cooled, made alkaline with sodium hydroxide, and extracted with ether (3 × 75 ml.). The combined ether extract, after washing with distilled water and drying over anhydrous sodium sulfate, was added to an ethereal solution of dry hydrogen chloride to yield a white precipitate. Recrystallization from a mixture of ethanol–ethyl acetate–ether yielded 2.1 g. (76%) of white needle-shaped crystals, m.p. 210°. The IR spectrum (KBr) exhibited maxima of μ: 3.9–4.9 (continuous), amine salt.

Anal.—Calcd. for $C_{21}H_{28}ClN$: C, 75.93; H, 9.17; N, 4.21. Found: 76.09; H, 8.97; N, 4.34.

REFERENCES

(1) A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunewald, and A. I. White, *J. Pharm. Sci.*, **58,** 340(1969).

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp. 109–111.

(3) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6,** 986(1954).

(4) W. H. Shelver and A. Burger, *J. Pharm. Sci.*, **52,** 250(1963).

(5) A. Kotz and A. Michaels, *Annalen*, **350,** 212(1906).

(6) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107,** 385(1953).

(7) P. S. Portoghese, H. Kupferberg, and A. Mikhail, *Pharmacologist*, **8,** 2(1966).

(8) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9,** 455 (1966).

(9) P. S. Portoghese, *ibid.*, **8,** 609(1965).

(10) K. W. Rosenmund and E. Karg, *Chem. Ber.*, **75,** 1850(1943).

ACKNOWLEDGMENTS AND ADDRESSES

Received June 18, 1970, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication September 17, 1970.

The investigation was supported in part by funds provided for biological and medical research by State of Washington Initiative Measure No. 171 and by Grant NB-02054, National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

The authors thank W. E. Johnson and N. S. Redhead for assistance in the determination and interpretation of the analgesic activity data.

*To whom inquiries should be addressed.

Use of an Analog Computer to Simulate and Interpret Data Obtained from Linear Nonisothermal Stability Studies

ALLEN I. KAY and THOMAS H. SIMON

Abstract □ An analog computer program was developed to simulate drug decomposition induced during linear nonisothermal stability studies. From the analog computer values used to generate the simulation curve best-fitting experimental data, the activation energy, the reaction rate constant at any temperature, and the predicted shelflife at that temperature can be determined. By using the decomposition data reported for the first-order, linear nonisothermal degradation of *N*-acetyl-*p*-aminophenol and the analog computer program presented here, kinetic parameters identical with published values were obtained. The analog computer program can be easily modified to accommodate nonlinear heating regimens as well as reactions of any order.

Keyphrases □ Linear nonisothermal stability studies—simulation □ Analog computer simulation—stability studies □ Shelflife prediction—kinetic parameters □ Diagram—analog computer program

The customary procedure for predicting the shelflife of a drug involves the determination of the degradation rate constant at a few elevated temperatures, the determination of the activation energy, and finally the extrapolation of this information to room temperature. This requires large numbers of samples and ultimately a great deal of personnel time. By means of a rapid and simple concentration–time–temperature study in which temperature is changed at a preselected rate, it is possible to obtain these parameters in 1 or 2 days.

The concept of using programmed elevated temperatures to arrive at the kinetic parameters required to predict shelflife is not new. Borchardt and Daniels (1) obtained the rate, order, and activation energy for the decomposition of benzenediazonium chloride by analysis of the slope, height, and area of a differential thermal analysis curve. Davies (2) followed a chemical reaction by observing the change in optical density of one reactant with time as its temperature was progressively raised. Reaction kinetics were also followed using differential scanning calorimetry (3) and thermogravimetric analysis (4).

Various heating regimens have been employed. Cole and Leadbeater (5) studied the reaction rate of several compounds. They employed the temperature program designed by Rogers (6) in which the inverse of the temperature was varied logarithmically with time. Eriksen and Stelmach (7) obtained the necessary kinetic parameters from a single experiment, using the following time–temperature relationship:

$$\frac{1}{T} = \frac{1}{T_0} - at \qquad \text{(Eq. 1)}$$

where a is a reciprocal heating constant, and T_0 and T are the absolute temperatures at the initial time and at time t, respectively. Zoglio *et al.* (8) followed the first-order decomposition of *N*-acetyl-*p*-aminophenol and procainamide hydrochloride as the temperature was raised linearly with time according to the expression

$$T = bt + C \qquad \text{(Eq. 2)}$$

where b is the heating rate and C is the initial temperature. These authors employed digital computation to obtain 384 slopes or rate constants, which were then used to generate a series of degradation curves corresponding to various activation energies. The analytical

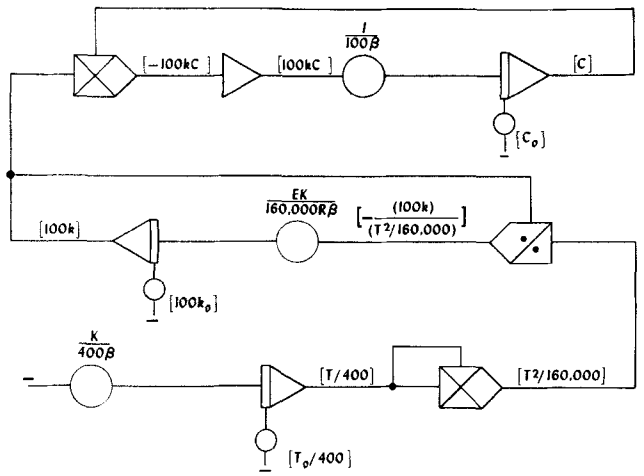

Figure 1—*Scaled computer program for simulation of first-order decomposition induced during linear nonisothermal stability studies.*

data were superimposed over the model curves to obtain the energy of activation for the reaction. The use of digital computation eliminates the need for manual slope estimation, which is generally regarded as a major drawback of some of the previous methods (1, 2).

An analog computer program was developed which is designed to simulate drug decomposition induced during nonisothermal stability studies. The method is illustrated for the case of first-order degradation induced during a linear nonisothermal experiment. The data given by Zoglio *et al.* (8) were plotted, and analog computation was used to obtain the degradation curve best fitting the experimental data points. The rate constant at 35° and the energy of activation, obtained directly from the computer values, were in excellent agreement with those reported by Zoglio *et al.* (8).

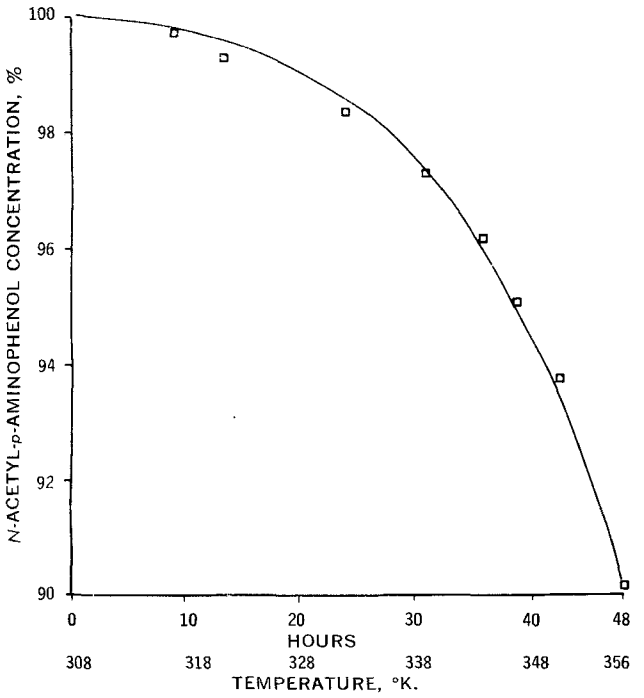

Figure 2—*Analog computer simulation of the nonisothermal hydrolysis of* N-*acetyl*-p-*aminophenol in aqueous solution (pH = 2).*

Table I—Analog Computer Scaling Table

Problem Variable	Rounded-Up Maximum	Computer Variable
C	1 (normalized)	$[C]$
k	0.01	$[100k]$
T	400	$[T/400]$
T^2	160,000	$[T^2/160,000]$

THEORY

The basic equations employed are as follows:

$$-\frac{dC}{dt} = kC^a \qquad \text{(Eq. 3)}$$

where a is the order of the reaction, C is the drug concentration at time t, and k is the observed rate constant which can be obtained from the expression

$$k = Ae^{-E/RT} \qquad \text{(Eq. 4)}$$

where E is the energy of activation, A is the frequency of molecular collisions, T is the absolute temperature, and R is the molar gas constant (1.987 cal. deg.$^{-1}$ mole^{-1}).

Differentiating with respect to temperature yields

$$\frac{dk}{dT} = \frac{kE}{RT^2} \qquad \text{(Eq. 5)}$$

If temperature is varied linearly with respect to time, the following relationship exists:

$$T = T_0 + Kt \qquad \text{(Eq. 6)}$$

where T_0 is the starting temperature and K is the heating rate.

Differentiating with respect to time yields

$$\frac{dT}{dt} = K \qquad \text{(Eq. 7)}$$

Thus

$$\frac{dk}{dt} = \frac{KkE}{RT^2} \qquad \text{(Eq. 8)}$$

EXPERIMENTAL

Based on the rounded-up maximum values given in Table I and a time scaling factor[1] of $\beta = 0.1$, the following scaled differential equations were used to construct the analog computer program shown in Fig. 1.

$$\frac{d[C]}{d\tau} = -\left\{\left(\frac{1}{100\beta}\right)[100k][C]\right\} \qquad \text{(Eq. 9)}$$

$$\frac{d[100k]}{d\tau} = -\left\{\left(\frac{EK}{160{,}000R\beta}\right)\left[-\frac{[100k]}{[T^2/160{,}000]}\right]\right\} \qquad \text{(Eq. 10)}$$

$$\frac{d[T/400]}{d\tau} = -\left(\frac{-K}{400\beta}\right) \qquad \text{(Eq. 11)}$$

The equations were solved using an Electronic Associates Inc. Analog/Hybrid Computing System equipped with a series 1140 Variplotter recorder.

Equation 9 is a special case of Eq. 3 and describes first-order degradation. The analog computer can be programmed to solve Eq. 3 for reactions other than first order by incorporating additional analog computer components into the program which will raise the concentration term to an appropriate power. Equation 11 describes a linear time–temperature relationship. Other heating regimens can be simulated. If the equation describing the relationship between temperature and time is known, it can be incorporated directly into the computer program. If the equation for the time–

[1] $\beta = \tau/t$ where τ is computer time in seconds and t is problem time in hours.

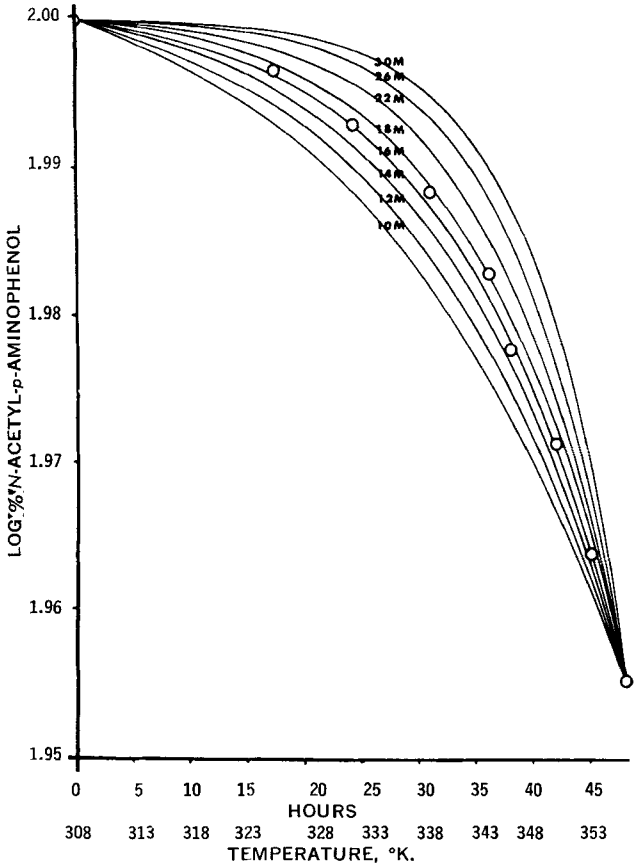

Figure 3—*Nonisothermal hydrolysis of* N-*acetyl*-p-*aminophenol in aqueous solution (pH = 2). Curves were generated using digital computation (Ref. 8).*

temperature relationship is unknown, the temperature of the system can be measured at various time intervals and a function generator can be employed to provide temperature as a function of time.

The usefulness of the analog computer program for prediction of shelflife based on evaluation of kinetic data obtained from nonisothermal stability studies was investigated utilizing data reported by Zoglio *et al.* (8) for the linear nonisothermal hydrolysis of *N*-acetyl-*p*-aminophenol. These authors obtained their experimental data in only 48 hr. Ampuls initially containing a solution of 0.15% *N*-acetyl-*p*-aminophenol in 0.2 *M* phosphate buffer were heated in an oven at the rate of 1°/hr. from 35–83°. Ampuls were removed at convenient time intervals and analyzed for intact drug.

The percentage of intact drug remaining was plotted as a function of time (temperature), and the analog computer program was employed to simulate first-order decomposition of a drug according to the time–temperature relationship consistent with the experiment. The decomposition curve best fitting the experimental data points was obtained by varying the initial rate constant (rate constant at 35°) and the energy of activation until the degradation curve matched the data points (Fig. 2). This was easily accomplished since the analog computer program was constructed to allow isolation of these kinetic parameters on separate potentiometers. The values of the initial rate constant, k_0, and the energy of activation were obtained directly from their potentiometer settings.

RESULTS AND DISCUSSION

The degradation curve best fitting the experimental data corresponded to that having an activation energy of 17 kcal./mole and an initial rate constant of 2×10^{-4} hr.$^{-1}$. Both values are in excellent agreement with those reported by Zoglio *et al.* (8).

The basis for the approach of Zoglio *et al.* (8) is that a degradation curve can be described by a series of slopes or rate constants and that the arithmetic average of these instantaneous rates of change can be assumed to be equal to the total drug degradation during the experiment divided by the time span required for the experiment.

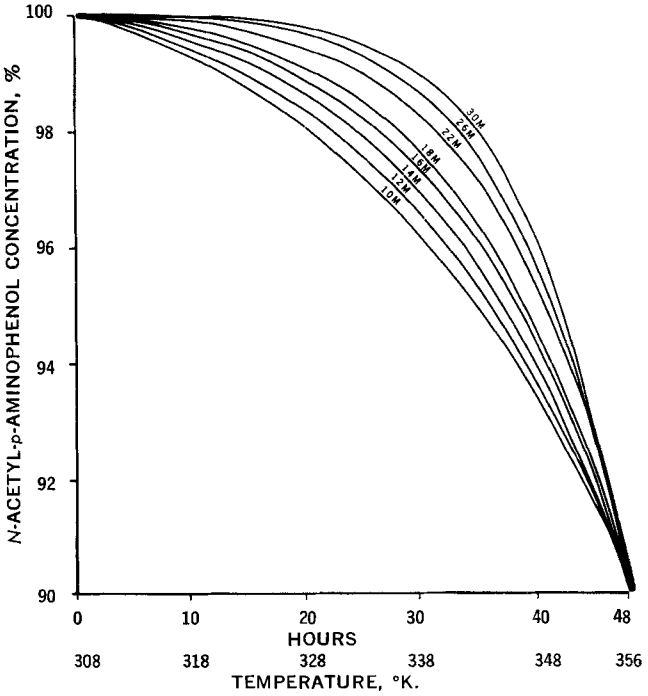

Figure 4—*Degradation curves generated using analog computation. Activation energies were selected and* k_0 *was varied so that curves were forced through initial and final concentration levels.*

Since a large number of rates (384) was obtained for each particular activation energy, this assumption is valid. These rates were then used to synthesize a series of degradation curves on a first-order scale (Fig. 3). The experimental data were then plotted on the same graph containing the family of curves, and the energy of activation was obtained by inspection and interpolation.

Figure 4 shows a series of decomposition curves generated using the analog computer. An activation energy ranging from 10–30 kcal./mole was arbitrarily selected for each curve, and k_0 was varied so that each curve was forced through the initial and final concentration levels. This method is similar to the approach followed

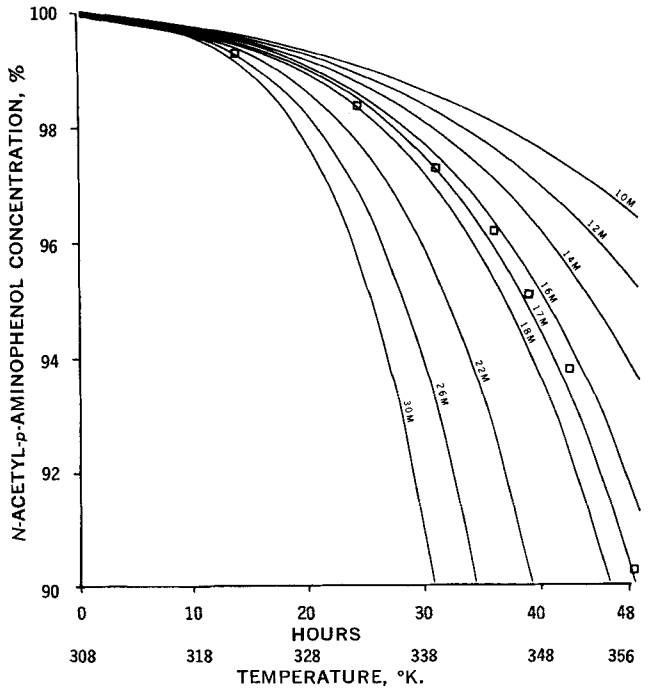

Figure 5—*Degradation curves generated by setting* k_0 *at* 2×10^{-4} *hr.*$^{-1}$ *and varying the energy of activation.*

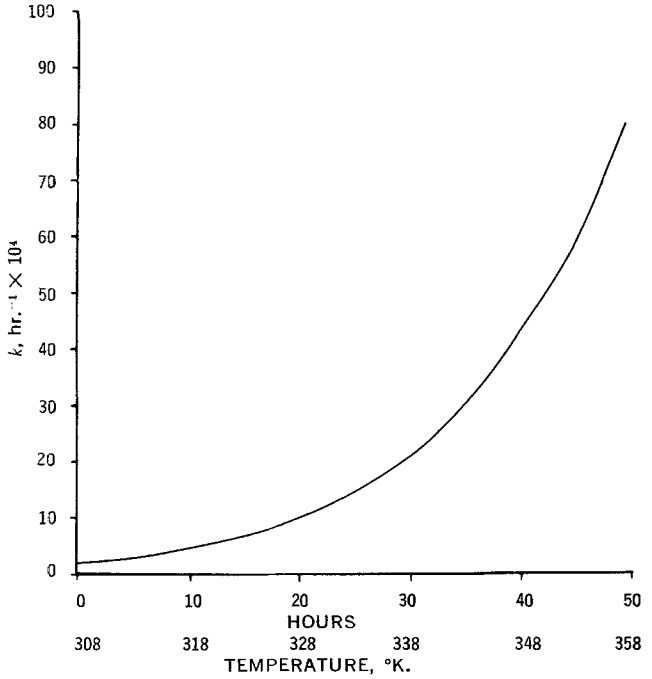

Figure 6—*Degradation rate constants generated as a function of temperature (time).*

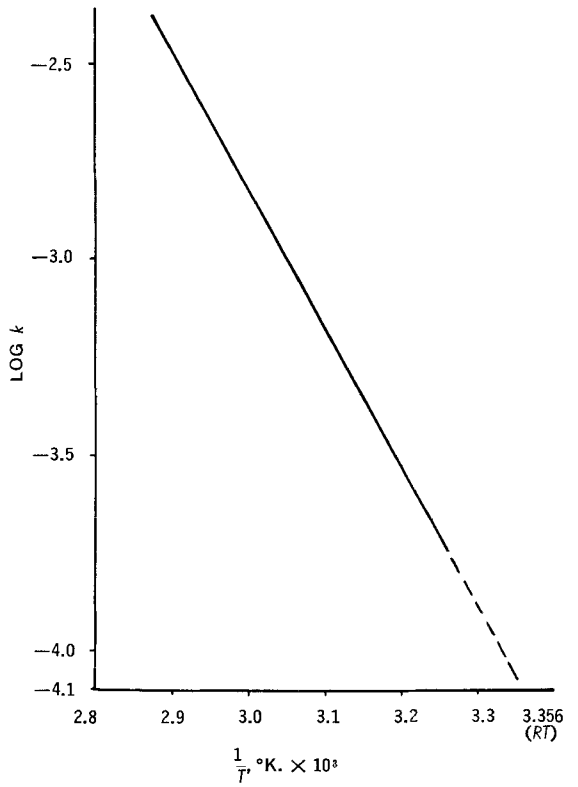

Figure 7—*Arrhenius plot which can be extrapolated to obtain the degradation rate constant at room temperature.*

by Zoglio *et al.* (8); the similarity between the curves obtained using analog simulation and those obtained employing digital computation (Fig. 3) indicates that either method can be used ultimately to predict shelflife. However, since only one curve can be correct for a particular experiment, this curve can be obtained simply and rapidly using the analog computer program presented here, which allows simultaneous adjustment of k_0 and activation energy. All experimental data points are used in the simulation, which should increase accuracy and reduce the possibility of a serious mistake should one experimental point be incorrect.

If the rate constant at the initial temperature was experimentally determined by analysis of a few samples under isothermal conditions, then the value of k_0 could be inserted into the analog computer program and degradation curves could be drawn varying only the energy of activation. This method is illustrated in Fig. 5. The initial rate constant was taken as 2×10^{-4} hr.$^{-1}$. This method sacrifices time but increases sensitivity. Comparison of Figs. 4 and 5 indicates that the same change in activation energy results in a greater displacement of the concentration–time–temperature curve when k_0 is fixed. However, such an approach is seldom necessary since the value of the initial rate constant obtained using analog simulation should be sufficiently sensitive to allow confident prediction of shelflife.

Either the experimentally determined or the computer-generated k_0 value can be incorporated into the program, which is designed to generate degradation rate constants as a function of time (temperature) so that k values can be graphically displayed (Fig. 6), and by means of a log function generator directly yield an Arrhenius plot. Alternately, these values can be taken for subsequent plotting (Fig. 7). By extrapolating to 25°, the rate constant for the hydrolysis of *N*-acetyl-*p*-aminophenol at room temperature was found to be 8.07×10^{-5} hr.$^{-1}$, corresponding to a shelflife of 55 days.

By using the analytical data obtained from a single, linear, nonisothermal stability study and the analog computer program presented here, kinetic parameters required to predict shelflife were obtained. Manual analysis of heights, slopes, or areas of curves is not required, since the analog computer provides instantaneous graphical solutions to the differential equations employed. Although the method was illustrated for first-order degradation induced using a linear heating program, it is applicable to other heating regimens and for reactions other than first order.

REFERENCES

(1) H. J. Borchardt and F. Daniels, *J. Amer. Chem. Soc.*, **79**, 41 (1957).

(2) R. E. Davies, *J. Phys. Chem.*, **63**, 307(1959).

(3) W. E. Franklin, C. H. Mack, and S. P. Rowland, in "Analytical Calorimetry," R. S. Porter and J. F. Johnson, Eds., Plenum, New York, N. Y., 1968, p. 181.

(4) E. S. Freeman and B. Carroll, *J. Phys. Chem.*, **62**, 394(1958).

(5) B. R. Cole and L. Leadbeater, *J. Pharm. Pharmacol.*, **18**, 101 (1966).

(6) A. R. Rogers, *ibid.*, **15**, 101T(1963).

(7) S. P. Eriksen and H. Stelmach, *J. Pharm. Sci.*, **54**, 1029 (1965).

(8) M. A. Zoglio, J. J. Windheuser, R. Vatti, H. V. Maulding, S. S. Kornblum, A. Jacobs, and H. Hamot, *ibid.*, **57**, 2080(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 27, 1970, from the *Pharmaceutical Research and Development Laboratories, Warner-Lambert Research Institute, Morris Plains, NJ 07950*

Accepted for publication September 1, 1970.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, April 1970.

The authors express their gratitude to L. Kirschner for his technical assistance.