capsule[3] was orally administered with 100 ml of water. The ampicillin was in trihydrate form.

(e) *Capsule* B—One 500-mg (as potency) ampicillin anhydrate capsule[4] was orally administered with 100 ml of water.

The maximum plasma concentration after intravenous injection is much higher than that after oral administration of the same dose. Therefore, a quarter of the oral dose was used for the intravenous dose in order to avoid saturation in drug disposition.

Urine samples were collected immediately before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hr after oral dosing, or at 20 and 40 min and 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hr after intravenous dosing. After the urine volume was measured, a portion was frozen until assayed.

Assay of Ampicillin—The antibiotic concentration was determined by reversed-phase high-pressure liquid chromatography (HPLC). The chromatograph[5] was equipped with a UV detector[6] adjusted at 220 nm. The stationary phase was octadecylsilane chemically bonded on totally porous silica gel (particle size 5 μm), packed in a 150-mm stainless steel column[7] (4-mm i.d.). The mobile phase was a mixture of methanol–0.0167 *M* phosphate buffer (pH 7.0, 1:2 v/v). The flow rate was 0.6 ml/min and column oven temperature was set at 28°. Peak area was used for quantitation[8].

Evaluation of Moments and Statistical Analysis—The urinary recovery, *f*(percent), and the mean residence time, MRT(hour), were evaluated from the time course data for the urinary excretion by means of the linear trapezoidal integration and extrapolation (1). The statistical evaluation of the differences in MRT and *f* values between dosage forms and subjects was achieved by two-way ANOVA. The subsequent pairing test was carried out when significant differences were found ($p < 0.05$).

Table I—Mean Residence Time, MRT(hr), of Ampicillin Products

Dosage Form	Subject 1	2	3	4	Mean ± *SD*
Intravenous injection	0.766	0.752	0.816	0.752	0.772 ± 0.026
Solution	2.53	2.00	2.78	2.10	2.35 ± 0.32
Powder A	3.18	2.95	2.88	2.56	2.89 ± 0.22
Capsule A	3.40	3.98	3.33	2.23	3.24 ± 0.63
Capsule B	3.08	2.73	2.51	2.24	2.64 ± 0.31

Table II—Percent Urinary Recoveries, *f*(%), of Ampicillin at Infinite Time

Dosage Form	Subject 1	2	3	4	Mean ± *SD*
Intravenous injection	83.4	86.9	64.1	77.5	78.0 ± 8.7
Solution	39.0	37.2	37.8	52.5	41.6 ± 6.3
Powder A	45.2	38.9	39.0	45.8	42.2 ± 3.3
Capsule A	40.9	31.9	30.7	42.2	36.4 ± 5.2
Capsule B	38.7	29.2	26.1	31.2	31.3 ± 4.6

RESULTS

Mean Residence Time and Urinary Recovery—Figure 1 shows the time courses for the cumulative urinary excretion of ampicillin administered to Subject 2 in various dosage forms. The MRT and *f* values are listed in Tables I and II. In calculating the moments, the contributions of the extrapolated area to MRT and *f* values were evaluated. The increases of MRT and *f* by extrapolation to infinite time were <1%, which demonstrates that the urinary time courses were measured in an adequate period of time. The differences in MRT and *f* values among the dosage forms were statistically significant at the 0.01 level by ANOVA. The MRT and *f* values after intravenous injection are very different from those after any other oral dosage forms. For example, ampicillin is retained in the

[2] Pentrex for injection, Banyu Pharmaceutical Co. Ltd., Tokyo, Japan.

[3] Pentrex capsules, Banyu Pharmaceutical Co. Ltd., Tokyo, Japan.
[4] Solcillin capsules, Takeda Chemical Industries, Ltd., Osaka, Japan.
[5] Model TRIROTAR-III, Japan Spectroscopic Co., Tokyo, Japan.
[6] Model UVIDEC-100-III, Japan Spectroscopic Co., Tokyo, Japan.
[7] Develosil ODS-5, Nomura Chemicals, Seto, Japan.
[8] CHROMATOPAC C-R1A, Shimadzu, Kyoto, Japan.

GI tract and the body for ~3 hr when the trihydrate capsule (Capsule A) is orally administered, whereas only 46 min of residence time follows intravenous injection. The differences in MRT values are insignificant at the 0.05 level between Powder A and Capsule A, between Solution B and Capsule B, and between Powder A and Capsule B. The differences in f values are insignificant at the 0.05 level between Powder A and Capsule A, between Solution A and Powder A, between Solution A and Capsule A, and between Capsule A and Capsule B. Therefore, from the viewpoint of extent and rate of bioavailability, it follows that Powder A and Capsule A are bioequivalent, but that any other pairs are not bioequivalent at the 0.05 level.

Mean Absorption Time and Extent of Absorption—The following discussions are based on the assumptions (1) that the pharmacokinetic system is linear, and the oral response is given by the convolution of weight functions which correspond to each step, such as disintegration, dissolution, absorption, and disposition.

The mean absorption time, MAT, and the fraction of dose absorbed, F, for a drug administered orally have been defined as (1, 2):

$$MAT = MRT_{po} - MRT_{iv} \quad \text{(Eq. 1)}$$

$$F = f_{po}/f_{iv} \quad \text{(Eq. 2)}$$

where po and iv reveal oral and intravenous bolus administrations, respectively. MAT expresses the mean overall time since a drug is administered until it enters into the systemic circulation. Table III lists the MAT (hour) and F (percent) for four ampicillin dosage forms. The MAT values are estimated by the subtraction of the average of MRT_{iv} from that of MRT_{po}. Absorption rate from the solution is the fastest of all oral dosage forms. Absorption from Capsule B, which contains ampicillin anhydrate is as fast as that from the solution, but absorption from Capsule A, which contains the trihydrate form, is clearly slower than that from the solution. Difference in MAT values between these two capsules is 0.60 hr (36 min). The fact that the MRT_{iv} is less than the MAT of any oral dosage form shows that the pharmacokinetic profile of ampicillin is flip-flop (14).

Mean Disintegration Time and Mean Dissolution Time—Though the discussion below can be applied to tablets and sustained-release preparations, the case of capsules is considered here as a representative example. Prior to the absorption of released drug through the GI wall, a drug administered as a capsule undergoes *in vivo* disintegration of the capsule shell and subsequent dispersion of drug powder, and dissolution of the dispersed drug into GI fluid. Therefore, the MAT for capsules was separated into three steps as follows (Scheme I):

Table III—MAT, MDT, F, and F_{rel} of Orally Administered Ampicillin Preparations

	Solution	Powder A	Capsule A	Capsule B
MAT (hr)	1.58	2.12	2.47	1.87
MDT (hr)	—	0.54	0.89	0.29
F (%)	53.3	54.1	46.7	40.1
F_{rel} (%)	—	101.4	87.5	75.2

$$MAT_{capsule} = T_1 + T_2 + T_3 \quad \text{(Eq. 3)}$$

where T_1 is the mean time for the disintegration of a capsule, T_2 is the mean time for the dissolution of dispersed drug powder, and T_3 is the mean time for the absorption of the released drug. Accordingly, it is possible to estimate the *in vivo* mean time of each step by comparing the MAT values for several different dosage forms. When a drug is administered as a solution:

$$MAT_{solution} = T_3 \quad \text{(Eq. 4)}$$

When a drug is administered as a powder (or suspension):

$$MAT_{powder} = T_2 + T_3 \quad \text{(Eq. 5)}$$

The mean *in vivo* dissolution time, MDT, was defined (3):

$$MDT_{capsule} = MAT_{capsule} - MAT_{solution} \quad \text{(Eq. 6)}$$

In the same manner, we define the mean *in vivo* disintegration time, MDIT, as follows:

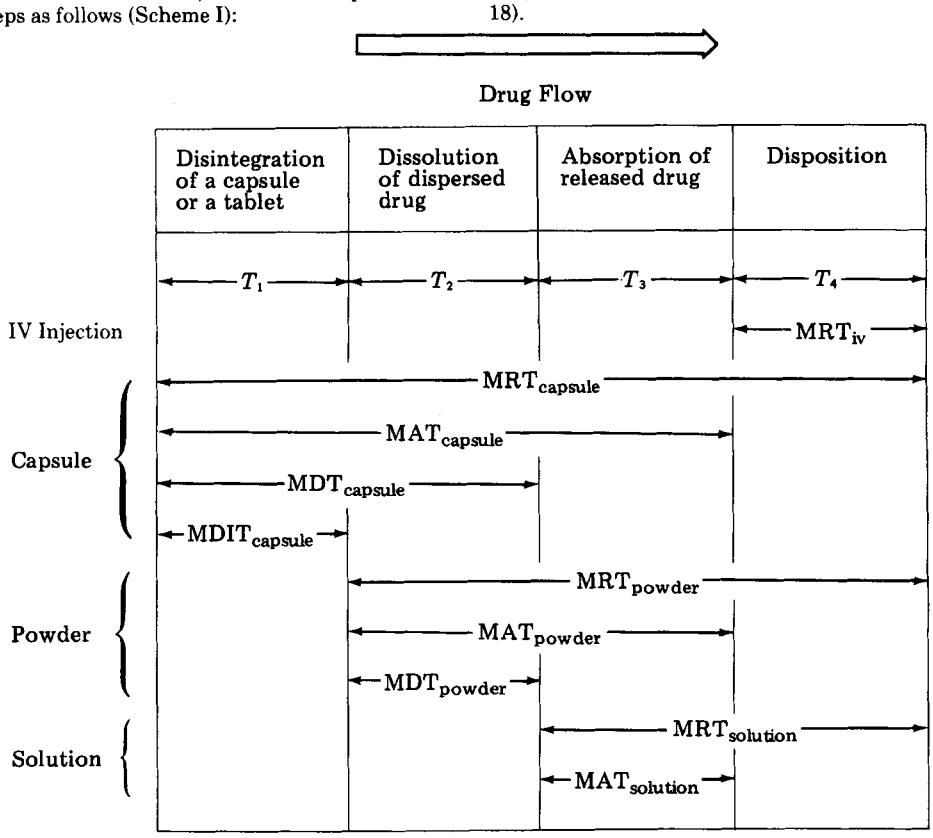
$$MDIT_{capsule} = MAT_{capsule} - MAT_{powder} \quad \text{(Eq. 7)}$$

Substitution of Eq. 1 into Eqs. 6 and 7 yields:

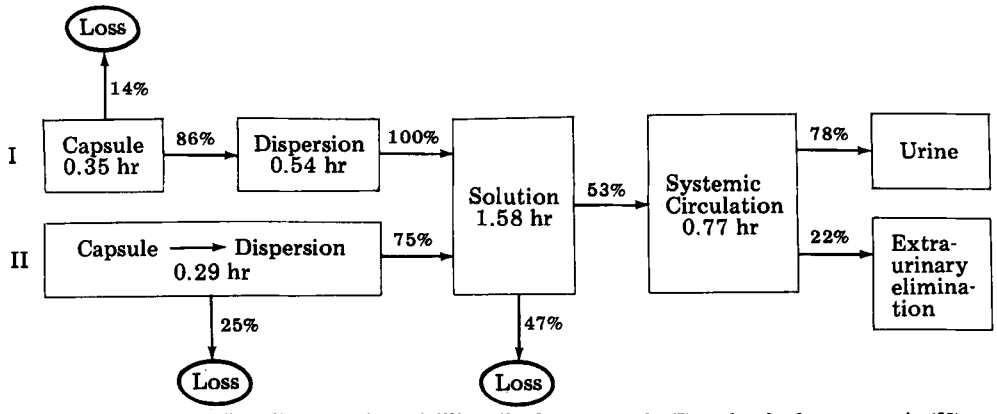
$$MDT_{capsule} = MRT_{capsule} - MRT_{solution} \quad \text{(Eq. 8)}$$

$$MDIT_{capsule} = MRT_{capsule} - MRT_{powder} \quad \text{(Eq. 9)}$$

Table III lists the MDT values for three solid dosage forms. The MDIT of Capsule A is 0.35 hr which is statistically negligible, and it means that the disintegration of capsule shell in the GI tract is a very rapid process. The MDT of Capsule A is greater than that of Capsule B, which coincides with the previously reported fact that the *in vitro* dissolution rate of anhydrous ampicillin is faster than that of the trihydrate form (15–18).



Scheme I—Illustration of the meanings of the MRT, MAT, MDT, and MDIT.



Scheme II—Drug flow diagram of ampicillin trihydrate capsule (I) and anhydrate capsule (II).

The zero moment of each step for a capsule can be separated as:

$$F_{capsule} = F_1 \cdot F_2 \cdot F_3 \qquad \text{(Eq. 10)}$$

where F_1, F_2, and F_3 reveal the ratio of ampicillin amount which transfers as an intact form from step to step. The zero moments for solution and powder thus become:

$$F_{solution} = F_3 \qquad \text{(Eq. 11)}$$

$$F_{powder} = F_2 \cdot F_3 \qquad \text{(Eq. 12)}$$

Corresponding to MDT, the relative extent of absorption, F_{rel}, is defined as:

$$F_{rel} = F_{capsule\ (or\ powder)}/F_{solution} \qquad \text{(Eq. 13)}$$

The F and F_{rel} values are listed in Table III.

Drug Flow Diagram of Ampicillin Products—Scheme II depicts the drug flow diagram summarizing the drug flow after oral administration of two kinds of ampicillin capsules. The intrinsic MRT, which is a time component related to each step in the total MRT, is given in the box and the transfer ratio from step to step is written on the arrow. It should be noted that this box exhibits a quite different concept from the classical compartment. We call the box a component. This is very similar to the strong component concept (19). The detailed discussion is given later.

The absorption kinetics of some ampicillin products were compared by means of a previous method (20), but that report did not give a clear explanation for the incomplete absorption of orally administered ampicillin. Scheme II clearly shows that some portions of ampicillin are lost before entering the systemic circulation. This may be due to incomplete disintegration of a capsule or incomplete dissolution or degradation to an unavailable form. In the case of the trihydrate form, the loss in the disintegration process is 14%, but the dissolution of the dispersed drug is perfect, whereas the loss of the anhydrate form in the dissolution process is 25%.

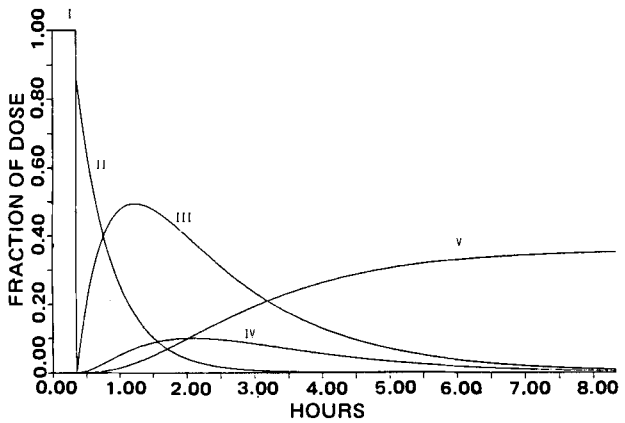


Figure 2—*Computer simulations of ampicillin amount* versus *time curves in five components for the trihydrate form. The drug levels are simulated by a convolution method. Key: (I) capsule form; (II) dispersed drug; (III) released drug in the GI tract; (IV) drug amount in body; (V) amount of urinary excreted drug.*

The interesting observation is that the intrinsic MRT of released drug in the GI tract is the greatest of all time components, and it means that the absorption of released ampicillin is the rate-determining step. Therefore, the dissolution rate does not appreciably affect the plasma peak levels. Besides, the transfer ratio from solution to systemic circulation is the lowest (53%) of all transfer ratios. It is suggested that the pharmaceutical improvement of absorption in the released state (esterification, *etc.*) is more effective than that of dissolution in order to obtain high plasma peak levels.

Simulations of Ampicillin Levels in Each Component—To simulate the ampicillin levels in each component shown in Scheme II, the following approximation was adopted. It was assumed that all the steps except for disintegration were expressed by the monoexponential equations, and that the disintegration step was represented by the lag time, because the collapse of a capsule is expected to occur abruptly. Actually the lag time was observed in the experimental time course data for a capsule form. The weight function of each step except for disintegration is represented by:

$$G_i = \frac{F_i}{T_i} \times \exp\left(-\frac{t}{T_i}\right) \qquad i = 2, 3, \text{ and } 4 \qquad \text{(Eq. 14)}$$

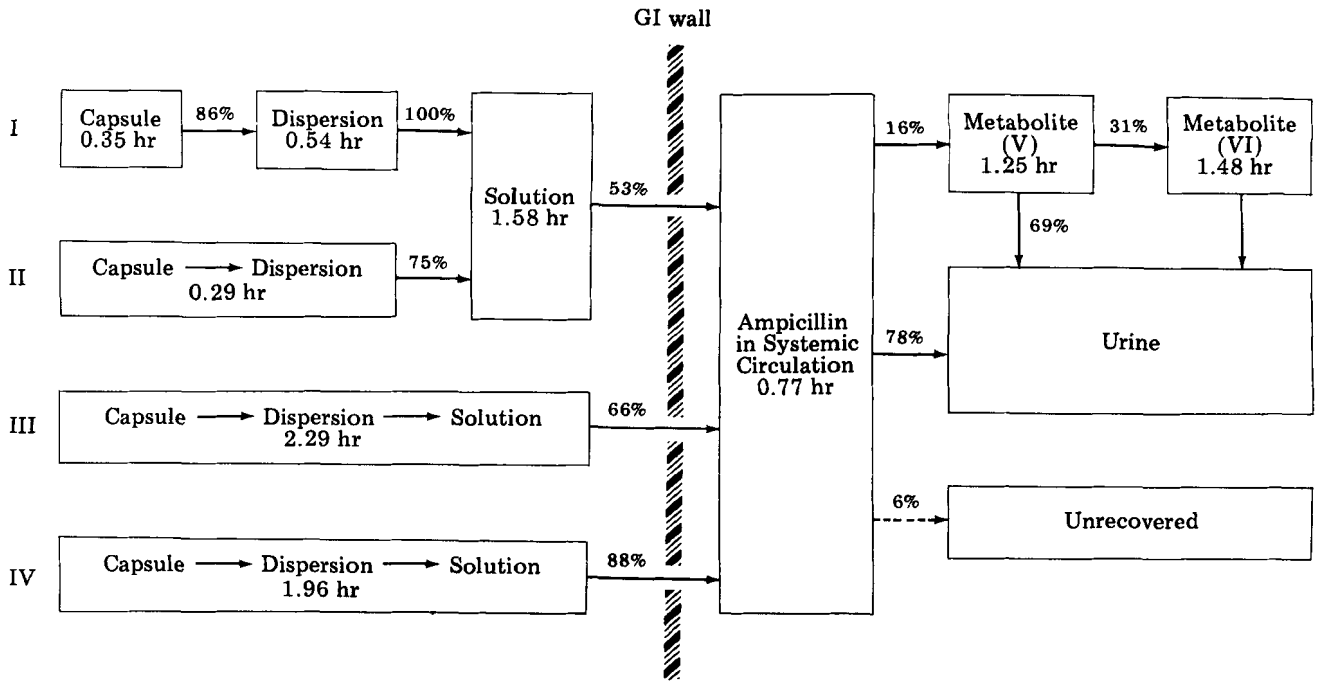
where 2, 3, and 4 reveal the dissolution, absorption, and disposition processes, respectively. It is noted that the zero and first moments of G_i *versus* time curve just become F_i and T_i, respectively.

Figure 2 shows ampicillin fraction *versus* time curves in five components after oral administration of trihydrate capsules. Drug levels in the body are much less than those in the GI tract, and the area under the curve (*AUC*) of body levels (Curve IV) is only 25% of released drug (Curve III).

DISCUSSION

Bioavailability is defined as the rate and extent of absorption of a drug from its dosage form (21). The absolute bioavailability is determined by a comparison of the measured characteristics after oral and intravenous administration, so long as instantaneous and complete bioavailability is assumed for intravenous injection. The zero moment (*AUC* or urinary recovery) expresses the amount profile, and the first moment (MRT) expresses the time profile. Therefore, the rate of absolute bioavailability is represented by the MAT, and the extent of absolute bioavailability is the fraction of dose absorbed (F). The relative bioavailability is determined by comparing the absorption behavior of a test preparation of a drug with that of its standard preparation. Thus, the MDT or MDIT is the indication of the rate of relative bioavailability, when solution or powder is specified as the reference standard. The extent of relative bioavailability is expressed by F_{rel}.

The absorption time of pharmaceutical alternatives can be compared by using MAT. Though MAT is a useful index of the overall absorption time of several drug products, the intravenous administration is not always possible because of toxicity or hydrophobicity of a drug. The MDT and MDIT can be useful in that case. Pharmaceutical equivalents, which lead to the identical resolved state in the GI tract, are compared in terms of MDT. In the case of poorly soluble drugs, the use of semiaqueous solutions, *e.g.*, polyethylene glycol–water solution, has been proposed as the reference standards in estimating MDT (3). However, since polyethylene glycol can have an effect not only on the dissolution process but also on the GI wall as an adjuvant, the latter effect could interfere in estimation of MDT. Hence, the MDIT is a useful indicator for relative bioavailability of very poorly soluble drugs.



Scheme III—Drug flow diagram of ampicillin and its prodrugs. Key: (I) ampicillin trihydrate; (II) ampicillin anhydrate; (III) hetacillin potassium; (IV) talampicillin hydrochloride; (V) α-aminobenzyl penicilloic acid; (VI) α-aminobenzyl penamaldic acid.

It is of interest to correlate *in vitro* tests with *in vivo* bioavailability. Because MDT and MDIT are just the extracted characteristics of *in vivo* dissolution and disintegration from a complicated biopharmaceutical process, the *in vitro* dissolution and disintegration tests can be directly correlated to these quantities.

The component is a concept that should be distinguished from the classical compartment. The compartment is related to the pharmacokinetic model which is expressed by simultaneous ordinary differential equations. The complete mixing or the steady state is assumed in a certain compartment. The number of compartments in a system is determined according to the number of exponential terms in a pharmacokinetic equation that fits well to the experimental time course data. In contrast, the component is derived from the moment analysis, which is a model-independent method. A component specifies a biological or physicochemical state of a drug, that is, in a capsule, in intestinal fluid, in plasma, as a prodrug, or as a metabolite. The drug flow diagram constructed by components gives the intuitive information about rate and extent profiles of a drug in the GI tract and systemic circulation. The diagram can be more detailed as the experimental information increases. For example, Scheme III shows the more detailed flow diagram of four ampicillin preparations. This diagram was prepared by combining the data in this article with those reported previously (8). Six percent of absorbed ampicillin was unrecovered as shown by the dotted arrow. This process is not yet confirmed and another disposition route is possible.

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