[Chem. Pharm. Bull. 15(7) 994~1001(1967)]

UDC 615.41-03-07

123. Manabu Hanano: Studies on Absorption and Excretion of Drug. Ⅶ.*1 A New Estimation Method for the Release of Drugs from Dosage Forms and the Availability *in vivo*.*2

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The convolution equation was introduced to estimate a drug release from various dosage forms in the gut.

$$X(t)=\int_0^t F(\theta)G(t-\theta)d\theta$$

From the application of the equation, the drug release *in vivo* $F(t)$ was calculated from comparison of blood level or urinary excertion of drug and/or the metablites between the ingestions of a dosage form, $X(t)$, and the dissolved solution, $G(t)$. The evidence of merits of this method and the deviation of the results from the real value caused by the approximation for numerical calculation were investigated by means of a theoretical model.

The actual sulfamethylthiadiazole release from the tablet in human gut was estimated from the urinary excretion by using this calculation method also.

(Received October 19, 1966)

The release rate *in vivo* of drugs from various dosage forms is one of the most important property concerning the effectiveness of drugs, since the release rate often determines the over-all absorption and then affects the blood level of drugs as shown in the recent pharmaco-kinetic study.[1] In fact, there were some instances of actual therapeutic failure which was considered to be caused by the ineffectiveness due to the slow release of drugs from the dosage forms and the poor availability, or by the intolerable effect due to the sudden change of the release property when the patients were controlled for a long time by the drug.[2] The importance of studies on the dissolution or the release property *in vivo* has been emphasized by the recent development of pharmaceuticals of sustained-release and long acting drugs. Nevertheless, our knowledge about the release of drug *in vivo* is still poor especially in human due to insufficient number of the published data. This paucity of data would be doubtless barrier to progress the standard method *in vitro* to test the clinical usefulness of the dosage form, for example, the disintegration tests and dissolution rate.

The absorption rates of drugs after the oral administration were estimated by Wagner, *et al.*[3] The absorption rate can also represent the release itself, if it is a rate determinant in the whole absorption process. The estimation of the release rate from this point of view is limited to the cases in which the absorption rate from the solution form is much faster than that from the solid forms, of course.

The real drug release distinguished clearly from the absorption was calculated successfully by Stelmach, *et al.*[4] using an analog computer. Their calculation theory, however, would not be so easy to turn to practise, since it requires the pharmaco-kinetic model which can express the time course of either blood level or urinary

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*1 Part Ⅵ: This Bulletin, **14**, 166 (1966).

*2 Presented to the 86th Annual Meeting of the Pharmaceutical Society of Japan, Toyama, April, 1966.

*3 Hongo, Tokyo (花野 学).

1) E. Nelson, I. Schaldemose: J. Am. Pharm. Assoc., Sci. Ed., **48**, 489 (1959).
2) G. Levy: Arch. intern. Pharmacodyn., **152**, 59 (1964).
3) J.G. Wagner, E. Nelson: J. Pharm. Sci., **52**, 610 (1963).
4) H. Stelmach, J.R. Robinson, S.P. Eriksen: *Ibid.*, **54**, 1453 (1965).

excretion after the ingestion of an immediately release drug. The composition of pharmacokinetic model with the parameters of the rate constants is only possible when the metabolic fate of the drug is clear. Even though the fate is very clear and the model can be simplified to only two successive steps of first order, the estimation of the parameters will consume a long time to follow up the time course of blood level or excretion in urine. Therefore, the development of the calculation theory which does not need any parameter would be very helpful to measure the release rate *in vivo*.

The Convolution Equation

In the present report, a convolution integral equation was introduced for the estimation of the release rate. The blood level of drug or the urinary excretion after oral ingestion of dosage form is compared directly with that after a solution ingestion, and then the drug release rate can be calculated by the de-convolution operation. A pair ingestion experiments, namely, of the aimed dosage form and of its aqueous solution, are necessary for the estimation and also the identity of the processes on the metabolism and the excretion as well as the absorption following the release between both experiments have to be assumed in the theoretical base of this method. Although the reproducibility of these pharmacokinetic parameters within same subject is still questionable in most drug. Levy, *et al.*[5] reported that the solution ingestion were reproducible enough when the same subject was used repeatedly for a short interval. Many merits can be pointed out from this comparison method. Since the pharmacokinetic parameters are not necessary, many experimental difficulties accompanied with the composition of the model can be eliminated in this comparison method. The consumption of time for the estimation of release is extremely shorten than the other methods because the data for the calculation are not necessary after the finishment of release, even for the estimation of the availability in this method.

A release rate is expressed by a function of time, no matter how complex the process is, as

$$\frac{dD}{dt}=F(t) \qquad (1)$$

where D indicates the quantity of released drug in the gut after the ingestion of unit dose.

The absorption itself after the release of drug in the gut would be very fast process and can be approximately expressed by the single step of first order. A first order net work is assumed for the rats process of the absorption in this theory, while the real value of rate constant is not necessary to estimate for further calculation. Sometime, the absorption is regulated mainly by the intrinsic factors than the quantity of the drug remaining in the gut. In such cases as mentioned above like vitamin absorption, this theory is beyond the application, of course.

For the approach to drug kinetics in body, many investigators considered a model of two open compartments with first order reactions with instaneous or continuous introduction of material. In the mathematical model the variation of the amount X of material in the i-th compartment can be written as

$$\frac{dX}{dt}=\sum_{j=1}^{n}k_{ji}X_j-\sum_{j=1}^{n}k_{ij}X_i \qquad (2)$$

where k_{ij} indicates the transfer constant from the i-th to the j-th compartment.

5) G. Levy, L. E. Hollister : J. Pharm. Sci., **53**, 1446 (1964).

Segre[6] showed that the application of transfer function which is derived from the Laplace transform permits a more straightforward approach.

The Laplace transform of the equation 2 becomes

$$(s+K_i)x_i-\sum_{j=1}^{n}k_{ji}x_j=x_{i0} \tag{3}$$

where : x_i and x_j= Laplace transforms of X_i and X_j

$$K_i=\sum_{j=1}^{n}k_{ij}$$

x_{i0}= value of X for $t=0$

s= auxiliary variable introduced with Laplace transformation.

If no drug and metabolite exists in each compartment at the time of ingestion, x_{i0} is zero and then the equation 3 becomes

$$\frac{x_i}{x_j}=\sum_{j=1}^{n}\frac{k_{ij}x_j}{s+K_i} \tag{4}$$

The ratio of two Laplace transforms x_i and x_j for any two connected compartments of the system, b, and a, is called the "transfer function between a and b,"

$$\frac{x_b}{x_a}=g(s) \tag{5}$$

Since the absorption process is approximated with a first order net system, the whole process from drug release to the excreted metabolite in the urine can be connected by a transfer function. This function indicates as

$$\frac{x(s)}{f(s)}=g(s) \tag{6}$$

where $x(s)$ indicates the Laplace transform of quantity of an urinary excreted metabolite, $X(t)$, $f(s)$ indicates that of drug release rate, $F(t)$, and $g(s)$ is the transfer function between the drug release and the metabolite excretion.

The antitransform of the transfer function $g(s)$ is called the "weighting function" between the release and the excretion.

$$L^{-1}\{g(s)\}=L^{-1}\left\{\frac{x(s)}{f(s)}\right\}=G(t) \tag{7}$$

The weighting function $G(t)$ corresponds to the function $X(t)$ in the urine when the drug is released in unit amount for an infinitesimal time, *i.e.* when $f(s)=1$ (unit impulse). When $f(s)$ is not given by an impulse, is follows that

$$x(s)=f(s)g(s) \tag{8}$$

and

$$X(t)=\int_0^t F(\theta)G(t-\theta)\,d\theta \tag{9}$$

The equation 9 is called the convolution.

6) G. Segre : Ann. N. Y. Acad. Sci., **96**, 913 (1962).

The Numerical Calculation with a Model

For actual estimation on the drug release, the de-convolution of the equation 9 can be carried out numerically. An example of such calculation can be shown with the cumulative urinary excretion curve after the ingestion of drug as follow. The urinary excretion curve after the aqueous solution ingestion in smoothed by arbitrary method, for example, a graphic integration of the excretion rate. Then, $G(t)$ is given approximately by the series of reading on the curve at equal interval Δt. $X(t)$ is given in the quite same fashion from the data after the ingestion of drug preparation of a dosage form. The approximate numbers for $G(t)$ and $X(t)$ are shown with the order of intervals as G_1, G_2, ····· and X_1, X_2, ·····, respectively. The following operations are carried out as in the ordinary division;

X_1	X_2	X_3	G_1	G_2	G_3
$=F_1G_1$	$-F_1G_2$	$-F_1G_3$	F_1	F_2	F_3
	$=F_2G_1$	$-F_2G_2$			
		$=F_3G_1$			

where F_1, F_2, ····· give the approximate values of $F(t)$ which are drug release ratios or the availability curve.

Since the integral equation is approximated by an ordinal summation in this numerical calculation, the length of interval will make the result deviate from the real value more or less. In order to investigate the relationship between the interval and the deviation, the next theoretical model was calculated with different intervals. Levy, *et al.*[7] pointed out that the dissolution of drug from a tablet can be sufficiently approximated by a rate process of the first order after a shorter lag at the initial stage. Therefore, the successive first order process was set up for the model of this investigation as follows,

$$\underset{\text{(T) Lag Time for Drug Release}}{\text{Tablet}} \xrightarrow{0.25\ \text{hr.}} \underset{\text{Drug Release}}{\xrightarrow{k_1=0.693\ \text{hr.}}}$$

$$\underset{\text{(S)}}{\text{Solution}} \xrightarrow[\text{Absorption}]{k_2=3\ \text{hr.}} \underset{\text{(B)}}{\text{Body}} \xrightarrow[\text{Excretion}]{k_3=0.3\ \text{hr.}} \underset{\text{(X or G)}}{\text{Urine}}$$

For the cumulative urinary excretions after the ingestion of an unit dose by the solution form, $G(t)$ and the tablet, $X(t)$, the following differential equations are given in this system, respectively,

$$\left.\begin{aligned} \frac{dS}{dt} &= -k_2S \\ \frac{dB}{dt} &= k_2S - k_3B \\ \frac{dG}{dt} &= k_3B \end{aligned}\right\} \qquad (10)$$

7) G. Levy, J.R. Leonards, J.A. Procknal: J. Pharm. Sci., **54**, 1719 (1965).

$$\left.\begin{aligned} \frac{dT}{d\tau} &= -k_1 T \qquad \frac{dX}{d\tau} = k_3 B \\ \frac{dS}{d\tau} &= k_1 T - k_2 S \qquad \tau = t - 0.25 \\ \frac{dB}{d\tau} &= k_2 S - k_3 B \end{aligned}\right\} \tag{11}$$

where t indicates time in hours after the ingestion.

From the integral of the equations 10 and 11 with the initial conditions, S=1 at $t=0$, and T=1 at $t=0$, and the substruction of the actual rate constants into k the excretion processes are written as follows, respectively.

$$\begin{aligned} G(t) &= 1 + 0.111 \exp(-3t) - 1.111 \exp(-0.3t) \\ X(t) &= 0 \quad 0 \leqq t \leqq 0.25 \end{aligned} \tag{12}$$

$$\begin{aligned} X(t) &= 1 + 1.180 \exp(-0.693t) - 0.071 \exp(-3t) - 2.112 \exp(0.3t) \\ t &> 0.25 \end{aligned} \tag{13}$$

Fig. 1 shows the cumulative urinary excretion curves obtained by the numerical calculation of the equations 12 and 13.

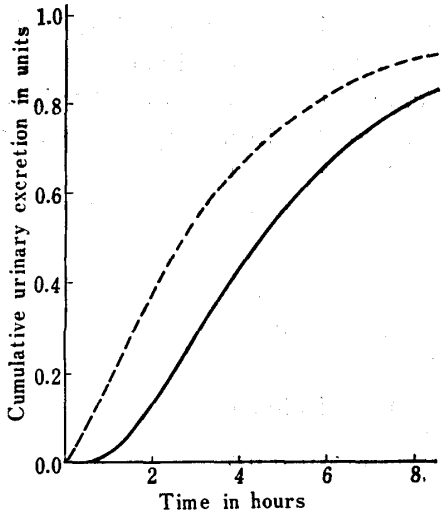

Fig. 1. Cumulative Urinary Excretions in Model

Solid line: Tablet ingestion
Dotted line: Solution ingestion

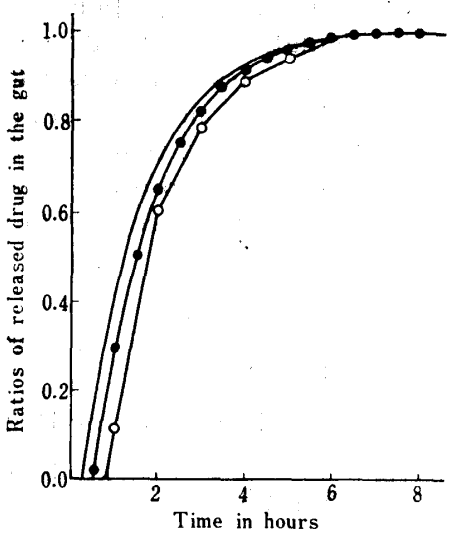

Fig. 2. Drug Release Curve in the Model

Solid line: True release
Doted line: Estimated by half an hour interval
Circule: by an hour interval

The results of the numerical de-covolution are shown in Fig. 2. In this figure, the drug release ratios are compared between the real values and those calculated numerically using the method mentioned above with intervals of half an hour and an hour.

As shown in Fig. 2, the calculated curves deviated from the real line with increasing intervals. Table I listed the parameters obtained graphycally.

The time for a half drug release can be read directly on the drug release curve, and the extrapolation gives the lag time. The half life for the real drug release

Table I. Estimated Parameters of Drug Release Process in Model

Intervals (hr.)	Time (hr.) for half drug release (A)	Lag time (hr.) for drug release (B)	Half life (hr.) for drug release rate (C = A − B)
True	1.25	0.25	1.00
0.5	1.50	0.45	1.05
1.0	1.75	0.70	1.05

process can estimate from subtracting the lag time from the time for a half drug release.

As shown in the table the half life by which the rate constant is calculated can be estimated with very minor deviation. The lag time, however, is so sensitive to the length of interval that the accuracy would be doubtful.

The release ratios for eight hours which were estimated by various intervals are shown in Table II. The release ratios after a sufficiently long time from the ingestion could be a good indicator of the availability of the drug.

Table II. Estimated Release Ratios for Eight Hours

Intervals (hr.)	0.5	1	2	4
Release Ratios for Eight Hours	0.9958	0.9940	0.9916	0.9908

As shown in Table II, these ratios are extremely close to the unity which is the real availability and therefore this calculation is useful for the estimation of availability. Since the data until eight hours are used instead of the complete collection of excreted drug, the sampling time for availability estimation can be extremely shorten by this method. If the very minor difference of the ratios between half an hour and four hours intervals is allowed to ignore, the availability could be estimated accurate enough from the two step quick operation using four hour intervals.

Release of Sulfamethylthiadiazole from the Tablet

The release rate and the availability of sulfamethylthiadiazole from the plain tablet which contains the sulfonamide and methylcellulose half and half was measured after the administration to a healthy male adult, by determining the free sulfonamide excreted in the urine colorimetrically. The results are shown in Fig. 3, in which the average excretion rate at every urine sample was drawn as the upper boundaries of rectangles. The smooth line was drawn as the areas of the rectangles would be as nearly equal to the corresponding areas under the smooth line as possible. The areas under this line were used for further numerical calculation instead of the observed values.

Fig. 4 shows the drug release curves which were calculated by the de-convolution as mentioned above using half an hour and an hour intervals, respectively. The tendency to unstable of the resulting release ratios in the shorter interval calculation will be attributed to the accumulation of experimental errors. The change to the longer interval for the calculation would be very useful to avoid such unstable as seen in the figure.

In Table III, the estimated parameters of the sulfonamide release process from the tablet are shown, as assuming the process consists of a long time and the following first order release process as well as the model case descrived above. These parameters

was estimated from the release curve calculated by using half an hour interval as described in theoretical model.

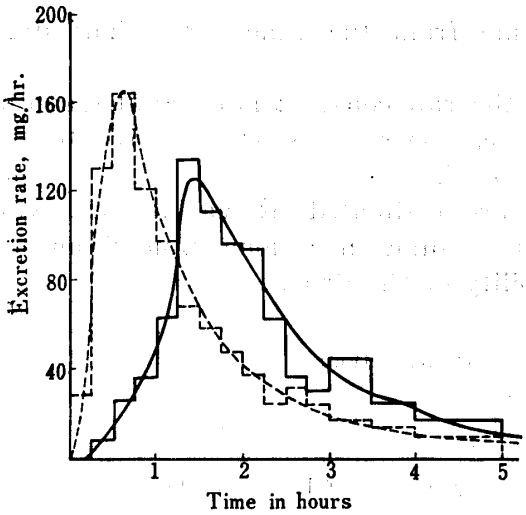

Fig. 3. Urinary Excretion Rate of Free Sulfamethylthiadiazole

Solid line: After the tablet ingestion
Dotted line: the solution ingestion

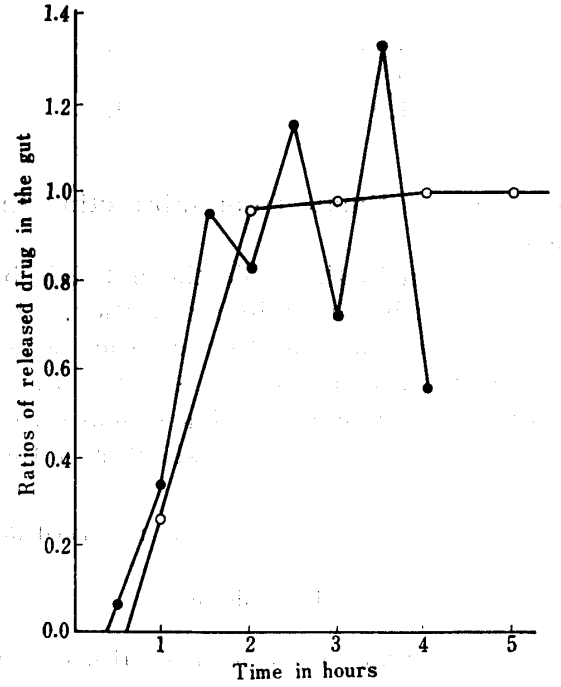

Fig. 4. Drug Release of Sulfamethylthiadiazole from the Tablet

Dotted line: Estimated by half an hour interval
Circule: by an hour interval

TABLE III. Estimated Parameters of Sulfamethylthiadiazole Release from the Tablet *in vivo*.

		(hr.)
50% Drug release time (A)		1.13
Lag time (B)		0.38
Half life of drug release (A−B)		0.75
Half life of elimination	Solution	1.9
	Tablet	1.8
Availability (Calculated by 2.5 hr. interval)		98.9%

Experimental

Tablet Formation——Fine particle of sulfamethylthiadiazole was mixed with the same amount of methylcellulose. Flat faced, 1.25 cm. diameter tablets of this mixed powder were prepared by means of a specially modified Carver model B hydraulic press. The compression was 1362 kg. approximately 1000 kg./cm^2. The tablet disintegrated in less than 6 minutes in water at room temperature with slow shaking. The weight of the tablet administered was 544.6 mg. and the dosage taken was 272.3 mg. of sulfonamide.

Administration of Drug——A male adult, 35 years old, in apparent normal health took the tablet and 200 ml. of 1% $NaHCO_3$ soln. on a fasting stomach in the morning. No food was taken until the last urine collection completed. The subject was instructed to drink water in an amount sufficient to allow him to collect urine samples. After one week, the same experiment was repeated by 200 ml. of 1% $NaHCO_3$ soln. which dissolved the tablet previously in stead of the tablet ingestion.

Urine Collection and Assay——The urine samples were collected in every 15 min. for the beginning 3 hr., 30 min. for the next an hour and an hour for the final. The volumes voided were noted and an aliquot taken and stored at about 2° until assay. The assay for the free sulfonamide in the urine was carried out by the Bratton and Marshal procedure.

The data of sulfamethylthiadiazole ingestion were taken by the authors under Dr. Eino Nelson, school of pharmacy, the state university of New York at Buffalo, Buffalo, N. Y. The authors are deeply grieved to hear of his loss.

8) A. C. Bratton, E. K. Marshall Jr. : J. Biol. Chem., **128**, 537 (1939).