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124. Hisashi Nogami and Manabu Hanano: Studies on Absorption and Excretion of Drug. Ⅷ.*1 The Release Rate *in vivo* of Antipyretic and Analgesic Drugs from Commercial Sugar Coated Tablets.*2

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The drug release property from the six commercial sugar coated tablets which contain antipyretic and analgesic igredients were estimated from comparison of the urinary excretions after the oral ingestion of tablets and the dissolved solutions in human. The igredients are sulpyrine, aminopyrine, phenacetin, bucetin, N-acetyl-*p*-aminophenol, salicylamide and Al-acetylsalicylate. The over-all mean value of the time of fifty per cent drug release in the gut was 1.62 hr. The mean availability was as good as 96.2 per cent. The release rate of Al-acetylsalicylate was slower than the others in statistically significant and also the instances of poor availability of the drug were observed. The merits of the convolution equation method for the estimation of release rate *in vivo* were demonstrated in the case of the compounded drug.

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Many kinds of dosage forms of antipyretic and analgesic drugs are commercially available in Japan. They are sugar coated tablets, plain tablets, capsules, granules, sustained-release capsules and suspensions. The release *in vivo* of drug from these dosage forms and the availability are the most interesting subject from the point of view concerning the therapeutic characteristics of the forms and also the technical level of the industries.

In the present report, the release rate of the antipyretic and analgesic drug from the commercial sugar coated tablets were estimated after the ingestion in human subjects using the method described in the preceding report.

The convolution equation for estimation of the release of drug is expressed as

$$X(t)=\int_0^t F(\theta)G(t-\theta)\,d\theta \qquad (1)$$

where $X(t)$ and $G(t)$ indicate the urinary excretion of drug or its metabolites after ingestion of a given dosage form and the dissolved form in water, respectively: $F(t)$ indicates the release rate of the drug from the given dosage form as the function of time. The metabolic fate of the drug is often complex and the several different metabolites are excreted in urine simultaneously. Sometime, the complete separation of every metabolite is so much difficult that a partial sum of the metabolites or the physical or biological magnitude which is expressed by a linear association of quantity of the metabolites is used for the indicator of the release properties. When $I(t)$ indicates such magnitude, for example, the optical density in colorimetrical assay, radio activity in tracer experiment and biological activity in bioassay, a linear equation is expressed as

$$I(t)=\sum_{i=1}^{n} a_i X_i(t) \qquad (2)$$

where $X_i(t)$ indicates the excreted i-th metabolite and a_i indicates the coefficient of the metabolites with the magnitude, $I(t)$. Substituting the equation 1 to 2, the summation of integral equation is given as

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*1 Part Ⅶ: This Bulletin, **15**, 994 (1967).

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

*3 Hongo, Tokyo (野上 寿, 花野 学).

$$I(t)=\sum_{i=1}^{n}a_i\int_0^t F(\theta)G_i(t-\theta)\,d\theta \qquad (3)$$

where $G_i(t)$ indicates the excreted i-th metabolite after the ingestion of aqueous solution of the drug.

The equation 3 can be rearranged as

$$I(t)=\int_0^t F(\theta)\sum_{i=1}^{n}a_iG_i(t-\theta)\,d\theta \qquad (4)$$

From the definition of $H(t)$ as the corresponding magnitude of $I(t)$ after the ingestion of the aqueous solution of drug, the equation 4 is rewritten as

$$I(t)=\int_0^t F(\theta)H(t-\theta)\,d\theta \qquad (5)$$

The equation 5 indicates the expanded utility of the convolution equation for the estimation of the release by bioassay, tracer technique and chemical assay of mixed metabolites.

The release rate of aluminum acetylsalicylate from the tablet containing ethoxybenzamide was possively estimated from this theory. Because the color in ferric solution by the extract of dichlorethane from the acidified urine is not contaminated by ethoxybenzamide and the metabolites unlike the hydrolyzed urine. Although the intensity of the color is not proportional to total salicylate, it can be indicated a linear equation of quantities of free salicylate and salicylurate. Therefore, the convolution equation 5 is available to estimate the release of aluminum acetylsalicylate from the incorporation of the other salicylate which is not the precursor of dichlorethane extractive salicylate metabolites.

Experimental

Materials——Six sugar coated tablets which were commercially available in winter (1965～1966) were investigated. They are produced by six major pharmaceutical industries in Japan. The containing antipyretic and analgesic igredients and the recommended dose for adult after every meals are listed as follows.

Tablet 1 contains sulpyrine 30 mg., N-acetyl-*p*-aminophenol 45 mg., other 4 neurotropic drugs and 2 vitamins in a tablet, and the dose is 4 tablets. Tablet 2 contains salicylamide 500 mg., phenacetin 165 mg., other 3 neurotropic drugs and 4 vitamins in 3 tablets, and the dose is 3 tablets. Tablet 3 contains bucetin 100 mg., ethoxybenzamide 100 mg., Al-acetylsalicylate 180 mg., other 4 neurotropic drugs and ascorbic acid in 3 tablets, and the dose is 3 tablets. Tablet 4 contains aminopyrine 16 mg., N-acetyl-*p*-aminophenol 50 mg., other 4 neurotropic drugs and 5 vitamins in a tablet, and the dose is 3 tablets. Tablet 5 contains aminopyrine 30 mg., phenacetin 50 mg., other 6 neurotropic drugs and thiamine in 3 tablets, and the dose is 3 tablets. Tablet 6 contains Al-acetylsalicylate 65 mg. as acetylsalicylate, N-acetyl-*p*-aminophenol 30 mg., other 4 neuropropic drugs and 2 vitamins in a tablet, and the dose is 4 tablets.

Ingestion of Drug and Urine Collection——The tablets of industry recommended dose are given to male adults, healthy volunteers 25 to 35 years old, with 200 ml. of water on a fasting stomach. No food was taken during the beginning 2 hr. The subject was instructed to drink water in an amount enough to allow him to collect urine samples. After 4 days elapsed, the same experiment was repeated by the solution dissolved the tablet previously in 200 ml. of water, although the dissolution is incomplete in Al-acetylsalicylate. The urine samples were collected for 30 min. just before ingestion of drug for the blank, in every 30 min. for the beginning 3 hr., in 1 hr. for the next 2 hr. and the final sample at 10 hr. after ingestion in most cases.

Metabolites and Their Assay in Urine——For the drugs of N-acetyl-*p*-aminophenol, bucetin and phenacetin, the conjugated *p*-aminophenol was determined by the indophenol coloric reaction after hydrolysis of the urine as described by Nelson, *et al.*[1] For aminopyrine and sulpyrine, free and acetylated 4-aminoantipyrine was determined by producing the azo dye after hydrolysis as described by Brodie, *et al.*[2] For

1) E. Nelson, T. Morioka: J. Pharm. Sci., **52**, 864 (1963).
2) B. B. Brodie, J. Axelrod: J. Pharmacol. Exptl. Therap., **99**, 171 (1950).

salicylamide and Al-acetylsalicylate of Tablet 6, salicylate in hydrolyzed urine was determined colorimetrically by iron complex. For Al-acetylsalicylate of Tablet 3, the color of iron complexes by free salicylate and salicylurate was measured from dichlorethane extract of unhydrolyzed urine as same as described by Smith, *et al.*[3]

Experimental Panel——The experiments were designed separately for the tablets from 1 to 3 and from 4 to 6. For each set, a randomized block design was set up and 3 volunteers completed the ingestions of 3 tablets and the corresponding solutions. The other 3 volunteers were followed the other 3 tablets and solutions.

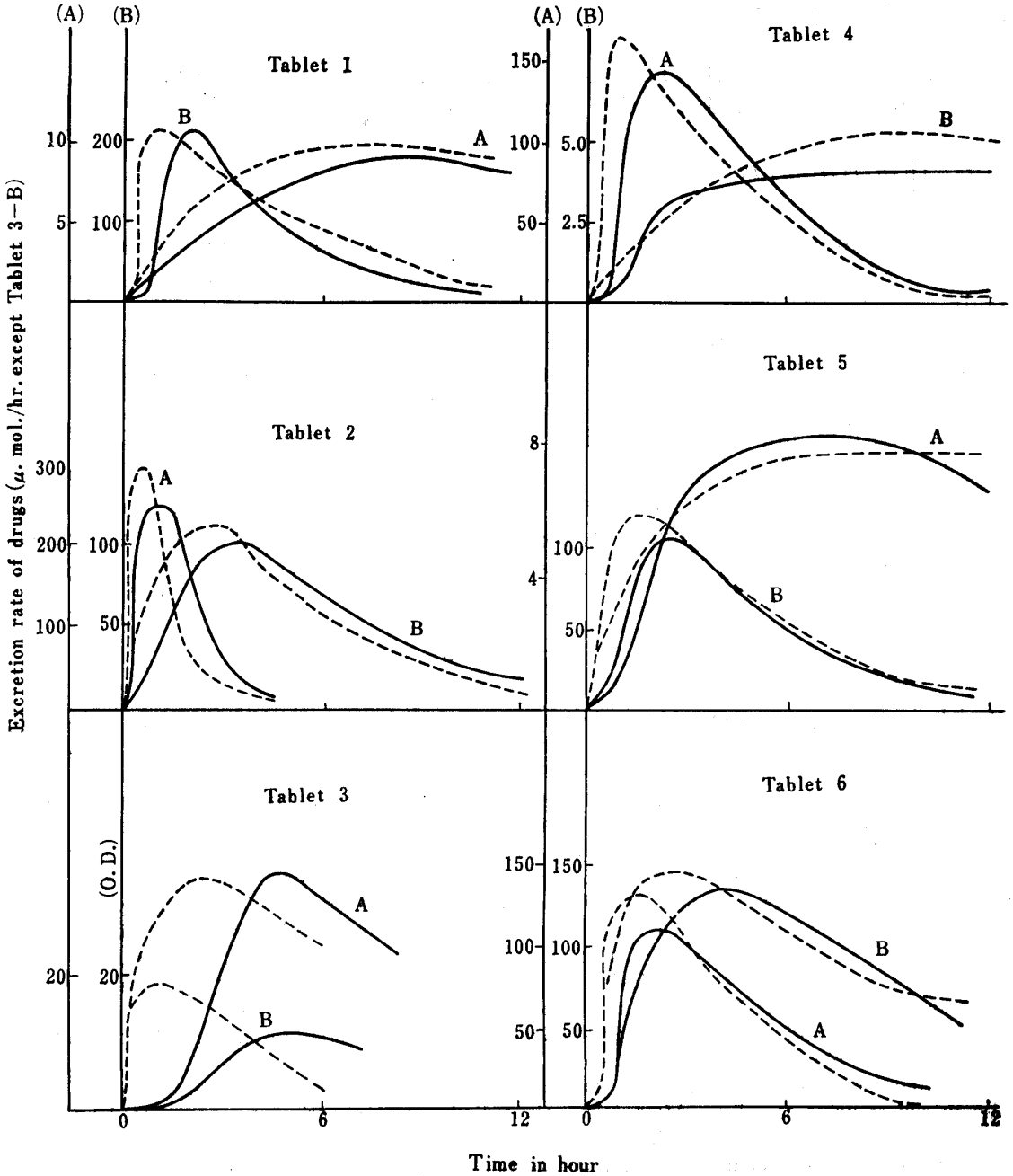

Fig. 1. The Instances of Urinary Excretion Rate versus Time Curve of the Drug and/or Its Metabolites

Solid Line: After Tablet Ingestion	Dotted Line: Solution Ingestion
Tablet 1, A: Sulpyrine	B: Acetylaminophenol
Tablet 2, A: Salicylamide	B: Phenacetin
Tablet 3, A: Bucetin	B: Al-acetylsalicylate
Tablet 4, A: Acetylaminophenol	B: Aminopyrine
Tablet 5, A: Aminopyrine	B: Phenacetin
Tablet 6, A: Acetylaminophenol	B: Al-acetylsalicylate

3) P. K. Smith, H. L. Gleason, C. G. Stoll, S. J. Ogorzalek: J. Pharmacol. Exptl. Therap., **87**, 237 (1946).

Results and Discussion

The examples of urinary excretion resulted in subject H for the Tablet 1, 2 and 3, and subject I for the Tablet 4, 5 and 6 are shown in Fig. 1. The solid and dotted lines express the urinary excretion rates versus time after the ingestion of the tablet and the corresponding solution, respectively. The lines were smoothed by the graphic area method as described in the preceding paper.

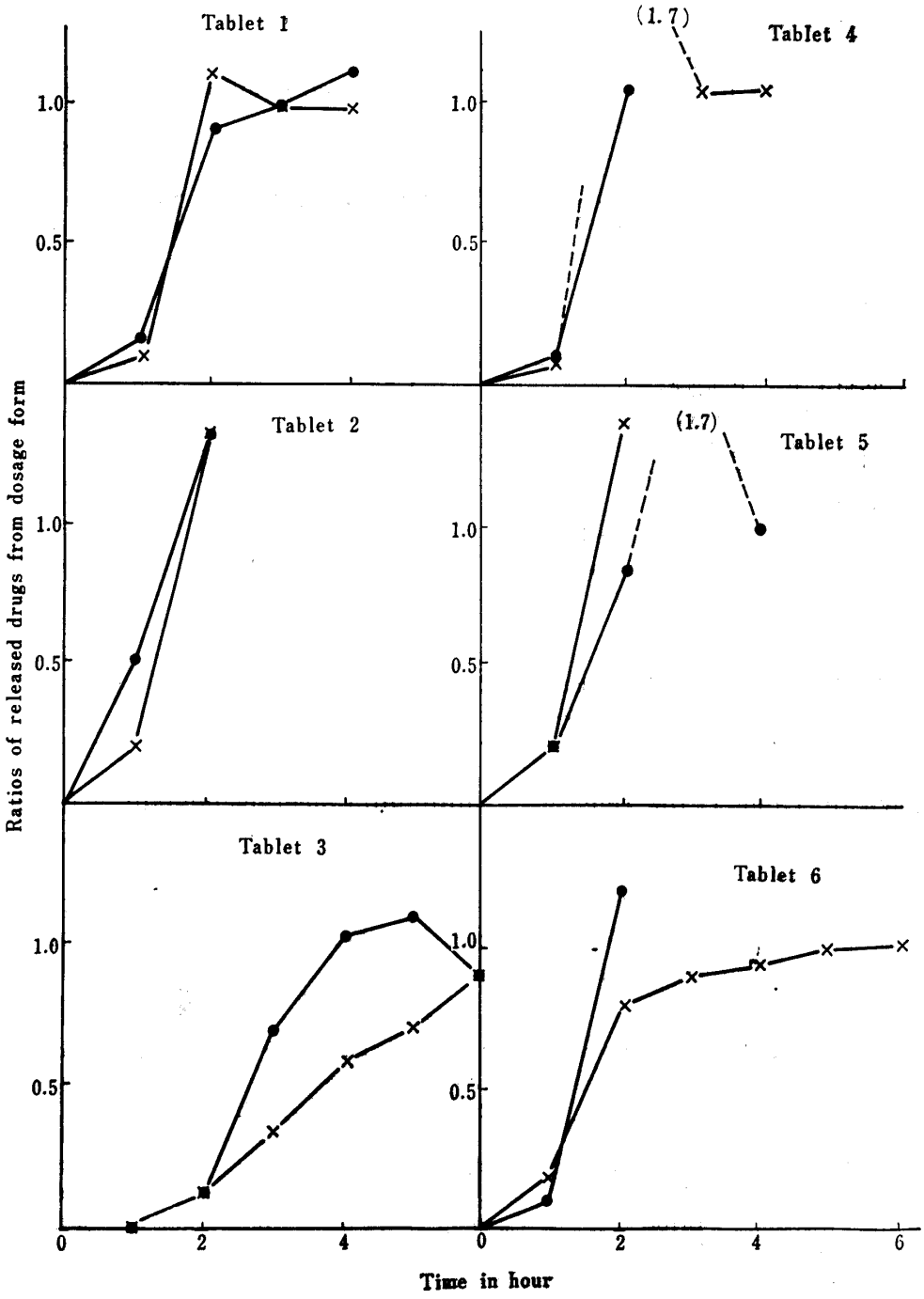

Fig. 2. The Instances of Estimated Release Ratio versus Time Curve (Availability Curve) of the Tablets

Key: See Fig. 1, Dot; A in Fig. 1, Cross; B in Fig. 1.

As shown in Fig. 1, the excretion curve for tablets, solid lines, were so clearly delayed from the corresponding solution, dotted lines, that the releases of drug from the sugar coated tablet were possibly estimated without difficulty.

Fig. 3 shows the examples of the release ratio curves, corresponding the data shown in Fig. 1. They were obtained by the de-convolution from the smoothed cumulative excretion data which are the area under the lines in Fig. 1 as described in the preceding report.

As shown in Fig. 2, the sigmoid lines connecting the segment data were found in every experiment, although some instances indicated the unstable tendency. The sigmoids also indicate the reliability of the approximation by the first order rate process and lag time of the release.

The times for the fifty per cent releases estimated graphically from the lines as shown in Fig. 2 are listed in Table I.

Table I. The Time of 50% Release of Drug from the Sugar Coated Tablet in the Human Guts

Sample	Medication	Time of 50% release in hours		
		Subject I	II	III
Tablet 1	Sulpyrine	1.5	1.7	1.5
	Acetylaminophenol	1.4	1.2	1.5
Tablet 2	Salicylamide	1.0	1.1	1.0
	Phenacetin	1.3	1.1	1.1
Tablet 3	Bucetin	2.6	2.1	1.8
	Al-acetylsalicylate	3.5	3.5	3.8
Tablet 4	Acetylaminophenol	1.4	1.3	1.2
	Aminopyrine	1.3	1.4	1.4
Tablet 5	Aminopyrine	1.4	0.8	1.2
	Phenacetin	1.3	1.1	0.6
Tablet 6	Al-acetylsalicylate	1.5	2.7	2.3
	Acetylaminophenol	1.4	1.8	1.5

As shown in Table I, the release of aluminum acetylsalicylate was slower than the others and the times of the fifty per cent releases were sufficiently longer in statistically significant in both Tablet 3 and 6.

The analysis of variance of these data was carried out separately to the sets of experimental panel, namely, a set of Tablet 1, 2 and 3, and the other of Tablet 4, 5 and 6. The results are shown in Table II.

Table II. The Analysis of Variance for the Time of 50% Release *in vivo*.

		S.S.	D.F.	M.S.
Tablet 1~3	Drug	14.08	5	2.816[a)]
	Man	0.04	2	0.02
	Error	0.15	10	0.015
	Total	14.27		
Tablet 4~6	Drug	2.56	5	0.512[b)]
	Man	0.08	2	0.040
	Error	1.23	10	0.123
	Total	3.87		

a) $p<0.01$ *b*) $p<0.05$

The slow release of aluminum acetylsalicylate demonstrated in this experiment shows good coincidence with the report of Levy, *et al.*[4] using the powder of aluminum acetylsalicylate. As pointed out in the report, the slow release will be atributable to the very slow dissolution of aluminum acetylsalicylate powder than the tablet disintegration property in the gut. The drug incorporated with the aluminum in the tablet also indicated the slow release very evidently in Tablet 3 but not so in Tablet 6. This result may be considered as if the aluminum can disturbe the release of the incorporated substance from the tablet. However, it should be noticed that the tablets in this experiment were made by the different production, so that the incorporated drug can also differ in the release property according to the manufacturing process of the tablet.

The lag times of the release process after the ingestion were estimated from the extrapolation of the straight line connecting between an hour and two hours release on the release ratio curve, and listed in Table Ⅲ. The values resemble in every tablet except Tablet 3 as shown in the table.

Table Ⅲ. The Lag Time of Drug Release *in vivo*.

Sample	Medication	Lag time in hours		
		Subject Ⅰ	Ⅱ	Ⅲ
Tablet 1	Sulpyrine	0.8	0.9	0.5
	Acetylaminophenol	0.9	0.9	1.0
Tablet 2	Salicylamide	0.4	0.6	0.1
	Phenacetin	0.8	0.7	0.8
Tablet 3	Bucetin	1.7	1.5	1.0
	Al-acetylsalicylate	1.5	1.2	0.9
Tablet 4	Acetylaminophenol	0.9	0.8	0.9
	Aminopyrine	0.9	0.6	0.8
Tablet 5	Aminopyrine	0.7	0.5	0.5
	Phenacetin	0.8	0.8	0.0
Tablet 6	Al-acetylsalicylate	0.6	0.9	1.0
	Acetylaminophenol	0.9	0.9	1.0

Thus the normal subtraction of the lag time from the corresponding time of fifty per cent release gives the first order rate constant for the dissolution process. The rate constants are listed in Table Ⅳ.

Table Ⅳ. The Estimated Rate Constants of First Order for the Release Process *in vivo*.

Sample	Medication	Rate constant of release process (hr^{-1})		
		Subject Ⅰ	Ⅱ	Ⅲ
Tablet 1	Sulpyrine	0.99	0.87	0.69
	Acetylaminophenol	1.39	2.31	1.39
Tablet 2	Salicylamide	1.16	1.39	0.77
	Phenacetin	1.39	1.73	2.31
Tablet 3	Bucetin	0.77	1.16	0.87
	Al-acetylsalicylate	0.35	0.30	0.24
Tablet 4	Acetylaminophenol	1.39	1.39	2.31
	Aminopyrine	1.73	0.89	1.16
Tablet 5	Aminopyrine	0.99	2.31	0.99
	Phenacetin	1.39	2.31	1.16
Tablet 6	Al-acetylsalicylate	0.77	0.39	0.53
	Acetylaminophenol	1.39	0.77	1.39

4) G. Levy, B. A. Sahli : J. Pharm. Sci., **51**, 58 (1962).

As shown in Table IV, only aluminum acetylsalicylate in Tablet 3 and 6 indicated the significantly slow rate constants of the first order release process. The most interesting fact was that the tendency of slow release rate of the drug incorporated with the aluminum was disappeared in the real rate constants while such drug showed statistically significantly slow release in the over-all process. The quick estimation of the availability was carried out by using the deconvolution from the data of the cumulative urinary excretion for 6 hours. Table V shows the percentage of availability which means the release ratio for 12 hours after the ingestion. This is a practically accurate approximation as reported in the preceding report.

Table V. The Percentages of Availability of the Tablets

Sample	Medication	Availability (%)			
		Subject I	II	III	Mean
Tablet 1	Sulpyrine	94.4	82.8	76.3	84.5
	Acetylaminophenol	72.0	115.8	107.9	98.6
Tablet 2	Salicylamide	115.3	110.2	103.5	109.7
	Phenacetin	101.1	93.0	84.0	92.7
Tablet 3	Bucetin	111.1	99.4	79.9	96.8
	Al-acetylsalicylate	77.9	116.9	56.0	83.6
Tablet 4	Acetylaminophenol	99.2	96.6	109.1	101.6
	Aminopyrine	111.1	98.8	96.7	102.2
Tablet 5	Aminopyrine	110.4	98.7	99.6	102.9
	Phenacetin	80.4	107.2	88.7	91.8
Tablet 6	Al-acetylsalicylate	99.2	53.6	108.4	87.1
	Acetylaminophenol	93.7	112.0	100.7	102.1

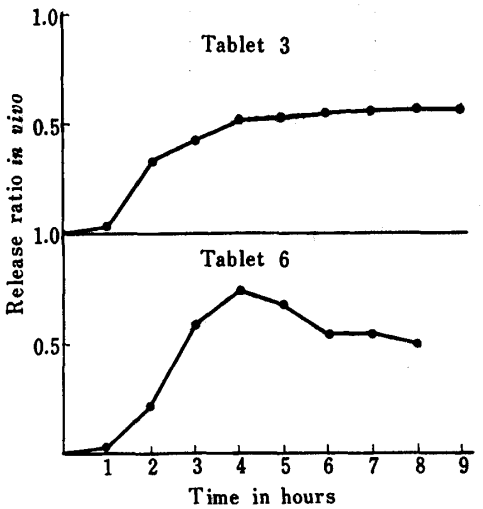

Fig. 3. Two Instances of Poor Al-acetylsalicylate Release Curve *in vivo*

As shown in Table V, the availabilities are probably good in average, although the estimated values showed rather larger variation than that expected from the complete recovery method.[5] The two interesting instances of poor availability were observed on the aluminum of Tablet 3 and 6. Fig. 3 shows the release curves of the instances.

As seen in Fig. 3, both curves show the saturation pattern and the poor availabilities do not seem to be caused by the insufficient time of the urinary sampling.

The results of this experiment indicate that most commercial sugar coated tablets of antipyretic and analgesic drugs in Japan showed excellent availability when they were administered in empty stomach, and that the drug release rate in human gut from these tablets was estimated to be 1.62 hours for 50% release in the over-all average. The limitation of the disintegration time in Japanese Pharmacopeia VI is 1.5 hours for sugar coated tablet and all tablets in this experiment had to pass this test at least at the sampling test in the industries before the supply in commercial. The time of fifty per cent release *in vivo*, 1.65 hours, was incidentally close to the limitation of

5) D. Melnick, M. Hochberg, B. L. Oser : J. Nutrition, **30**, 67 (1945).

the disintegration test *in vitro*, 1.5 hours. The actual disintegration time would have been shorter than the limitation and the release time represents the fifty per cent value, no more than end point, so that this investigation clearly showed the inadequacy of the *in vitro* test if the disintegration test is considered to indicate the real release rate in the gut. Since the disintegration test does not measure the real dissolution of drug, the considerable deviation from the release *in vivo* can be expected in the test on the slightly soluble drug. As described above, the release rate was extremely slow in the case of aluminum acetylsalicylate. The mean time for fifty per cent release of aluminum acetylsalicylate was 2.88 hours, but the mean other than aluminum acetylsalicylate was 1.14 hours.

The over-all mean availability reached to 96.2 per cent. This value is quite sufficient for the sugar coated tablet and indicates the high technical level of the industries. It is also considered that the disintegration test of Japanese Pharmacopeia Ⅶ is almost good if it is only used for the assurance to the physiological availability within this investigation at least. Two instances of poor availability of aluminum acetylsalicylate, however, should be noticed to show the limitation of the test. Consequently, a test *in vitro* which is commensurable with the real release in the gut is strictly desired in stead of the Pharmacopeia test, and the dissolution test reported by Levy, *et al.*[6] should be noticed for this purpose.

A part of expenses for this work was defrayed by the Grant-in-Aid from the Ministry of Welfare, which is gratefully acknowledged.

6) G. Levy, B. A. Hayes : New Engl. J. Med., **262**, 1053 (1960).