viscosity were studied on Days 1, 2, 4, 7, 14, 30, and 60. Day 1 corresponded to the day the emulsions were prepared.

When stored at high comparable temperatures for the study period, emulsions stabilized by a quaternary amine (cetylpyridinium chloride) were more stable than those stabilized by a surfactant precursor amine (2-amino-2-methyl-1,3-propanediol) and linoleic acid. All emulsions stored at room temperature (25°) and at 0° were stable.

Photomicrographs were used to study droplet size change. High surfactant concentrations retarded droplet size growth. A sudden increase of droplet size preceded demulsification, as was very evident at high temperatures.

A rapid decrease in viscosity preceded demulsification. At high temperatures, the cetylpyridinium chloride-stabilized emulsions formed loose gels and exhibited erratic readings.

Thixotropy was demonstrated as the emulsions were allowed to age at least 2–4 weeks. It was manifested by the change in viscosity readings as the stress was increased from 0.6 to 6.0 r.p.m. and then reversed from 6.0 to 0.6 r.p.m.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 27, 1970, from the *College of Pharmacy, University of Utah, Salt Lake City, UT 84112*

Accepted for publication June 26, 1973.

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

Supported in part by an AFPE fellowship and an NSF traineeship.

The authors thank Mr. Gottlieb Schneebeli for the phase-contrast photomicrography.

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Preformulation Studies II: Stability of Drug Substances in Solid Pharmaceutical Systems

J. TINGSTAD▲ and J. DUDZINSKI

Abstract □ The stability of drug substances in solid pharmaceutical systems is discussed. Theoretical models for various situations are proposed and their practical implications are considered.

Keyphrases □ Preformulation theory—stability of drug substances in solid pharmaceutical systems □ Drug stability in solid pharmaceutical systems—theory, preformulation □ Solid drug systems—stability of drug substance, theory

The stability of drug substances in solid pharmaceutical systems has been discussed in some detail previously (1–11 and the references cited therein). However, further treatment of the subject seems desirable for the following reasons.

1. In spite of the importance of solid dosage forms, there are relatively few quantitative reports on their chemical stability, primarily because of the complexities and difficulties involved.

2. This paper presents a somewhat different point of view than those of most references cited previously.

3. Some theoretical concepts need further clarification and application to practical stability studies.

DISCUSSION

Quantitative chemical stability studies on drug substances in solid dosage forms are difficult to perform for two primary reasons. First, analytical results tend to have more scatter because tablets and capsules are distinct dosage units rather than the true aliquots encountered with stability studies on drug substances in solution. Second, tablets and capsules are heterogeneous and discontinuous systems involving gas (air and water vapor), liquid (*e.g.*, adsorbed water), and solid phases, all of which can vary in concentration during an experiment.

Analytical error can be minimized by ensuring that content uniformity is satisfactory before initiating stability studies. The problems arising from the heterogeneity associated with these systems are more difficult to overcome, but the primary prerequisites for dealing with them are an awareness of their existence, an under-

standing of their nature, and an appreciation of their practical significance. Some of these problems are as follows.

1. There can be a considerable time lag before physical pseudo-equilibrium is established. For example, appreciable time may elapse before the concentration of water (liquid and vapor phases) comes to equilibrium (1). This is especially true for gelatin capsules, because water present in the capsule shell must equilibrate with that in the formulation and in the surrounding air space.

2. This equilibrium can be upset by opening the container to remove samples for assay, since water vapor can then escape from containers stored at elevated temperatures.

3. If the container is pervious to gaseous diffusion, the stability picture may become confused. For example, Table I shows that at 60°, a water-labile component of a tablet formulation was considerably more stable in a water-permeable blister package than in a sealed glass bottle; at room temperature and 70% relative humidity, the situation was reversed. The tablets, manufactured and packaged at room temperature, probably lose considerable water through the film at 60°, thereby improving stability. At room temperature and 70% relative humidity, the diffusion of water vapor is in the opposite direction.

4. A number of phase changes could take place during the stability study. For example, salicylic acid from aspirin hydrolysis would be in solution until the saturation point is reached and then a solid phase would separate. In addition, sublimation and subsequent deposition of salicylic acid crystals on the dosage form and surface of the container often take place.

5. Solid-state reactions (*e.g.*, oxidation by atmospheric oxygen) may occur simultaneously with solution reactions, and the degradation rates may not be additive (5).

6. Because of the low water volumes involved, kinetic studies may be complicated by chemical equilibrium phenomena and other factors (7).

7. An increase in temperature increases reaction rates and (usually) solubility; this would have a double effect on the overall degradation rate (12). However, this may be partially offset by the lowered concentration of liquid water at higher temperatures.

These problems can be minimized by observing four fundamental rules when conducting quantitative kinetic studies on solid dosage forms. First, as mentioned earlier, content uniformity must be within satisfactory limits. Second, tightly sealed glass containers should be used unless an alternative package is involved. Third, the amount of water present in the dosage form should be determined, since the rate of degradation often depends on the amount of water present. Furthermore, the equilibrium between liquid and vapor phases varies with temperature; consequently, it would be more accurate to determine water concentration at each storage temperature. One approach is to add a measured amount of water to the formulation (5), but part of this water vaporizes into the air space in the container. Consequently, water determinations done on the stored samples have more meaning (10), especially when elevated temperatures are involved.

The fourth rule is that a separate, sealed sample should be taken for each assay point and water determination. If not, water equilibrium can be upset when the container is opened to remove samples. If these rules are observed, meaningful data can be gathered in many cases. The treatment of some of these data may involve relatively complex mathematics (1, 7, 10), but for many systems a few basic, relatively simple, theoretical concepts will suffice. These concepts are as follows.

1. The three most common reactions encountered in stability studies on solid systems are: (*a*) hydrolysis in solution (*e.g.*, aspirin); (*b*) oxidation, either in solution or in the solid state (*e.g.*, vitamin A); and (*c*) reactions between two ingredients.

2. When both Class (*a*) and Class (*b*) reactions are involved, the reaction rates can be additive or antagonistic. For example (assuming no oxidation in solution), adding water to a dry system would initiate hydrolysis but could decrease solid-state oxidation, probably by water adsorption on solid surfaces (5).

3. Class (*a*) reactions are usually zero order in solid dosage forms unless all of the reactant is in solution; then first-order kinetics usually prevail. However, in some situations (*e.g.*, if an acidic or basic degradation product catalyzes the reaction), the kinetics are more complicated. Class (*b*) reactions can be of various orders, although they are often first order if sufficient oxygen is present. Class (*c*) reactions can be of various orders, depending on the concentrations and solubilities of the reactants.

Table I—Degradation of Water-Labile Component of a Tablet Formulation in Two Different Packages under Different Storage Conditions

Package	—Amount Lost (%) in 8 Weeks at— 60°	Room Temperature (70% Relative Humidity)
Blister	11.6	7.0
Glass	84.4	0

4. A particular model or system should be carefully defined. For example, the Class (*a*) reactions described here assume that the reactant dissolves in an adsorbed film of water and that the concentration of adsorbed water is directly proportional to the total amount of water present. The discussion here of Class (*b*) reactions is limited to oxidation in the solid state. Finally, the mathematics describing a Class (*c*) reaction would be different, depending on whether one assumed solid state or solution reactions.

5. Although the models described here are consistent with many reported data, this consistency does not prove that degradations are occurring *via* mechanisms proposed in the model. The mechanisms of degradation for each individual situation would have to be proven by the usual rigorous procedures.

Because of the relatively small amounts of water present in these systems, concentrations (in solution) of degradation products may become significant as the reaction proceeds; then chemical equilibrium phenomena may complicate the kinetics (7). Furthermore, in some cases the drug substance may be less stable in a solid system with a small amount of water present than when the same ingredients are dissolved or suspended in a relatively large quantity of water (10). Nevertheless, many solid systems behave predictably according to the first three concepts above, especially during the first 10–40% of the reaction. Therefore, it would be useful to take a more detailed look at those predictable situations. Only Class (*a*) and Class (*b*) reactions will be considered here.

Figure 1 illustrates the effect of adding water to a solid system involving a relatively insoluble drug substance that degrades only in aqueous solution [Class (*a*), with assumptions mentioned in the fourth concept above]. With no water present, no degradation occurs. As successive amounts of water are added (assuming all of it is available as solvent), the amount of drug substance degrading per unit time increases proportionally:

$$d = k_0 \times v \qquad \text{(Eq. 1)}$$

where, for example, d is the amount degraded in 1 day, k_0 is the apparent zero-order rate constant[1] (in milligrams per milliliter per day), and v is the volume of water (in milliliters) present in the solid system. For example, if k_0 = 1 mg./ml./day and v = 0.1 ml., then d = 0.1 mg.; then if the water content is doubled to 0.2 ml., d would also double. Since the point is never reached where all of the drug substance is in solution, the plot consists of a single straight line with a slope of k_0.

In Fig. 2, the same assumptions are made except that the drug is relatively soluble. Up to point A, the amount of water present is not enough to dissolve all of the drug substance and the situation is identical to that in Fig. 1. After point A, all of the drug substance is in solution and first-order kinetics prevail:

$$d = (1 - e^{-k_1}) \times c \times v \qquad \text{(Eq. 2)}$$

where d and v have the same meaning as in Eq. 1, c is the initial concentration of drug substance (in milligrams per milliliter), and k_1 is the first-order rate constant in reciprocal days. Here, adding more water does not change the value of d (ignoring other dilution effects) because, for example, doubling v automatically decreases c by one-half. Thus, the slope is (ideally) zero when first-order kinetics pre-

[1] As pointed out previously (12), the apparent zero-order rate constant k_0 is equal to the first-order rate constant k_1 times the solubility of the drug substance in the solvent at the experimental temperature. Consequently, when the temperature is raised in accelerated studies, k_0 is increased by two factors: the temperature effect on k_1 and the temperature effect on the solubility of the drug substance.

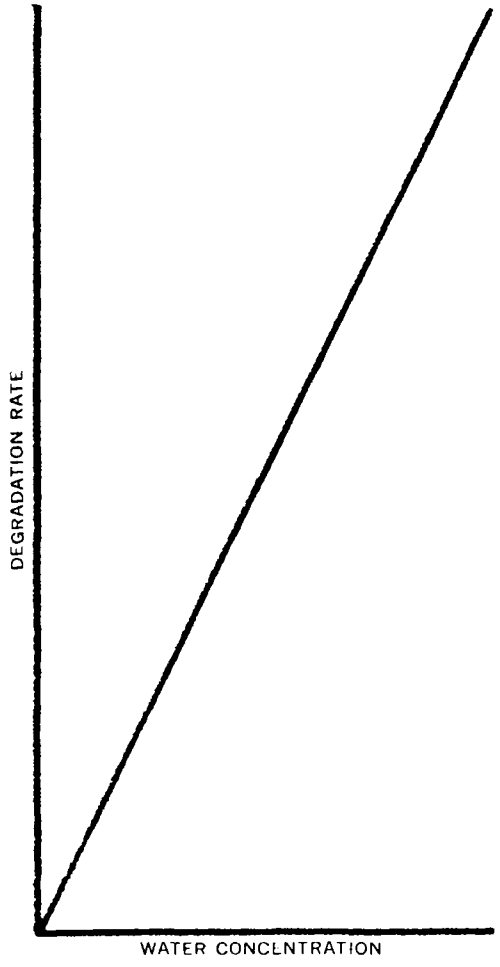

Figure 1—*Model plot showing the effect of water concentration on the stability of a relatively insoluble drug substance that degrades only in aqueous solution.*

vail and equal to k_0 when zero-order kinetics dominate. This concept was touched on by others (5, 11) and will be discussed later.

In Fig. 3, the drug substance is relatively insoluble and subject to both oxidation in the solid phase and hydrolysis in solution. At point A, with no water present, the effect of oxidation is evident; there is appreciable degradation in the absence of water. From A to B, hydrolysis enters the picture, but its effects are partially hidden because the two reactions are antagonistic. That is, the presence of water reduces the effects of oxidation (*e.g.*, by adsorbing on and

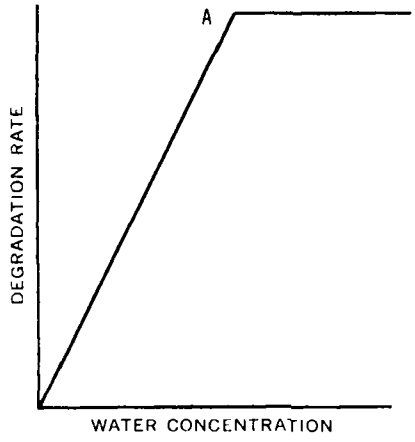

Figure 2—*Model plot showing the effect of water concentration on the stability of a relatively soluble drug substance that degrades only in aqueous solution. At point A, all of the drug substance is in solution.*

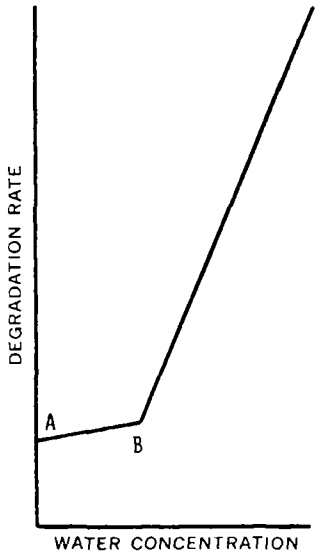

Figure 3—*Model plot showing the effect of water concentration on the stability of a relatively insoluble drug substance that degrades both in the solid state and in aqueous solution. See text for explanation.*

partially protecting the surface of the solid). After point B, the effects of oxidation become relatively constant and the situation more closely resembles that in Fig. 1. If the drug substance in Fig. 3 was water soluble, the plot would eventually plateau as in Fig. 2. Because a nonhydrolytic reaction is partially involved, the slope of the second portion of the plot is less likely to equal k_0. If the two reactions were simply additive, or if the hydrolytic reaction was much faster than the oxidative, the AB portion of the plot would be insignificant. The effect of hydrolysis alone could be determined by eliminating oxygen from the system.

In some situations, the data will not fit the models, but this is not unusual for theoretical models representing complex systems. The report on thiamine hydrochloride (10) is a case in point, but even here a good portion of the data fits the theoretical model. Examples from the literature and these laboratories can be used to illustrate the utility of the three models presented in Figs. 1–3.

Maulding *et al.* (11) obtained a plot identical to that in Fig. 1 using aspirin, a compound that fits the requirements of: (*a*) relatively low solubility, and (*b*) degradation primarily by hydrolysis. The zero-order nature of aspirin degradation in these systems is illustrated in that report, as well as in Fig. 4, based on data from these laboratories. In addition, the data of Leeson and Mattocks (1) can be plotted zero order, assuming an initial lag time (Fig. 5). Figure 6,

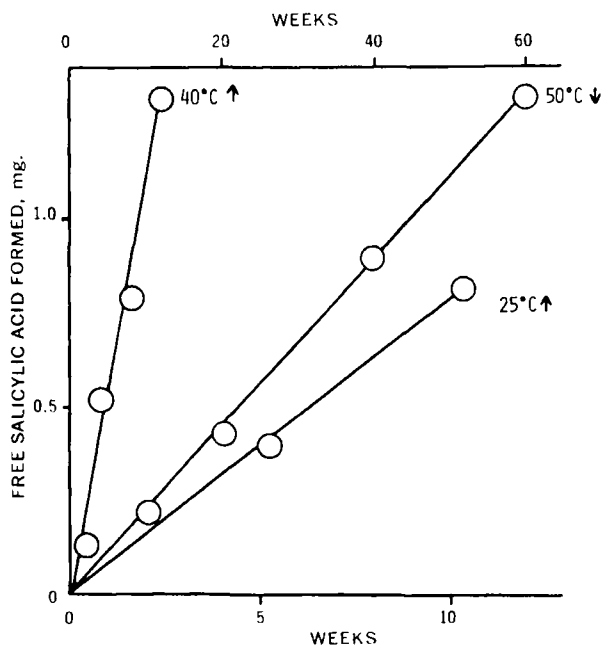

Figure 4—*Plot showing the zero-order nature of aspirin degradation in a solid system. The arrows show to which abscissa the plots refer.*

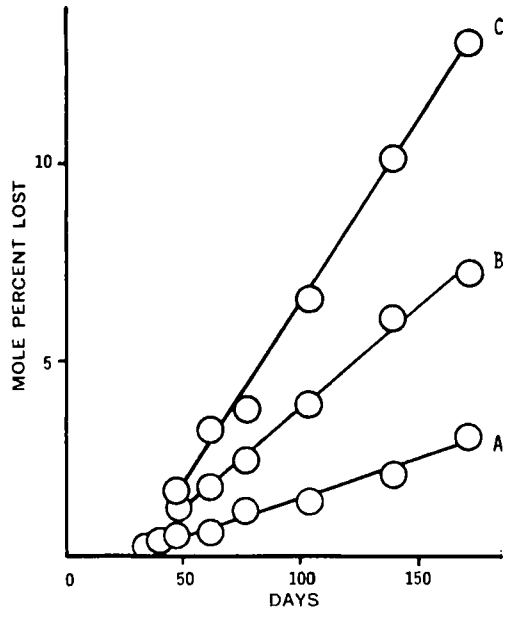

Figure 5—*Plot showing the zero-order nature of aspirin degradation in a solid system [50° data of Leeson and Mattocks (1)]. Key: A, 46.02 mm. vapor pressure of water; B, 68.30 mm.; and C, 74.20 mm.*

representing data from an experimental drug substance in these laboratories, also closely resembles Fig. 1.

The degradation of vitamin A in tablets was found to be first order rather than zero (2) but, as noted earlier, degradation involves more than simple hydrolysis. While the data of Tardif (3) were plotted first order, some of the plots (*e.g.*, thiamine and ascorbic acid at 50°) appear to exhibit zero-order characteristics. Furthermore, if all the thiamine was in solution (possible, especially at the higher temperatures), this would give first-order kinetics. These examples illustrate that many situations do fit the theory when examined in this way.

Thiamine hydrochloride meets the general criteria for compounds yielding the plot seen in Fig. 2. However, the situation is complicated by equilibrium phenomena and other factors, as discussed by Carstensen *et al.* (10). Nevertheless, a significant portion of the reaction follows zero-order kinetics (Fig. 7), and the plot in Fig. 4 of their report suggests that, under ideal conditions (*i.e.*, assuming no chemical equilibrium effects), a plot similar to that in Fig. 2 of this paper would result.

The situation represented in Fig. 3 finds a close parallel in the report of Carstensen *et al.* (5) on vitamin A acetate. Figure 8 is a plot of their data, and it is practically identical to the ideal case depicted in Fig. 3. The ordinate in Fig. 8 is the sum total of the vitamin A lost at all temperatures at a given water concentration. Data from 55°, 85° (4 days only), and 70° (8 days only) were not used because: (*a*) in some cases the concentration of vitamin A reached zero, and it is not known at which point in that time interval the value became zero; and (*b*) the second data points at 70 and 85° showed a drastic reduction in degradation rate, which raises questions about their validity (these data were also rejected by the authors in their calculations).

From Fig. 8 it is quite evident that in their system vitamin A

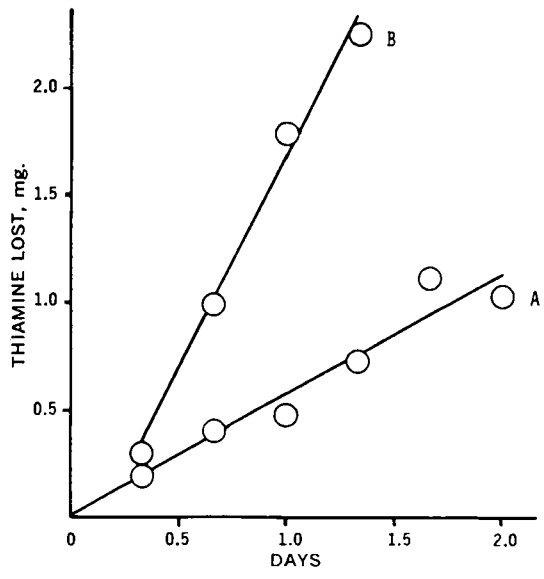

Figure 7—*Plot showing the zero-order nature of thiamine hydrochloride degradation in a solid system [55° data of Carstensen* et al. *(10)]. Key: A, 4% moisture; and B, 5% moisture.*

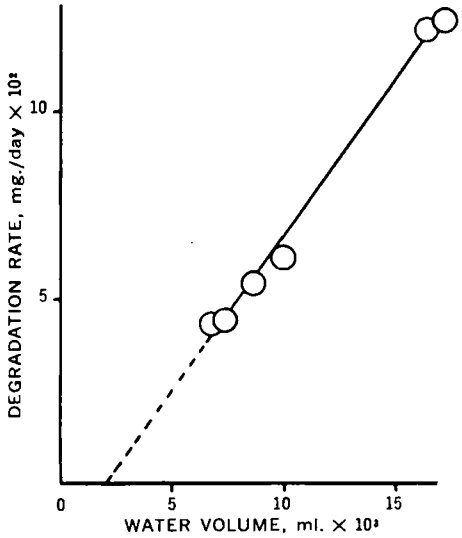

Figure 6—*Plot of actual data for experimental drug substance (confirms the validity of the model in Fig. 1).*

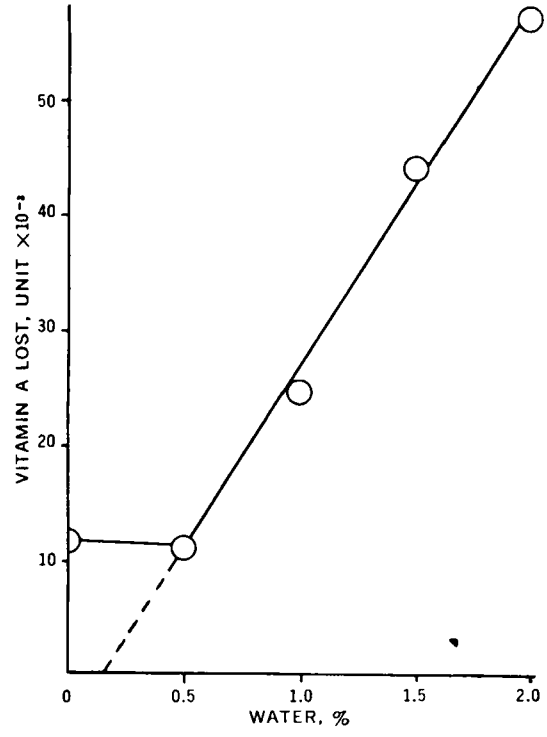

Figure 8—*Plot showing the effect of water concentration on the stability of vitamin A acetate in a solid system [data of Carstensen* et al. *(5)]. See text for explanation.*

acetate degrades significantly in the absence of water. When 0.5% water is added, the stability picture remains essentially the same, indicating that the water's contribution to degradation is offset by the partial protection it affords against solid-state oxidation. As more water is added, however, the degradation rate increases linearly with water concentration, indicating that the contribution of solid-state oxidation has plateaued and the effects of hydrolysis are becoming more evident.

The vitamin A acetate report (5) provides another example of the usefulness of the concepts and models presented in this paper. In discussing the theory behind their presentation, the authors (5) stated: "If vitamin A degrades by functional dependence of water content, then a $(1 + a)$ order reaction may be expressed as $dC_a/dt = -K \cdot C_A \cdot C^a_{H_2O}$ [their Eq. 1] where C denotes concentration and the subscripts denote vitamin A acetate and water." From their data, they reached the conclusion that the apparent value of a is 2–3, a relatively high order.

If one assumes that zero-order kinetics prevail for the water-dependent degradation (a reasonable assumption, since vitamin A acetate is relatively water insoluble), then their Eq. 1 reduces to our Eq. 1 when the value of a is unity. A slightly different interpretation of their data yields values of a that are close to unity and confirm the validity of the model in Fig. 3. That interpretation is as follows.

From the sharp break in the slope in Fig. 8, it is evident that the 0–0.5% range of water concentration is atypical. That is, their Eq. 1 assumes a continuous function and, for their system, the function can be considered continuous only between 0.5 and 2.0% added water. Therefore, the "water added" concept should, in our opinion, start from their 0.5% mark. Thus, their 0.5, 1.0, 1.5, and 2.0 values for "percent water added" should (more correctly) be taken as 0, 0.5, 1.0, and 1.5%, respectively. For example, their 1.5% is, more correctly, 1.0% (*i.e.*, 1.5 − 0.5). Recalculating their data using the corrected values of water added yields the following values for a: 85°, 0.90; 70°, 0.87; 55°, 1.45; 25°, 1.46; and 5°, 1.42. Considering the complexity of the system, experimental values of 0.87–1.46 (average = 1.2) against a theoretical value of unity is good confirmation of the validity of the model in Fig. 3.

CONCLUSION

Stability data for solid dosage forms, gathered under suitably controlled conditions, can often be successfully interpreted using the schematic models presented in Figs. 1–3.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 10, 1973, from the *Development and Control Division, Endo Laboratories, Inc., Subsidiary of E. I. du Pont de Nemours and Company, Inc., Garden City, NY 11530*

Accepted for publication June 28, 1973.

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Sodium-Ion Electrode: Continuous Monitoring of Tablet Dissolution *via* Flowing Streams

T. E. NEEDHAM, Jr., L. A. LUZZI▲, and W. D. MASON

Abstract □ The use of a continuous flowing stream apparatus to follow tablet dissolution was studied. A dissolution chamber using a commercially available filter unit was designed to follow tablet dissolution through use of either a sodium-ion electrode or a spectrophotometric analytical module. The effect of variation of flow rate on the dissolution profile and the ability of the apparatus to differentiate between the common tablet parameters of hardness and drug potency were shown.

Keyphrases □ Tablet dissolution—determination in continuous-flow equipment using sodium-ion electrode or UV spectrophotometry differentiation between parameters of hardness and drug potency □ Dissolution equipment, tablets—continuous-flow system using sodium-ion electrode or UV spectrophotometry, differentiation between parameters of hardness and drug potency □ Sodium-ion electrode system—used to determine tablet dissolution in continuous-flow system

The importance of *in vitro* testing of tablet and capsule dissolution and its relationship to drug availability are accepted facts. The correlation of *in vitro* to *in vivo* data shows the need for a versatile and flexible apparatus which, through adjustment of its parameters to the variance in dissolution profiles of different tablets, can succeed in matching such data. A second but equally important consideration is a reduction in the time and labor required for such *in vitro* analysis. By using the technique of continuous analysis in flowing streams to monitor dissolution, the entire profile can be recorded and experimental error can be reduced to a minimum.

In recent years, equipment for studying the dissolution of solid dosage forms under conditions of continuous flow has been presented. The arguments for using a continuous-flow method and the theoretical considerations involved have been documented (1, 2). These authors suggested that the continuous-flow