Simplified Method for Determining Chemical Stability of Drug Substances in Pharmaceutical Suspensions

J. TINGSTAD▲, J. DUDZINSKI, L. LACHMAN, and E. SHAMI

Abstract □ A simplified method for determining the chemical stability of drug substances in pharmaceutical suspensions is described. The applicable theory is discussed, and a suitable example from the literature is presented. The value of the method is confirmed experimentally using aspirin.

Keyphrases □ Stability, chemical—drugs in suspensions, simplified method, calculations using aspirin □ Suspensions—simplified method for determining chemical stability of drug substances □ Drug stability in pharmaceutical suspensions—simplified method for determination of chemical stability □ Preformulation studies—simplified method for determining chemical stability of drug substances in pharmaceutical suspensions, example using aspirin, equations

One of the most common and important preformulation studies is the determination of a drug substance's chemical stability in aqueous systems. The usual procedure is to dissolve the compound in suitably buffered water or, if necessary, in a mixed solvent system and then to perform classical kinetic experiments. However, many drug substances have low aqueous solubilities, and it is often desirable to determine the chemical stability of the compound suspended in water. In addition, it is often important to perform accelerated chemical stability studies on suspension formulations. Relatively few such experiments have been reported (1–5), primarily because: (*a*) kinetic studies on drug substances in solution are easier to perform and lend themselves to more sophisticated treatment, and (*b*) with suspensions the kinetic calculations are complicated by the change in drug solubility with temperature. This report describes a simplified method for determining the chemical stability of drug substances in aqueous suspension, one that does not require solubility determinations and yet lends itself to classical mathematical treatment.

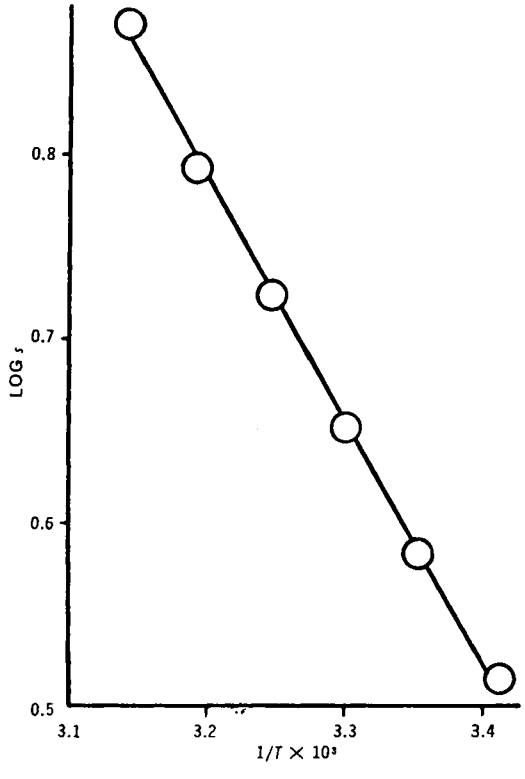


Figure 1—*Plot of log solubility of undissociated aspirin* versus *the reciprocal of the absolute temperature from data of Edwards* (6).

THEORY

Many drug substances in solution degrade according to first-order kinetics:

$$-dc/dt = kc \qquad \text{(Eq. 1)}$$

where c is the concentration of reactant, t is time, k is the rate constant, and dc/dt is the rate at which the concentration decreases. When the system involves a drug substance in suspension, the concentration in solution usually remains constant because, as the reaction proceeds, solid drug substance dissolves and the solution remains saturated with respect to undegraded reactant. Equation 1 then becomes:

$$-dc/dt = k_0 \quad \text{or} \quad -dc/dt = ks \qquad \text{(Eq. 2)}$$

where k_0 is the apparent zero-order rate constant (equal to ks), k is the first-order rate constant of Eq. 1, and s is the solubility of the

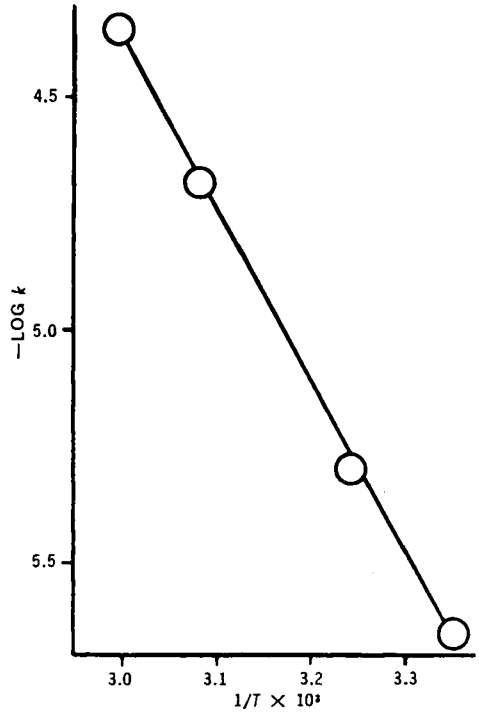


Figure 2—*Plot of log reaction rate constant of undissociated aspirin* versus *the reciprocal of the absolute temperature from data of Garrett* (7).

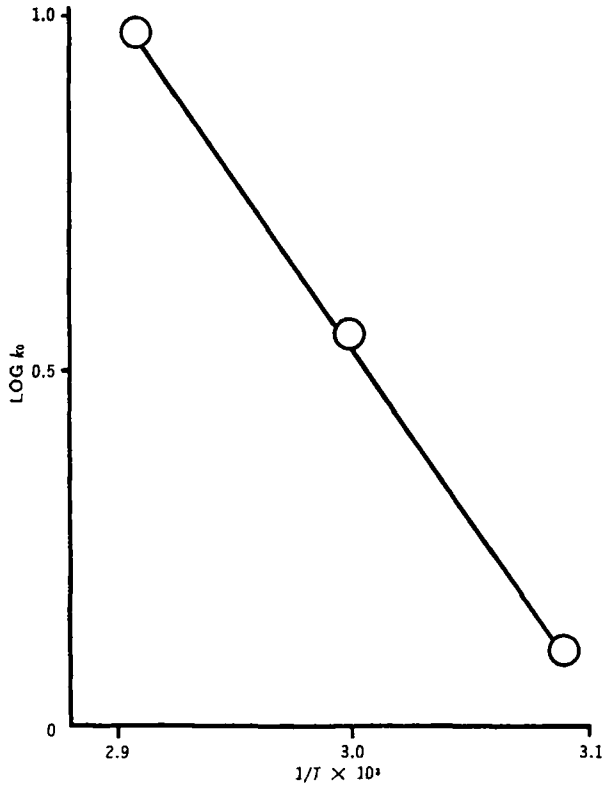


Figure 3—*Plot of log (apparent) zero-order reaction rate constant* versus *the reciprocal of the absolute temperature from data of James (2) for aspirin suspension.*

drug substance at the given temperature (and equal to c of Eq. 1).

When the reaction is studied at various temperatures, the apparent zero-order rate constant (k_0) will vary because of the temperature effect on the first-order rate constant and on the solubility of the drug substance in the solvent. One way to proceed is to determine its solubility at the various reaction temperatures, calculate k from the experimentally determined values of k_0 and s, and then estimate the room temperature stability from the heat of activation and the solubility at 25° (1).

Under certain conditions, room temperature stability can be estimated without determining the solubility of the drug substance at any temperature. These conditions are: (*a*) drug substance degradation takes place only in solution and according to first-order kinetics, (*b*) the drug substance–solvent system obeys the classical relationships to temperature with respect to solubility and rate of reaction, and (*c*) the dissolution–degradation kinetics are not dissolution rate limited.

From Eq. 2 it can be said that:

$$k_0 = ks \qquad \text{(Eq. 3)}$$

Taking logs of both sides yields:

$$\log k_0 = \log k + \log s \qquad \text{(Eq. 4)}$$

The classical relationship between reaction rate and temperature is:

$$\log k = -\frac{\Delta H_a}{2.303RT} + \text{a constant} \qquad \text{(Eq. 5)}$$

where k is the reaction rate constant, ΔH_a is the molar energy of activation, R is the gas constant, and T is the absolute temperature. Similarly, the relationship between solubility and temperature is:

$$\log s = -\frac{\Delta H_f}{2.303RT} + \text{a constant} \qquad \text{(Eq. 6)}$$

where s is the solubility at absolute temperature T, and ΔH_f is the molar heat of fusion.

Substituting from Eqs. 5 and 6 into Eq. 4 gives:

$$\log k_0 = -\frac{\Delta H_a + \Delta H_f}{2.303RT} + \text{a constant} \qquad \text{(Eq. 7)}$$

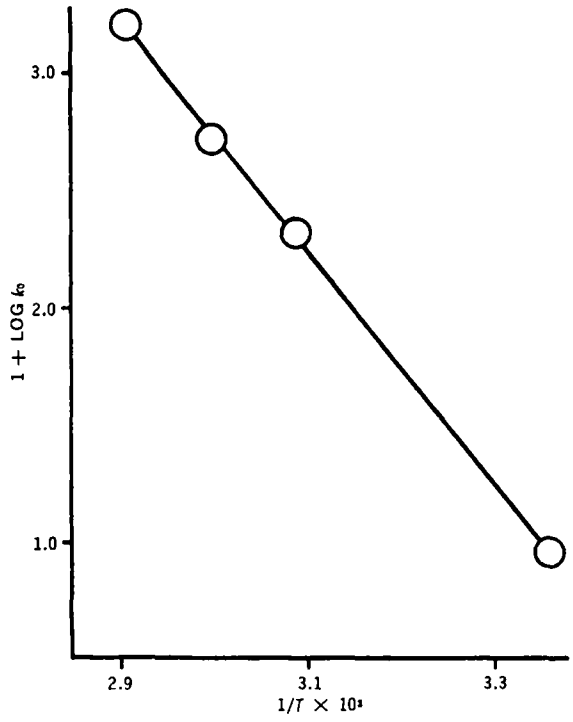


Figure 4—*Plot of log (apparent) zero-order reaction rate constant* versus *the reciprocal of the absolute temperature for experimental aspirin suspension.*

Thus, a plot of log k_0 *versus* $1/T$ should yield a straight line with a slope of $-(\Delta H_a + \Delta H_f)/2.303R$. By this method, room temperature stability can be estimated from studies at elevated temperatures without determining solubilities or first-order rate constants for the drug substance in solution.

EXAMPLE

An example from the literature, involving several unrelated sources, will help clarify the method and indicate its usefulness. Edwards (6) determined the solubility of aspirin as the undissociated acid (pH 1) at various temperatures, and a plot of log s *versus* $1/T$ (Fig. 1) yields a straight line with a slope of -1327. Garrett (7) determined the first-order rate constants for aspirin degradation in solution at pH 1.1 at various temperatures, and a plot of log k *versus* $1/T$ (Fig. 2) gives a straight line with a slope of -3698. Thus, $(\Delta H_a + \Delta H_f)/2.303R$ for this system is estimated to be $-(1327 + 3698)$ or -5025 kcal./mole. Therefore, a plot of log k_0 *versus* $1/T$ (see Eq. 7) for a suspension of aspirin at pH $\sim$ 1 should result in a straight line with a slope of approximately -5000 kcal./mole. Plotting the data of James (2) in such a manner (Fig. 3) results in a straight line whose slope is -4817 kcal./mole. Only data from 50, 60, and 70° were used because only those data were obtained on the same suspension formula.

EXPERIMENTAL

Because only three points were used to determine the slope in Fig. 3, a limited stability study on aspirin in suspension was performed to confirm the usefulness of the abbreviated method. Twelve hundred milligrams of aspirin USP (80 mesh) was placed in 50-ml. vials containing 20 ml. of 0.1 *N* sulfuric acid, which had been preheated to the experimental temperature. The vials were stoppered and stored at 70, 60, 50, and 24.5°. Duplicate samples were removed at appropriate times and quenched in an ice bath, and the entire contents were assayed for salicylic acid by the method of Tinker and McBay (8).

RESULTS AND DISCUSSION

The pH of both the fresh and degraded suspensions was 1.4. Plotting the stability data according to Eq. 7 yields a straight line

(Fig. 4) with a slope of −5002 kcal./mole, confirming the usefulness of the method.

Four points should be emphasized concerning kinetic studies on drug substances in suspension.

1. Data should be reported as "amount degraded" rather than "amount remaining" or "percentage lost," since (for example) for a given drug substance a suspension having a potency of 20 mg./ml. will degrade at the same rate as one containing 10 mg./ml. but the "percentage lost" is one-half as much.

2. If the drug substance under study is acidic or basic, it will often act as the primary buffer in the system, since solid drug substance is always in excess.

3. Because the solvent system is saturated with drug substance, concentrations of degradation products may reach a point where they affect the reaction rate, causing deviations from zero-order kinetics as the reaction proceeds.

4. In those cases where the simplified method fails because the system is dissolution rate limited, it may help to: (*a*) use a batch of drug substance with smaller particle size, and (*b*) agitate the stored samples. Estimations of room temperature stability based upon such conditions will err on the safe side.

CONCLUSION

Using the simplified procedure (for systems obeying the underlying assumptions stated under *Theory*), the room temperature stability of a drug substance in suspension can be estimated from elevated temperature studies (measuring amount degraded at various times) without determining solubilities or first-order rate constants. When the assumptions are not valid for a particular system, the abbreviated method will not work. The procedure is being presented here so that its applicability can be tested by investigators concerned with evaluating the stability of drug substances in suspension or suspension formulations.

REFERENCES

(1) J. V. Swintosky, E. Rosen, M. J. Robinson, R. E. Chamberlain, and J. R. Guarini, *J. Amer. Pharm. Ass., Sci. Ed.*, **45**, 37(1956).

(2) K. C. James, *J. Pharm. Pharmacol.*, **10**, 363(1956).

(3) G. Levy and R. D. Jones, *J. Amer. Pharm. Ass., Pract. Pharm. Ed.*, **19**, 546(1958).

(4) S. M. Blaug and J. W. Wesolowski, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 691(1959).

(5) H. V. Maulding, M. A. Zoglio, F. E. Pigois, and M. Wagner, *J. Pharm. Sci.*, **58**, 1359(1969), and references therein.

(6) L. J. Edwards, *Trans. Faraday Soc.*, **47**, 1191(1951).

(7) E. R. Garrett, *J. Amer. Chem. Soc.*, **79**, 3401(1957).

(8) R. B. Tinker and A. J. McBay, *J. Amer. Pharm. Ass., Sci. Ed.*, **43**, 315(1954).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 3, 1972, from the *Development and Control Division, Endo Laboratories, Inc., Subsidiary of E. I. duPont de Nemours and Company, Inc., Garden City, NY 11530*

Accepted for publication January 12, 1973.

▲ To whom inquiries should be directed.

Hydrindene Derivatives as Potential Oral Hypoglycemic Agents: *N*-Alkyl 1,2,3,3a,4,8b-Hexahydroindeno[1,2-*b*]pyrroles

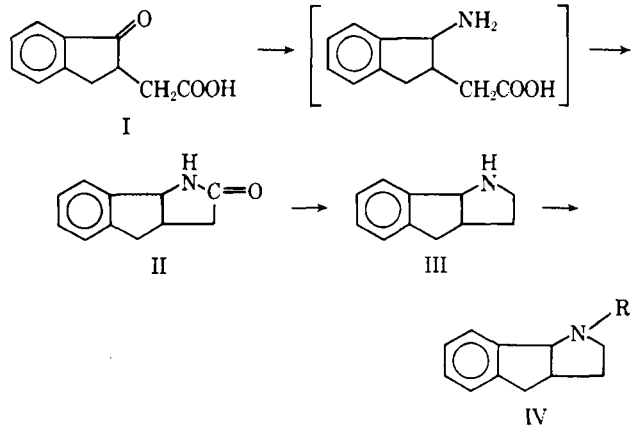
A. U. DE▲ and B. P. SAHA

Abstract □ A number of hexahydroindeno[1,2-*b*]pyrroles were synthesized and biologically evaluated. Only two compounds of this series showed some weak oral hypoglycemic activity. However, one compound inhibited epinephrine biosynthesis *in vitro* appreciably.

Keyphrases □ Hydrindene derivatives—*N*-alkyl 1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrroles synthesized and screened as potential oral hypoglycemic agents □ *N*-Alkyl 1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrroles—synthesized and screened as potential oral hypoglycemic agents □ Hypoglycemic agents, oral, potential—synthesis and screening of *N*-alkyl 1,2,3,3a,4,8b-hexahydroindeno-[1,2-*b*]pyrroles □ Heterocyclic compounds—synthesis of new class of hydrindene derivatives

In continuation of an investigation on hydrindene derivatives as potential oral hypoglycemic agents (1), it was considered worthwhile to synthesize isomeric indeno[1,2-*b*]pyrroles and test their activity. This new type of heterocyclic compound, although prepared earlier by different routes without any alkyl substitution at the nitrogen atom (2–4), was synthesized, in high yield (Scheme I), by a novel route by way of reductive amination.

1-Keto-2-indanylacetic acid (I) (5, 6), on being subjected to reductive amination with hydrogen and dry ammonia gas in absolute ethanol in the presence of Raney nickel catalyst, yields the corresponding pyrrolidone (II) in one step. Pyrrolidone (II), after reduction with lithium aluminum hydride in dry tetrahydrofuran, gives indeno[1,2-*b*]pyrrole (III). The pyrrolidone (II) shows the characteristic C=O and N—H stretching vibrations, while the indenopyrrole (III) shows only the N—H stretching vibrations. The indenopyrroles were



Scheme I