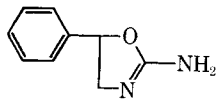
In Vitro Dissolution Rates of Aminorex Dosage Forms and Their Correlation with *in vivo* Availability

W. A. CRESSMAN, C. A. JANICKI, P. C. JOHNSON*, J. T. DOLUISIO†, and G. A. BRAUN

Abstract □ The object of the study was to develop an oral dosage form of aminorex which would produce prolonged, stable plasma levels of total drug. Since no definite set of dissolution conditions exists for the evaluation of the *in vivo* availability of a given drug, an arbitrary set of dissolution conditions was chosen. *A priori* it was assumed that a correlation existed between *in vitro* dissolution and *in vivo* availability. If this were true, changes in dosage form release characteristics could be evaluated *in vitro* before going to man. *In vivo* availability was determined in human subjects, by determination of total plasma radioactivity following administration of aminorex-^{14}C. Several of the subjects were crossed over from one dosage form to another. Good correlation was obtained between *in vitro* dissolution and *in vivo* absorption rates. *In vivo* absorption rates of intact drug were calculated from the plasma data for total radioactivity. A one-compartment open model was used to describe the system. Dosage forms which produced prolonged blood levels of radioactivity were found to give prolonged clinical response.

Keyphrases □ Sustained-release dosage forms—aminorex-^{14}C □ Aminorex-^{14}C dosage forms—*in vitro* dissolution rates, correlation *in vivo* availability □ Kinetic analysis—aminorex-^{14}C absorption, elimination □ Model, one-compartment—drug absorption □ Scintillometry—analysis

During the course of the development of a new nonamphetamine anorexigenic agent, aminorex,[1] it was decided to examine the possibility of once a day dosage.



Since there is no definitive set of dissolution conditions one can use to evaluate the *in vivo* availability of a given drug, an arbitrary set of dissolution conditions was chosen. *A priori* it was assumed that a correlation existed between *in vitro* dissolution and *in vivo* availability. If this were true, changes in dosage form release characteristics could first be evaluated *in vitro*. The *in vitro* results would be considered in light of observed *in vivo* plasma levels. Following initial studies *in vivo* with a dosage form having prolonged *in vitro* release characteristics, changes in release patterns would be monitored in the dissolution system before returning to man. Such a correlation would reduce the number of *in vivo* evaluations required to develop an acceptable prolonged-release dosage form.

There have been several studies published (1–6) on the evaluation of sustained-release drugs. However, there are little data in the literature correlating blood levels and dissolution rates for developmental sustained release formulations. This paucity of data is particularly evident if one looks for correlations of dissolution rate and plasma levels of compounds which are given in low doses. Low dose compounds present a special problem since it is difficult to determine the concentration of intact drug in the various tissues of the body. One approach used to demonstrate sustained release effects is multiple *in vivo* studies (1–4, 6) with sustained-and nonsustained-release formulations. Similarity between the plasma levels of drug produced by the sustained-release dosage form and immediate-release dosage forms administered three times daily is considered to be proof of a sustained-release effect. This method, however, usually assumes that one has an acceptable sustained-release formulation to be evaluated. A more quantitative correlation between dissolution rate and plasma levels was desired in this instance.

One of the easiest methods for evaluation of plasma levels of low dose material is the use of radioactively labeled compounds. A drawback of the method is that due to the low levels of radioactivity sometimes obtained, one still cannot conveniently separate the total plasma radioactivity into that of intact drug and that attributable to metabolite(s). Low plasma levels of radioactivity which could not be conveniently related to intact drug were obtained for the metabolic fate of aminorex.

Using data for total radioactivity per volume of plasma a pharmacokinetic model is proposed based on the work of Wagner and Nelson (7). This model has proven useful for correlating observed plasma levels with dissolution rates. It has been the authors' experience with this compound and others that the basic requirement of the model of first-order loss of radioactivity from plasma is a rather general one. It is realized that the rate constant for disposition of radioactivity generated by this method has no physiologic meaning; however, it provides a useful tool for evalu-

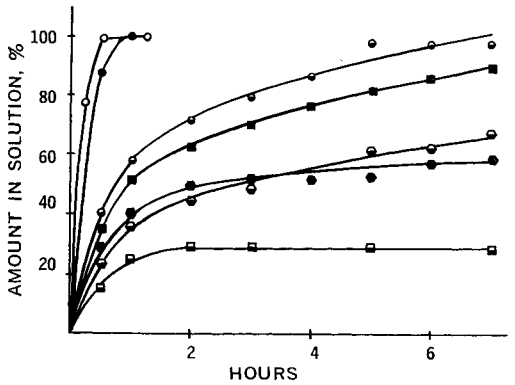


Figure 1—*Dissolution profiles of Dosage Forms B (●), C (○), D (▣), E (■), F (◒), G (◓) and H (●) obtained using the dissolution method described in the text.*

[1] Apiquel (2-amino-5-phenyl-2-oxazoline) McNeil Laboratories, Inc.

Table I—Various Formulations Used in this Study to Evaluate and Develop a Sustained-Release Dosage Form of Aminorex

Formula	Salt Form Used	Dosage Form	Dose/Tablet As mg. Free Base
A	Aminorex fumarate	Solution	7.5
B	Aminorex base	Nonsustained-release tablet	7.5
C	Aminorex pamoate	Nonsustained-release tablet	7.5
D	Aminorex pamoate	Sustained-release, nondisintegrating tablet	15
E	Aminorex fumarate	Sustained-release, nondisintegrating tablet	15
F	Aminorex fumarate	Sustained-release, nondisintegrating tablet	10
G	Aminorex fumarate	Sustained-release, nondisintegrating tablet	15
H	Aminorex fumarate	Sustained-release, nondisintegrating tablet	20

ating the extent of absorption of a drug administered in various dosage forms and formulations. The basic assumption of the model, as with others similar to it, is that the drug is absorbed intact and is not metabolized or degraded within the gastrointestinal tract.

Using the proposed model, plasma level data may be presented in a fashion which permits one to make a more quantitative estimate of the degree of correlation of absorption rate with dissolution rate. The data presented demonstrate that it is difficult to design a dissolution system which is sensitive to all changes in formulation without using the hindsight technique, *i.e.*, develop a system *in vitro* which parallels differences which have been observed *in vivo*. Nevertheless, by using an arbitrary dissolution technique it was possible to distinguish between formulations of the drug having differing rates of *in vivo* availability.

EXPERIMENTAL

In Vivo Experiments—The *in vivo* experimental design consisted of four to six subjects per dosage form. For the evaluation of formulations of the aminorex pamoate salt only two subjects were used. Several of the subjects used in the above studies were crossed-over among several dosage regimens. The drug was administered before breakfast, following an overnight fast. No food was consumed for at least 2 hr. after dosing, water was permitted *ad libitum*. Food consumption 2 hr. after dosing was up to the subjects' individual desires. Blood samples were withdrawn at time intervals dictated by the specific dosage form, usually at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 12, and 24 hr. Total urinary output collections were made at 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hr. Plasma and urine samples were dissolved directly in scintillator and analyzed for total radioactivity using a Packard Tri-Carb[2] liquid scintillation spectrometer and internal standards. The amount of radioactivity present in each sample was expressed as mcg. of aminorex (base)/l. of plasma for plasma samples and as percent of total radioactivity administered for urine samples.

In Vitro Experiments—On the basis of preliminary experiments an *in vitro* dissolution method was arbitrarily chosen to determine differences in dissolution characteristics of the dosage forms to be studied. Correlation of *in vivo* and *in vitro* results from preliminary formulations was then used as a guideline for the development of "acceptable" sustained-release formulations. A formulation which gave prolonged, stable plasma levels over a period of 8–12 hr. and 100% availability was desired.

The *in vitro* procedure is a modification of the method of Levy and Hayes (8) and uses a 1000-ml., three-necked round-bottom flask filled with 750 ml. of dissolution medium and operated at 37 ± 1°. The solution is stirred at 50 r.p.m. with a Teflon paddle located 6 cm. from the bottom of the flask. Dissolution media are USP (9) simulated gastric fluid (without pepsin) for the first hour then USP (9) simulated intestinal fluid (without pancreatin) for the balance of the experiment. The results are plotted as percent of drug in solution *versus* time.

Following the development of a nondisintegrating tablet which was considered acceptable using the *in vitro* dissolution test, radioactive tablets were prepared using the same procedures on a much smaller scale. The *in vitro* dissolution rates of the radioactive tablets were determined and compared with the values obtained for the nonradioactive tablets. In all cases equivalent dissolution profiles were obtained for the radioactive tablets to be used in the human studies and the nonradioactive clinical tablets. The radioactive tablets were submitted for *in vivo* evaluation.

The aminorex-^{14}C used to prepare the various batches of tablets was diluted to the desired specific activity (approximately 50 μc./dose) by recrystallization except in the case of the sustained-release 15-mg. tablets of aminorex fumarate (Dosage Form G). For this batch aminorex-^{14}C was physically mixed with aminorex to produce the desired specific activity. Aminorex-^{14}C was specifically labeled with ^{14}C in the 2 position by cyclization of the amino alcohol with cyanogen-^{14}C bromide.

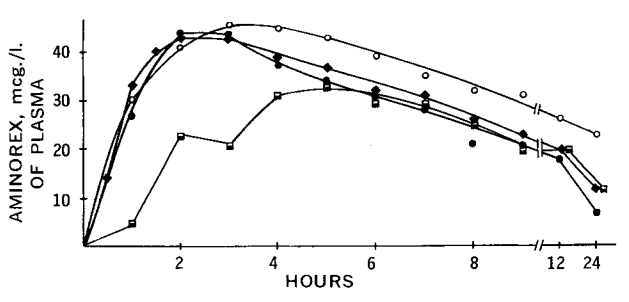


Figure 2—*Average plasma levels of radioactivity, expressed as micrograms of aminorex, obtained following oral administration of Dosage Forms A (◆), B (●), C (○), and D (■). A, B, and C contained 7.5 mg. of aminorex and D contained 15 mg. of aminorex.*

[2] Series 3000, Packard Instrument Co., La Grange, Ill.

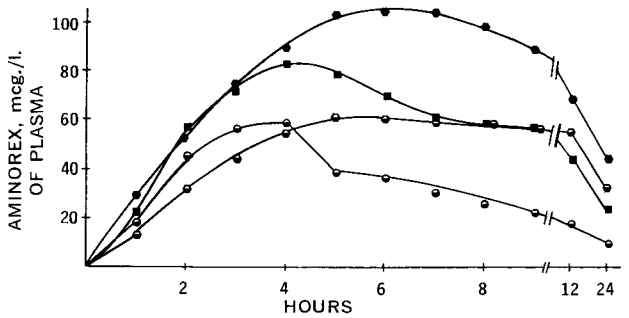


Figure 3—*Average plasma levels of radioactivity, expressed as micrograms of aminorex, obtained following oral administration of Dosage Forms of E (■), F (◒), G (◒), and H (●). E and G contained 15 mg. of aminorex, F contained 10 mg., and H contained 20 mg. of aminorex.*

Table II—Cumulative Urinary Excretion of Radioactivity Following Oral Doses of Aminorex (Values Are Expressed as Percent of Administered Dose)

Hours	Dosage Form A	B	C	D	E	F	G	H
2	12 (3.7)[a]	9 (1.6)	8 (1.3)	1 (0.1)	4 (1.7)	4 (2.2)	2 (0.4)	3 (0.8)
4	25 (3.1)	22 (2.5)	22 (4.7)	5 (0.2)	15 (4.8)	15 (7.4)	8 (1.8)	11 (1.8)
6	40 (3.1)	32 (3.7)	37 (2.6)	8 (0.8)	25 (6.7)	22 (8.8)	18 (4.8)	25 (5.0)
8	49 (6.2)	40 (4.1)	48 (3.9)	12 (1.4)	33 (5.9)	34 (9.4)	27 (4.8)	34 (4.9)
10	60 (5.7)	47 (4.0)	55 (0.4)	14 (1.8)	40 (6.1)	40 (8.5)	34 (5.3)	46 (5.4)
12	70 (5.4)	52 (4.1)	62 (0.8)	16 (1.6)	43 (6.5)	44 (7.6)	41 (5.7)	54 (5.9)
24	78 (5.9)	67 (2.5)	79 (2.9)	25 (0.1)	55 (4.6)	56 (4.6)	61 (3.0)	72 (6.0)
48	80 (5.0)	74 (3.9)	88 (0.4)	33 (3.5)	62 (5.2)	65 (3.7)	71 (0.2)	82 (4.1)
72	81 (6.0)	75 (4.1)	90 (1.0)	38 (4.9)	64 (5.0)	67 (3.8)	74 (3.1)	85 (1.5)
96	—	76 (4.7)	91 (0.6)	39 (5.4)	65 (4.9)	67 (3.8)	74 (3.1)	—
No. of subjects studied	4	5	2	2	5	4	6	5

[a] The values in parentheses are 1 *SD* for the data. The values are given for C and D only as a guide since two subjects were used in each instance.

Dissolution studies of all radioactive tablets showed no significant difference between the rate of release of aminorex when determined by chemical and radiochemical methods. Table I summarizes the various formulations studied.

RESULTS

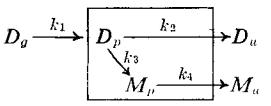
Details of the development of the various formulations tested and complete results of dissolution and stability studies on these dosage forms will be presented elsewhere. Only a summary of the results obtained is presented for comparison and correlation with the *in vivo* studies. Figure 1 presents the dissolution results obtained in the *in vitro* system for representative batches of each formulation. It is apparent from the figures that the nonsustained-release tablets, Dosage Forms B and C, were more rapid in their release of the drug than the various proposed sustained-release dosage forms which were studied.

The results obtained for plasma levels and urinary excretion of radioactivity are presented in Figs. 2 and 3 and Tables II and III. The plasma levels of radioactivity are plotted as their equivalent in mcg. of aminorex. It is probable that plasma radioactivity represents both intact drug and metabolite(s). For simplicity, however, it was decided to express the radioactive levels as mcg. of aminorex.

It is quite apparent from Figs. 2 and 3 that a sustained-release effect for aminorex fumarate and aminorex pamoate has been produced. The data also indicate that the pamoate sustained-release tablet (Dosage Form D) is not completely absorbed. Based on data presented later only 40% of the dose is absorbed. The sustained-release effect in the case of the fumarate salt is primarily a function of the tablet formulation since the fumarate salt is relatively water soluble (9.0 mg./ml.) and, is readily absorbed, Fig. 2. In the case of the pamoate salt it is more difficult to assign responsibility for the sustained release effect. This effect is probably a function of the formulation and the relative insolubility (0.06 mg./ml.–pH 7.5) of the salt form used. It would appear from the data that Dosage Forms G and H would be the most likely candidates for clinical trial. Both dosage forms were evaluated clinically (10) and found to have acceptable sustained release properties based on observed weight loss and prolonged reduced food intake.

A kinetic analysis of the plasma data was attempted in order to obtain a more quantitative comparison between the *in vitro* and *in vivo* studies. As indicated above, analogies can be drawn based on the blood levels observed in Figs. 2 and 3 and the dissolution rates obtained for various formulations. However, reduction of the plasma data to a form which was more readily comparable with the dissolution data was desired. If this could be done one might more readily evaluate the sensitivity of the dissolution system.

First-order plots, Fig. 4, of loss of radioactivity, expressed as drug, from the plasma for the 7.5-mg. tablets (Dosage Form B) and the 7.5-mg. oral solution of the fumarate salt (Dosage Form A) were fairly linear with half-lives of 7.7 hr. These values were determined by linear regression analysis. The linearity of these plots for loss of radioactivity from the plasma implies that one can consider plasma loss of radioactivity to be essentially first-order. Therefore, for the purpose of evaluating the dosage forms, a one-compartment model of the type suggested by Wagner and Nelson (7) is proposed. The complete model, for this system, might be considered to be:



c.p.m. in plasma

where D_g is the amount of unabsorbed drug in the gut, D_p is the amount of intact drug in the plasma, M_p is the amount of metabolite(s) in the plasma and D_u and M_u are the amounts of drug and

Table III—Average Plasma Levels of Radioactivity, Expressed as mcg. of Aminorex, Obtained Following Oral Administration of Various Dosage Forms of Aminorex [Values Expressed as mcg./l. (± *SD*)]

Hours	Dosage Form A	B	C	D	E	F	G	H
0.5	14 (11)	—	—	—	—	—	—	—
1	33 (7)	27 (18)	30 (16)[a]	5 (4)[a]	22 (14)	18 (6)	13 (3)	29 (5)
1.5	40 (4)	—	—	—	—	—	—	—
2	43 (4)	44 (8)	41 (6)	23 (1)	57 (12)	45 (22)	33 (12)	52 (7)
3	43 (4)	43 (9)	46 (3)	21 (1)	71 (17)	57 (20)	44 (14)	74 (10)
4	39 (5)	37 (10)	45 (14)	31 (12)	82 (24)	59 (14)	55 (16)	89 (12)
5	37 (3)	34 (7)	43 (15)	33 (8)	78 (22)	39 (9)	61 (18)	102 (18)
6	33 (3)	31 (6)	39 (13)	30 (3)	70 (18)	37 (6)	60 (15)	104 (17)
7	31 (4)	28 (6)	35 (11)	27 (1)	61 (16)	31 (6)	60 (14)	104 (20)
8	26 (4)	21 (5)	32 (14)	25 (3)	59 (16)	26 (5)	57 (12)	99 (20)
9	23 (3)	21 (6)	31 (13)	20 (2)	57 (18)	23 (5)	56 (14)	89 (20)
10	—	—	—	—	—	—	56 (13)	—
12	21 (4)	18 (7)	26 (12)	20 (6)	44 (14)	18 (6)	55 (14)	67 (15)
No. of subjects studied	4	5	2	2	5	4	6	5

[a] The standard deviations are given for C and D only as guides since two subjects were used in each instance.

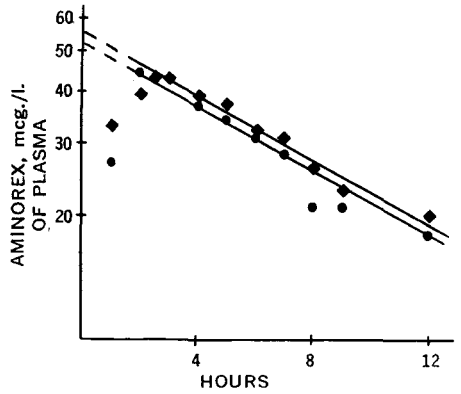


Figure 4—*First-order plot of the average plasma levels of radioactivity, expressed as micrograms of aminorex, obtained following oral administration of Dosage Forms A (◆) and B (●). A contained 7.5 mg. of aminorex as the fumarate salt in water solution and B contained 7.5 mg. of aminorex as the free base in a nonsustained-release tablet formulation.*

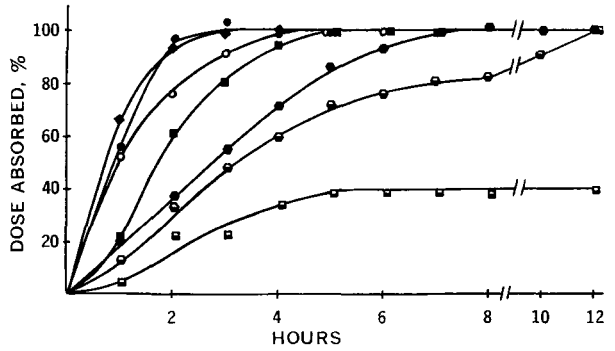


Figure 5—*Relative percent of the dose absorbed following oral administration of aminorex in Dosage Forms A (◆), B (●), C (○), D (■), E (■), G (◒), and H (●). The percent absorbed was calculated using the method of Wagner and Nelson (7) and Wagner (11) for a one-compartment open model. Dosage Form F is not given; see text for explanation.*

metabolite(s) in the urine. The rate constants k_1, k_2, k_3, and k_4, are the rate constants for absorption, metabolism, and excretion. If we assume a first-order loss of radioactivity from the plasma then the model reduces to:

$$D_g \xrightarrow{k_1} \boxed{D_p'} \xrightarrow{k_{e1}} D_{e1}'$$

c.p.m. in plasma

where D_g is the amount of unabsorbed drug in the gut, D_p' is the amount of radioactivity in the plasma expressed as micrograms of intact drug and D_{e1}' is the amount of radioactivity which has been lost from the plasma by a first-order process. The rate constant k_{e1} is a complex function of D_p, M_p, k_2, k_3, and k_4; however, the rate constant k_1 has not been altered by the modifications in the model. It is this rate constant or the values of D_g at specific points in time (if zero or first-order kinetics for absorption do not hold) which are of interest in attempting to quantitate the evaluation of the various dosage forms of aminorex.

Using the rate constant for plasma loss of radioactivity obtained by analysis of the data for the oral solution and the 7.5-mg. tablet (Dosage Forms A and B), and the method of Wagner and Nelson (7), A_t/V values were obtained for each dosage form. A_t is the amount of drug absorbed at time t, and V is a constant of the model, which is defined as the apparent volume of distribution of the administered radioactivity. These data are presented in Table IV.

Comparison of the A_t/V values obtained, Table IV, after absorption is complete would suggest that in all cases except the 10-mg. sustained-release tablet (Dosage Form F) and the pamoate sustained-release formulation (Dosage Form D) the fraction of drug absorbed is equivalent. Wagner (11) has published a method for estimating relative absorption of a drug in studies in which blood levels are measured after varying single and/or multiple doses. Modification of the method presented by Wagner (11) gives:

$$\frac{F}{V} = \frac{A_t/V}{D}$$

where F is the fraction of the administered dose D (in milligrams) which is absorbed. For different dose levels, if the volume of distribution among patients is considered to be constant, one can compare F/V at infinite time, denoted as $(F/V)_\infty$ and obtain comparisons of the relative absorption efficiencies of various dosage forms. The relative fraction of a dose which has been absorbed at any given time, t, can be calculated from $(F/V)_t/(F/V)_\infty$. This was calculated for each dosage form studied and the results are shown in Fig. 5. In all cases except the 15-mg. pamoate sustained-release formulation (Dosage Form D) the value of $(F/V)_\infty$ for the specific dosage form was used to calculate the relative percent of the dose absorbed.

Table IV—Values Obtained for A_t/V Using the Method of Wagner and Nelson (7) and the Model Proposed for Total Plasma Radioactivity[a]

Time, hr.	Dosage Forms A_t/V in mcg./l.							
	A	B	C	D	E	F	G	H
1	34.3	28.1	31.4	5.2	23.0	18.9	13.6	30.1
2	48.2	48.4	45.4	24.5	61.8	48.7	35.6	56.9
3	51.2	51.5	54.6	24.3	82.1	65.6	51.5	82.7
4	51.2	49.0	57.6	36.6	99.6	72.9	65.2	107.2
5	52.0	49.3	59.7	41.6	102.6	57.0	77.3	129.4
6	51.1	49.3	59.6	41.4	101.7	58.3	81.7	141.0
7	—	48.8	58.7	40.9	98.5	55.4	87.1	148.7
8	50.6	—	58.9	41.6	101.4	53.3	89.4	154.2
9	—	—	—	38.6	104.9	—	—	—
10	—	—	—	—	—	—	98.7	153.0
12	52.6	50.4	63.0	43.9	105.4	53.1	107.7	147.6
				Dose, mg. base				
	7.5	7.5	7.5	15	15	10	15	20
				No. of Subjects				
	4	5	2	2	5	4	6	5
				$(F/V)_\infty$				
	6.9	6.7	8.0	2.8	6.9	—[b]	7.1	7.6

[a] All data were obtained from the average plasma level curves of Figs. 2 and 3 using the half-life of 7.7 hr, obtained for dosage forms A and B. [b] No value for $(F/V)_\infty$ was calculated due to the existence of a maximum in the A_t/V plot for this dosage form. See text for explanation.

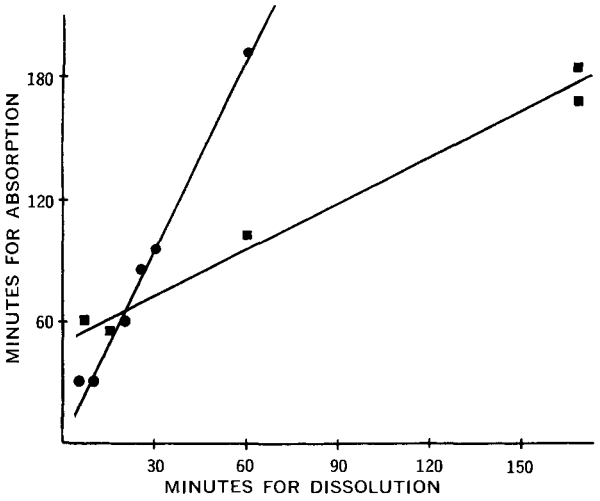


Figure 6—*Linear correlation obtained for the times of 25% dissolution* versus *25% absorption* (●) *and for the times of 50% dissolution* versus *50% absorption* (■) *for various dosage forms of aminorex. The correlation coefficients were 1.00 and 0.99, respectively.*

In the case of the pamoate sustained-release tablet the weighted mean value for $(F/V)_\infty$ of 7 was used as representative of 100% absorption, values for percent absorbed were calculated from this average value. Data for the 10-mg. sustained-release tablet (Dosage Form F) are omitted from Fig. 5 because of the presence of a peak in the A_t/V data for this formulation. This peak is indicative of the fact that perhaps the model is too simple or, on the basis of the observed plasma levels, some error was made in the determination of plasma levels of radioactivity after the fourth hour. The latter possibility would appear more likely since the model held for all other cases and the maximum value of A_t/V obtained for Dosage Form F never exceeded the values expected for this dose level.

The data of Fig. 5 correlate quite well with what one might predict from the *in vitro* data, Fig. 1. It should be noted that the pamoate plasma level studies were obtained using only two subjects per formulation. However, for the comparative purposes of this report they are included as supportive data. Comparison of the data of Fig. 5 with the *in vitro* data would suggest that the dissolution system, although adequate to determine sustained release properties, may not be as sensitive as one might desire. To illustrate this, compare the dissolution data of Dosage Forms G and H with the percent absorbed values of Fig. 5. However, by using an arbitrary dissolution system as a guideline it was possible to develop clinically acceptable and effective (10) sustained-release formulations of aminorex. Use of the proposed model for total radioactivity permitted reduction of the plasma data to a form more easily compared with dissolution rate data, without subsequent analysis for intact drug and/or metabolites. An estimate of the degree of correlation obtained between dissolution and absorption data is given in Fig. 6. In Fig. 6 the times for 25 and 50% dissolution are plotted *versus* the times for 25 and 50% absorption. A good linear correlation was obtained with correlation coefficients of 1.00 and 0.99 for the 25 and 50% values, respectively.

The mechanism by which the dosage form produces its sustained-release effect is considered to be due to the nondisintegrating properties of the tablet. This phenomenon was observed *in vitro*. Proof of such a mechanism *in vivo* has not been definitely established; however, it is supported by the fact that the tablets do produce a sustained-release effect which is not attributable to the salt form used.

REFERENCES

(1) E. Rosen and J. V. Swintosky, *J. Pharm. Pharmacol.*, **12**, 237T(1960).

(2) P. C. Johnson and Y. F. Masters, *J. Lab. Clin. Med.*, **59**, 993(1962).

(3) E. Rosen, T. Ellison, P. Tannenbaum, S. M. Free, and A. P. Crosley, *J. Pharm. Sci.*, **56**, 365(1967).

(4) A. J. Hadler, *J. Clin. Pharmacol.*, **8**, 113(1968).

(5) E. H. Wiseman and N. J. Federici, *J. Pharm. Sci.*, **57**, 1535(1968).

(6) A. A. Sugerman and E. Rosen, *Clin. Pharmacol. Therap.*, **5**, 561(1964).

(7) J. G. Wagner and E. Nelson, *J. Pharm. Sci.*, **53**, 1392(1964).

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

(9) "The United States Pharmacopeia," 17th rev. Mack Publishing Co., Easton, Pa., 1965, pp. 1075–1076.

(10) Clinical data on file at McNeil Laboratories.

(11) J. G. Wagner, *J. Pharm. Sci.*, **56**, 652(1967).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 2, 1969 from the *Departments of Biochemistry and Pharmacy, McNeil Laboratories, Inc., Fort Washington, PA 19034*

Accepted for publication August 13, 1969.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Montreal meeting, May 1969.

The authors would like to acknowledge the contributions of Dr. J. Plostnieks who prepared the radioactive material and Dr. N. Batuyios who prepared all dosage forms used in the study.

* Department of Medicine, Baylor University, College of Medicine and Director, Radioisotope Laboratory, Methodist Hospital, Houston, Texas.

† College of Pharmacy, University of Kentucky, Lexington, Kentucky.