tracted from the number of rotations of the optical blank integrator, and the result was divided by the number of quanta absorbed by the solution to obtain the number of quanta per revolution of the integrator rotor.

Because of the difference in phototube response at different wavelengths, the calibration procedure was carried out for the most useful wavelengths of the mercury spectrum, *i.e.*, 254, 265, 281, 303, 313, 365, and 405 mμ.

## STABILITY OF THE INSTRUMENT

Short term stability of the instrument has been observed to be excellent with no noticeable drift after a 30-minute warm-up period. Long term stability has been checked at one wavelength (254 mμ) using the potassium ferrioxalate chemical actinometer system described by Parker (8) and later tested by Baxendale (9); the calculated values for quanta per revolution of the integrator rotor were within 1% of the original calculated values.

## SUMMARY AND CONCLUSIONS

An instrument for facilitating photochemical decomposition studies has been designed, constructed, and calibrated. The instrument supplies light of narrow bandwidth, which can be varied with respect to wavelength and to some extent with respect to intensity; the instrument provides for monitoring, recording, and integration of the incident and exit beams to and from the reaction mixture; it provides for keeping the reaction mixture at a constant and predetermined temperature and for stirring the mixture. Stoppered reaction cells exclude air when desirable. Short and long term stability of the instrument appear to be good, and response to light of any one wavelength with respect to intensity is practically linear.

Considering that the cost of the parts and materials to build the instrument was minimal, this instrument or a modification of it would be a useful tool for pharmacy laboratories doing photochemical decomposition studies.

## REFERENCES

(1) Fastie, W. G., *J. Opt. Soc. Am.*, **42**, 641(1952).
(2) *Ibid.*, p. 647.
(3) Miller, O. E., *ibid.*, p. 661.
(4) Price, J. C., unpublished thesis, University of Rhode Island, Kingston, 1963.
(5) Leighton, W. G., and Forbes, G. S., *J. Am. Chem. Soc.*, **52**, 3139(1930).
(6) Brackett, F. P., Jr., and Forbes, G. S., *ibid.*, **55**, 4459 (1933).
(7) Forbes, G. S., and Heidt, L. F., *ibid.*, **56**, 2363(1934).
(8) Parker, C. A., *Proc. Roy. Soc. (London)*, **A220**, 104 (1953).
(9) Baxendale, J. H., and Bridge, N. K., *J. Phys. Chem.*, **59**, 783(1955).

# Use of Models in Determining Chemical Pharmaceutical Stability

By LLOYD KENNON

**The area of chemical kinetics as it has been applied to the prediction of the stability of drugs in pharmaceutical formulations has been quite extensively discussed and reviewed during the past few years. In spite of this, a method has been developed which will, it is hoped, be especially useful in pharmaceutical product development work as distinguished from academic research studies in which the goals are to determine reaction rates or orders or to elucidate reaction mechanisms. The present method is based upon the construction of reference reaction paths which result logically when one considers the usual values of pertinent heats of reaction and considers normal shelf-life goals. Two results which have emerged from consideration of these paths are rules of thumb having a sound theoretical basis and a naturally arising logical assay schedule. The schedule arises because of the temperatures chosen for sample storage (RT, 37°, 45°, 60°, and 85°) and would change if another set of storage conditions was employed.**

MORE FREQUENT USE of chemical kinetics is now being made in the course of product development work in the pharmaceutical industry. The intrinsic value of such approaches is now considered to be significant—as the many academic and industrial publications in the scientific literature bear witness.

The pharmaceutical literature is replete with examples of stability data which are presented much in the same manner as product development laboratory reports. Many papers present tables which show stability assay results obtained after formulations were stored under the usual accelerated conditions or tables which indicate composition changes induced or prevented when modifications are made in the formulation under study. Although useful, such information must be considered qualitative or semiquantitative when compared to the results of more rigorous studies made since 1950 wherein parameters such as reaction rate constants and heats of activation were determined. It may be noted, however, that concepts such as kinetic studies and

Received May 27, 1963, from Bristol-Myers Products, Hillside, N. J.
Accepted for publication December 2, 1963.
Presented before the A.PH.A. Industrial Section Stability Symposium, A.PH.A., Miami Beach meeting, May 1963.

half-lives, as they relate to consumer products, were known and used before 1950 in other industries, especially in the food industry; as an example we may cite the two initial papers of Oswin (1), who studied the kinetics of package life. Also noteworthy is the fine, well-referenced review article concerning the prediction of drug and pharmaceutical formulation stability published by Garrett (2).

The use of kinetics as described in recent works is, however, not as straightforward as it might be; from the standpoint of the formulating pharmacist. The reason appears to be that most of the emphasis and effort have been placed on determining the exact kinetic paths followed by degrading drug compounds, rather than on correlating data to discover where the many roads led. However, as will be described, it is possible to correlate the data and construct certain kinetic paths which can be used for purposes of comparison during formulation development work. Such illustrative paths might be termed "reference decompositions" and serve then as models useful for making product stability evaluations.

It should be stressed that the method to be described here is aimed toward being especially useful in pharmaceutical development work as distinguished from academic research studies in which the goal is to determine precise reaction rates and reaction orders or to elucidate reaction mechanisms. Such studies require somewhat modified and more extensive experimental design. Studies of the latter type are still necessary and should be employed in cases where application of this shorter method indicates borderline or subminimal stability. The present approach, we also realize, may not be avidly embraced or endorsed by the purists; however, there is no intention to deprecate fundamental studies, but rather the intent is to use them to evaluate old empirical conclusions and methods and revise the latter so that intuition and empirically based relationships will be no longer necessary.

## RATIONALE AND CONSTRUCTION OF THE REFERENCE REACTION PATH

Initially it may be appropriate to make some comments on heats of activation and on the role they play in the present method. Heats of activation are related to reaction rate constants (through the well-known Arrhenius equation) such that a rate constant's rate of change with temperature is affected by the heat of activation. Thus the course of degradation, that is, the amount of breakdown as a function of time and temperature, followed by a compound depends only on the value of the heat of activation—not on the order of the reaction or on any other factors. To make the rate of degradation of a reference decomposition proceed as *unfavorably* as possible, that is, to allow the formulation to be stable at the higher temperatures for the maximum possible periods of time, one need only assign a very low value to the heat of activation. It may be useful to amplify the concept of the unfavorable reaction just mentioned. By "unfavorable" it is meant that the reaction course (*i.e.*, the stability assay results) would tend to be misleading because the assay results obtained on samples stored at the *higher* temperatures would stay high for *longer* periods of time. Normally, a formulator wants weak formulations to manifest their weaknesses after *short* periods of storage at elevated temperatures.

To construct the unfavorable reference reaction path under discussion, a suitably low value for the heat of activation, such as 10 Kcal./mole, must be chosen. Almost no measurable reactions (and in pharmaceutics we deal with reactions that are much slower than the instantaneous and hence barely measurable) have activation energies this low. Most activation energies are in the 15–60 Kcal./mole range and are virtually sure to be found within

TABLE I.—HEATS OF ACTIVATION OF DEGRADATIVE REACTIONS OF SELECTED DRUG COMPOUNDS[a]

| Compound | $\Delta Ha$ | Reference |
|---|---|---|
| Actinospectacin | 20 | 3 |
| APAP | 18 | 4 |
| Ascorbic acid | 16, 23, 23 | 5 |
| Aspirin | 13, 15, 18 | 6, 7 |
| Atropine | 13, 14, 25 | 8, 9 |
| BAL | 16, 24 | 10, 11 |
| Barbital | 11, 15, 16 | 12 |
| Benzocaine | 19 | 13 |
| *N*-Butylformamide | 20 | 14 |
| Chloramphenicol | 20, 20, 21, 21, 23, 24, 24, 35 | 15–18 |
| Chlorobutanol | 19 | 19 |
| Dye—FD&C Blue No. 2 | 22, 23 | 20 |
| Dye—FD&C Red No. 1 | 22, 47 | 20 |
| Dyes—Mixture of FD&C Yellow No. 6 and D&C Red No. 33 | 20 | 21 |
| Epinephrine | 23 | 22 |
| Filipin | 9 | 23 |
| Folic acid | 17, 27 | 5 |
| Fumagillin | 9, 17 | 24 |
| Glucose | 31, 31, 32 | 25, 26 |
| Homatropine | 11, 12, 13 | 9, 27 |
| Hydrocortisone | 7, 17, 20 | 28, 29 |
| Isoamyl nitrite | 20 | 30 |
| Methylphenidate | 15, 25 | 31 |
| Methylprednisolone | 14 | 32 |
| Morphine | 23 | 33 |
| Naphazoline | 5, 16 | 34 |
| 2-PAM | 17, 17, 29 | 35 |
| Pantothenyl alcohol | 20, 21 | 5, 36 |
| Phenethicillin | 18 | 37 |
| Prednisolone | 11 | 32 |
| Procainamide | 13, 13 | 13, 38 |
| Procaine | 12, 17 | 13, 39 |
| Riboflavin | 20 | 40 |
| Salicyl alcohol | 24 | 41 |
| Streptozotocin | 21, 21, 27 | 42 |
| Thiamine | 13, 21, 24, 25, 26, 26, 29 | 5, 36, 43 |
| Vitamin A | 15, 23 | 5 |
| Vitamin $B_{12}$ | 23, 26 | 5, 36 |

[a] Note: The listing of two or more values for the heat of activation indicates that different degradative pathways may be possible, that the reaction is composed of multiple steps, that more than one determination was made, or that different salts or reaction conditions were employed in the kinetic study.

the 10–100 Kcal./mole range. Table I, in addition to serving as a set of references to many quantitative kinetic studies, lists the heats of activation of degradative reactions of a number of drug compounds reported since 1950; the average value found was 19.8 Kcal./mole. Of course, it might be noted that these heats of activation necessarily fall in a range which made study of the reactions convenient. Many drug compounds' degradation reactions must have heats of activation higher than those listed in the table.

In addition to what has been said about the 10 Kcal./mole value, it should be pointed out that, of course, values lower than this exist (as shown in Table I), but reactions with such low heats of activation take place so readily that generally stable, salable products cannot be formulated, at least not without heroic measures being taken. This point is illustrated by the work of Tingstad and Garrett (23). In a study of filipin degradation a heat of activation of 9 Kcal./mole was found. The compound's stability picture was this: crystalline filipin had a half-life of 43 hours in air. The authors hasten to add that their study may have been too severe, because filipin stored at 25° exhibited "only" a loss of 25% after one year in a closed amber bottle.

One last concept that should be discussed concerns the fact that a specious relationship is not being drawn between thermodynamics and kinetics. Situations are possible wherein thermodynamic characteristics mirror kinetic behavior. Meloche and Laidler (44) studied substituent effects on the acid and base hydrolyses of various benzamides (unsubstituted, nitro, chloro, two different methyls). These workers found that changes in the hydrolysis rates were influenced mainly by changes in activation energy such that the rates of both alkaline and acid hydrolysis decreased as the activation energies increased. Values of 22.0 to 27.1 Kcal./mole were found for the acid hydrolysis reactions, 16.1 to 23.1 Kcal./mole for the alkaline. Furthermore, it is possible in a sense to change the heat of activation of a degradative reaction by changing the vehicle so that a different mechanism of decomposition is brought about. The work of Stern *et al.* (34) illustrates this concept effectively. These authors point out that naphazoline in acidic or neutral solution is "relatively stable," in basic solution it is "readily prone to hydrolysis"; the heat of activation of the hydrolytic reaction in acid is 16.4 Kcal./mole, in base 4.9 Kcal./mole.

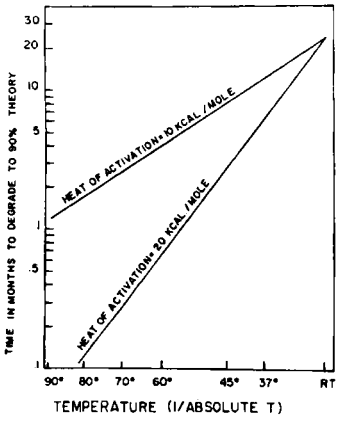


Fig. 1.—Two-year shelf-life goal reference decomposition.

TABLE II.—MAXIMUM AND MINIMUM TIMES AT WHICH POTENCY MUST BE AT LEAST 90% OF LABEL CLAIM WHEN STORED AT INDICATED TEMPERATURE TO OBTAIN A SHELF-LIFE OF TWO YEARS AT ROOM TEMPERATURE

| | Maximum | Minimum |
|---|---|---|
| 37° | 12 months | 6.4 months |
| 45° | 8.3 months | 2.9 months |
| 60° | 4.1 months | 3 weeks |
| 85° | 6 weeks | 2.5 days |

TABLE III.—ASSAY SCHEDULE

| | Times at which samples are to be assayed, months | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Temp., ° C. | 1 | 3 | 4 | 6 | 8 | 12 | 18 | 24 |
| 60 | X | X | X | | | | | |
| 45 | | X | X | X | X | | | |
| 37 | | | | X | X | X | | |
| RT | | | | | X | X | X | X |

The remaining parameter which must be specified before the reference reaction path can be constructed is the degree of stability desired. General consideration of pharmaceutical industrial practice indicates that a reasonable standard is that potency should fall no more than 10% from its original or its labeled concentration (if an overage is used) in two years when the product is stored at room temperature.

Thus, standard kinetic equations were used to calculate the paths which reactions would follow if a 10% potency loss (or a drop to 90% of label claim) in two years at room temperature is permitted. By choosing activation energies of 10 and 20 Kcal./mole, both of which are conservatively low, and plotting the time in months which a formulation would take to drop to 90% potency *versus* $1/T$, the graph (Fig. 1) illustrated results. Table II presents essentially the same data as the graph.

## USE OF THE GRAPH OR TABLE

From what has been stated so far and upon consideration of the picture presented by the graph and Table II, it can be seen that a logical course of action is presenting itself.

It is necessary only to see if the potency of a formulation is above 90% of its original or of its labeled concentration after storage at various temperatures for certain periods of time as compared to the model. If it is, the formulation is meeting the requirement of a two-year shelf-life, as far as kinetics will indicate, and apparently, formulation efforts were successful. Thus the formulation in question is assayed according to the schedule shown in Table III. If the assays are over 90% of label claim at the minimum times shown (indicated by the 20 Kcal./mole line on the graph) at the respective temperatures, the assays will be over 90% after two years at RT, in all probability; if the assays are still over 90% at the maximum times shown (indicated by the 10 Kcal./mole line on the graph), it is a certainty (kinetically speaking) that a potency of over 90% will be maintained after two years at RT. Naturally, values greater than 90% or values of 90% after longer times than those shown by the model indicate a shelf-life of more than two years. Studies at 85° are optional; this temperature may be too high for general use in stability prediction studies. Also, with regard to storage condi-

tions, the times and temperatures suggested in Tables II and III may be changed at will by choosing different points on the lines of the graph; *e.g.*, taking 70° as a storage temperature, the maximum and minimum times would be, respectively, 2.6 months and 9 days.

As implied, overages make no difference in the use of this method of evaluating stability characteristics. Overages are merely one means of assuring that potency will not be less than 90% of label claim after two years when greater stability cannot be built into the formulation in other ways. When using data from assays on formulas which contain overages, it is the per cent of *label claim* that should be used just as in the case of formulas in which there are no overages.

## NOTE ON POSSIBLE MISUSE OF THE GRAPH

As stated previously, this method is not intended to help in the determination of exact kinetic paths. Thus if, *e.g.*, the following two points were obtained: 80°, 1 month, and 45°, 4 months (to drop to 90%, etc.), it would appear that a line drawn through these points would cross the 25° line at about 10 months to indicate an unsuitable product. *This is not a true picture.* No line *should* be drawn through these points because the only aim in using this method is to see if the two points are above the 20 Kcal./mole line, which they are. Incidentally, in this example, two such points (if valid) would indicate an activation energy of about 8.8 Kcal./mole—something which is ruled out for reasons previously discussed as being an unreasonable possibility. The seeming paradox would have to be considered as due to experimental errors either in assay, timing, or temperature or due to the presence of additional degradative reactions. Naturally, two or more points which form a line with a *greater* slope than either of the two lines shown on the graph would tend to indicate a higher activation energy and longer than two-year shelf-life and would cause no concern.

## REFERENCES


(1) Oswin, C. R., *J. Soc. Chem. Ind.*, **64**, 67, 224(1945).
(2) Garrett, E. R., THIS JOURNAL, **51**, 811(1962).
(3) Garrett, E. R., and Umbreit, G. R., *ibid.*, **51**, 436(1962).
(4) Kosby, K. T., and Lach, J. L., *ibid.*, **50**, 113(1961).
(5) Garrett, E. R., *ibid.*, **45**, 171(1956).
(6) Leeson, L. J., and Mattocks, A. M., *ibid.*, **47**, 329(1958).
(7) Blaug, S. M., and Wesolowski, J. W., *ibid.*, **48**, 691(1959).
(8) Zvirblis, P., Socholitsky, I., and Kondritzer, A. A., *ibid.*, **45**, 450(1956).
(9) Patel, J. L., and Lemberger, A. P., *ibid.*, **48**, 106(1959).
(10) Rippie, E. G., and Higuchi, T., *ibid.*, **51**, 626(1962).
(11) *Ibid.*, **51**, 776(1962).
(12) Goyan, J. E., Shaikh, Z. I., and Autian, J., *ibid.*, **49**, 627(1960).
(13) Marcus, A. D., and Baron, S., *ibid.*, **48**, 85(1959).
(14) Garrett, E. R., and Weber, D. J., *ibid.*, **51**, 387(1962).
(15) Higuchi, T., and Bias, C. D., *ibid.*, **42**, 707(1953).
(16) Higuchi, T., Marcus, A. D., and Bias, C. D., *ibid.*, **43**, 129(1954).
(17) Higuchi, T., and Marcus, A. D., *ibid.*, **43**, 530(1954).
(18) Marcus, A. D., and Taraszka, A. J., *ibid.*, **48**, 77(1959).
(19) Nair, A. D., and Lach, J. L., *ibid.*, **48**, 390(1959).
(20) Scott, M. W., Goudie, A. J., and Huetteman, A. J., *ibid.*, **49**, 467(1960).
(21) Garrett, E. R., and Carper, R. F., *ibid.*, **44**, 515(1955).
(22) Schroeter, L. C., and Higuchi, T., *ibid.*, **47**, 426(1958).
(23) Tingstad, J. E., and Garrett, E. R., *ibid.*, **49**, 352(1960).
(24) Garrett, E. R., *ibid.*, **43**, 539(1954).
(25) Webb, N. E., Sperandio, G. J., and Martin, A. N., *ibid.*, **47**, 101(1958).
(26) Heimlich, K. R., and Martin, A. N., *ibid.*, **49**, 592(1960).
(27) Patel, J. L., and Lemberger, A. P., *ibid.*, **47**, 878(1958).
(28) Marcus, A. D., *ibid.*, **49**, 383(1960).
(29) Garrett, E. R., *ibid.*, **51**, 445(1962).
(30) Yunker, M. H., Szulczewski, D., and Higuchi, T., *ibid.*, **47**, 613(1958).
(31) Siegel, S., Lachman, L., and Malspeis, L., *ibid.*, **48**, 431(1959).
(32) Garrett, E. R., and Royer, M. E., *ibid.*, **51**, 451(1962).
(33) Yeh, S., and Lach, J. L., *ibid.*, **50**, 35(1961).
(34) Stern, M. J., King, L. D., and Marcus, A. D., *ibid.*, **48**, 641(1959).
(35) Ellin, R. I., Carlese, J. S., and Kondritzer, A. A., *ibid.*, **51**, 141(1962).
(36) Garrett, E. R., *ibid.*, **45**, 470(1956).
(37) Schwartz, M. A., Granatek, A. P., and Buckwalter, F. H., *ibid.*, **51**, 523(1962).
(38) Marcus, A. D., and Taraszka, A. J., *ibid.*, **46**, 28(1957).
(39) Higuchi, T., Havinga, A., and Busse, L. W., *ibid.*, **39**, 405(1950).
(40) Guttman, D. E., *ibid.*, **51**, 1162(1962).
(41) Schroeter, L. C., *ibid.*, **51**, 258(1962).
(42) Garrett, E. R., *ibid.*, **49**, 767(1960).
(43) Windheuser, J. J., and Higuchi, T., *ibid.*, **51**, 354(1962).
(44) Meloche, I., and Laidler, K. J., *J. Am. Chem. Soc.*, **73**, 1712(1951).


# Dioctyl Sodium Sulfosuccinate Tablet Coating

By WILLIAM L. SCHALKER and MURIEL C. VINCENT

**A tablet film coating process using dioctyl sodium sulfosuccinate was easily performed on tablets in a relatively short period of time using conventional coating equipment. The coating showed exceptional resistance to heat, light, and trauma. An inherent weakness to environmental moisture could be prevented. The coating has the advantage of being noncaloric in composition and does not hinder disintegration of the tablets.**

THE PHARMACEUTICAL industry has long been interested in tablet coating for the protection it affords the tablet ingredients which are adversely affected by environmental conditions, for the concealment of an unpleasant odor or taste, and for the elegant appearance it provides through a confectionary finish.

The numerous disadvantages of the usual sugar coating have lead to recent investigations for newer materials and methods of coating. In

Received May 8, 1961, from the College of Pharmacy, North Dakota State University, Fargo.
Accepted for publication August 8, 1963.
The authors gratefully acknowledge the American Cyanamid Co. for supplying the dioctyl sodium sulfosuccinate and Parke Davis and Co., The Upjohn Co., Eli Lilly and Co., and Abbott Laboratories for supplying several of the tablets used.
Presented to the Scientific Section, A.PH.A., Chicago meeting, April 1961.