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SOLID STATE REACTIONS - THEORETICAL AND EXPERIMENTAL ASPECTS

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INTRODUCTION

Any reaction occurring in the solid state will assume dramatically different characteristics from the same reaction proceeding in either a liquid or a gaseous state. The molecules of a solid oscillate within spaces confined by the solid crystalline structure; certainly any reaction requiring the migration of one or more atoms can be expected to occur with far greater facility in the liquid or gaseous phase. Yet modern investigations now show that the chemical activity of solids has been greatly underestimated. Solid state chemistry has long maintained a poorly defined terrain on the chemical landscape. However difficult to define quantitatively, solid state reactions present to us a new frontier in the investigation of chemical behavior.

Kinetics of the thermal and photolytic decomposition of solids are naturally subject to the normal laws of chemistry.

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The manner in which their kinetic behavior is controlled by these laws, however, is often subject to certain properties of solids that are difficult to define, much less quantitate. Among these are structure variations, degree of crystallinity, density, hygroscopicity, surface characteristics, melting point, and extent of solvation. Because of the intrinsic heterogeneity of the solid phase system, the reliable, adjustable parameters of classical solution kinetics are not at the disposal of the solid state kineticist. Therefore, his desire to elucidate a total reaction mechanism usually yields to an alternative but equally valuable objective: to locate and characterize the reaction-product interface by determining rate, energy profile and general kinetic form of the reaction.

The concept of "concentration" and "order of reaction" can no longer be well defined in the solid state. In liquid or gas reactions, the rate constant k is usually measured in the familiar units of sec^{-1} (first-order) or $1\text{-}mole^{-1}\text{-}sec^{-1}$ (second-order). The activation energy E_a is derived from the dependence of k on temperature according to the Arrhenius equation. These descriptive kinetic variables take on new dimensions, however, when applied to solid reactions. Reaction velocity must be interpreted as the change of product-layer thickness, weight, or quantity, as a function of time. Depending on which of these layer characteristics is followed during the reaction, and upon the geometry of the decomposing particle, k might be expressed in such unwieldy units as $g^2\text{-}cm^{-1}\text{-}sec^{-1}$ or $cm^2\text{-}sec^{-1/2}$. Even though actual data may generate these reaction variables, their strict interpretation remains elusive, strongly dependent upon certain "classical" assumptions that must be imposed upon the reaction system.

One of the more basic constraints that must be assigned to the kinetic model is that which describes the geometry of the solid particles. This physical property necessarily plays a strong role in determining the observed chemical behavior. Too often, however, significant differences in crystal geometry are only subtly reflected by the kinetic data. Consequently, any one of several contrasting mathematical models could be designed by the researcher, imposed upon the reaction system, and be found to satisfy the experimental data within an acceptable range of error. Mechanistic interpretations and ultimately the prediction of long-term chemical stability depend upon this selection, yet it often is a difficult - at times even an arbitrary - task to select the best model.

There are additional problems that can complicate the study of solid reactions. Solid decompositions are usually complex, multistep reactions which often involve the simultaneous participation of several phases. For instance, while oxidation occurs readily in the absence of moisture and hydrolysis is facilitated by the presence of moisture, both reaction mechanisms can occur at the same time depending on the experimental conditions. Furthermore, such reactions often proceed only on the surface of the solid substrate, introducing an equilibrium which defies the application of normal kinetic predictive techniques. Since the physical nature of a solid is apt to change over a broad range of temperature, different mechanisms of degradation can predominate as the conventional Arrhenius studies are pursued, rendering their interpretation difficult. Depending on the controlling mechanism of degradation, such as diffusion, chemisorption, etc., various temperature dependencies are observed.

The study of solid state reactions is fundamental to the development of a new drug candidate destined to be marketed as a solid dosage form. Kinetic studies must be undertaken to gain a basic understanding of the reaction mechanism so that stability of the drug can be predicted. From such information overage determinations, label statements, and expiration dating are ultimately evolved. Once formulated, however, a drug rarely exhibits the same mechanism of degradation as in its pure state. The addition of excipients only further exaggerates the heterogeneity already common to the pure drug. Many factors such as moisture, pH of the excipient surface, and volume of the container, can further affect the kinetic behavior of the active ingredient. Free or bound granulating solvents or moisture, differences in thermal capacity between drug and excipients, phase changes, and chemical equilibria also contribute to the complex nature of formulation stability studies. Only through such studies, however, can the most stable functional grouping, salt form, or polymorph of a drug be recognized and formulated in an optimal manner.

The industrial research pharmacist must primarily concern himself with the initial degradation of a formulation. Rapid decomposition of a formulation under reasonable conditions of storage is clearly unacceptable for a commercial product. Preformulation kinetics in these cases take on a more practical value: many solid state reactions, even those of formulated drug, are amenable to Arrhenius testing during the first 5-10% decomposition, even though an examination of their complete degradation profile might reveal a complex exponential or S-shaped curve. Careful interpretation of such Arrhenius data can provide adequate prediction of stability without demanding the complete elucidation of reaction mechanisms.

This article investigates the diverse selection of analytcal techniques available to the preformulation pharmacist, some of which are particularly effective for evaluating the drug in the presence of excipients. Also discussed are the equally important techniques that can be used to follow the appearance of degradation product; often this is more effective than studying the disappearance of the intact drug.

Since the development of a solid dosage form depends heavily upon stability testing, some knowledge of solid state behavior is necessary to interpret the results of kinetic studies with confidence. The primary kinds of reactions, their potential kinetic behavior, as well as implications of their temperature dependence are presented in this article.

CLASSIFICATION OF SOLID STATE REACTIONS

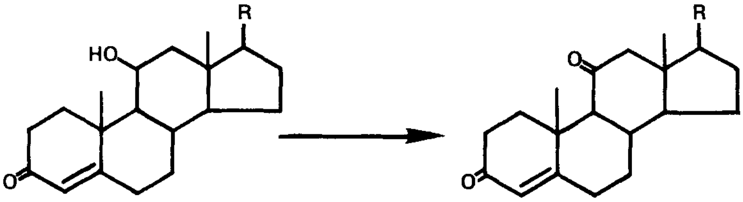
Solid state reactions fall into three general categories: solid-solid reactions, solid-gas reactions, and solid transformations including polymorphic transitions, rearrangements, phase changes and decomposition. Because of the difficulty encountered in studying heterogeneous solid reaction systems, little experimental work has been conducted to elucidate actual reaction mechanisms. It is known, for instance, that the tarnishing of metals involves ionic bonding. Most reactions of organic solids, however, occur via bonding mechanisms common to solution chemistry: hydrogen bonding, dipole-dipole and dipole-induced dipole interaction, charge-transfer complexation, or covalent bonding.

The proper analytical method can reveal the nature of interaction for many reactions. For example, construction of a phase diagram reveals the number and composition of the products formed. The stability of these complexes can be qualitatively evaluated by examining the flatness of their diagram maxima. Specifically, hydrogen bonding can often be detected by IR and NMR spectra, while charge-transfer interaction is best revealed by UV spectra. If the dipole moment of the complex is found to be much greater than that of either of the parent components, at least some dipole-dipole association must be occurring.

Solid drug-excipient interactions frequently take the form of adsorption, either physical adsorption or chemisorption. Physical adsorption occurs when the valency requirements of each adsorbate atom on the surface are satisfied by bonding to adjacent adsorbent atoms. The forces responsible for the adsorption are relatively nonspecific, usually of the van der Waals type. The energies involved are usually small, and both adsorption and desorption are normally rapid, leaving the substrate chemically intact upon desorption.

By contrast, chemisorption takes place only when the valency requirements of the surface adsorbate atoms cannot be fully satisfied by nearby atoms. The bond so formed between adsorbate and adsorbent results in the formation of a new species whose physicochemical properties might be quite different from those of the original molecules. Since chemisorption involves electron transfer and requires an appreciable energy of activation, it usually takes place at temperatures higher than those required for physical adsorption and may proceed relatively slowly. In addition, since the adsorbent surface can be chemically satisfied by a single layer of molecules, chemisorption is restricted to the formation of a monolayer. The extent of monolayer adsorption can be increased by creating new surfaces by heating, compression, vigorous grinding, or equilibration with a solvent.

Favorable geometry along the reaction coordinate is a primary factor in determining the ease of a solid state reaction. This is illustrated by the example in Scheme I which shows the air oxidation of steroidal 11-β-ols to 11-ones. While the solid state reaction is highly sensi-



SCHEME I

tive to the nature of R, implying that molecular arrangement within the crystal lattice exerts a major influence on rate, the oxidation in solution is independent of this functional group.[1] Also the tert-butylacetate ester of hydrocortisone is much more reactive than the corresponding ethyl ester. In addition, this reaction is influenced by the degree of solvent incorporation into the crystalline lattice. Thus, by controlling crystal packing by introducing the requisite functional group, the course of a solid state reaction can be predicted. This concept forms the basis for "crystal engineering."[2]

For solid-solid or solid-gas reactions to occur, two reactants must in some way come into contact with one another. The progress of such reactions depends upon the initial growth of product nuclei on the crystal surface. If nucleation proceeds rapidly on the surface, then the rate of decomposition is governed by the geometrical progression (mobility) of the reacting interface (boundary) between product and reactant. If the reaction becomes progressively impeded by build-up of the product layer, then the rate is diffusion-controlled. Whether in the solid or in the gas phase, the more mobile reactant must diffuse either through the product layer (bulk diffusion) or over the surface (grain boundary diffusion). When an induction period occurs and the reacting materials have little mobility, however, certain strains will form in the crystal. If the product and reactant lattices do not match, cracking may occur. The reaction chain then branches away, and the rate of decomposition becomes dependent on the propagation and termination probabilities of these various branching chains.

In many cases no formal boundary movements can be imposed upon a solid transformation. Once again the transformation depends upon the initial formation of product nuclei whose growth, triggered by some external stimulus such as heat or light, "infects" neighboring crystal lattices to provide an impulse for further transformation. Certain transformations and most decompositions are likely to develop reacting interfaces, however, if their propagation depends upon an external effect such as the penetration of light into a thick sample. Despite the very real significance of the geometry of reaction product growth, few studies have progressed beyond the theoretical to the practical implications of this aspect of solid state behavior.

SOLID-SOLID REACTIONS

1. Addition Reactions

$$A_{(s)} + B_{(s)} \rightarrow AB_{(s)} \qquad \text{(Eq. 1)}$$

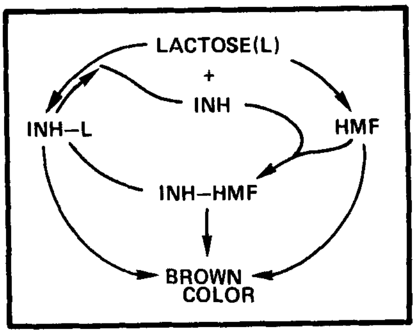
When two solids A and B interact as in Equation 1, a "reaction-product layer" forms between them. The molecules of more mobile reactant, A, must diffuse through this product layer to continue to react with the molecules of B. Studies of the reactions between picric acid and a wide range of more mobile compounds, such as naphthols, naphthalene, phenanthrene, anthracene, pyrocatechol, and resorcinol,[3,4] have revealed that the shape and size of molecules significantly affect their reactivity in the solid state. The planar, less bulky, more symmetrical molecules were found to react at a faster rate to form picrates since their diffusion occurred via surface migration. Generally, in such a reaction the surface of reactant A, which diffuses into B, is in a state of disturbance. Molecules at the surface may even sublime into the vapor phase or will, at times, drift as a solid over the surface.

The boundary movement or propagation of a solid addition reaction can take either of two courses as indicated in Scheme II. The product layer may advance either towards one of the two reactants (a) or towards both (b). The former behavior is more commonly observed since it occurs when one reactant is more mobile than the other. In the illustrated case (a), reactant A is the more mobile. If AB is not miscible with either A or B and if A is capable of diffusing through AB while B is not, then A will diffuse from the interface A/AB

SCHEME II

through the product layer and combine with B at the interface AB/B. The product layer will consequently move towards B. However, if both A and B can diffuse through the product layer, the product boundary will move on both sides corresponding to reaction (b). Generally speaking, the factors determining the direction of propagation are not clearly known. Where vapor phase diffusion is involved, however, it can be expected that the component having the higher vapor pressure will have a greater tendency to diffuse through the product layer.

Amine-carbonyl reactions (Schiff base) in the solid state proceed via addition reactions. The inactivation of formulated benzocaine by the granulating agent glucose, yielding the addition product benzocaine N-glucoside, serves as an example.[5] Another example is the "Maillard reaction" associated with the "browning" observed between lactose and amines. These reactions require a relatively low order of energy for initiation and, once begun, exhibit autocatalytic properties. An investigation of the discoloration of tablets containing amine salts formulated with lactose[6] has indicated that the liberation of free amine by basic lubricants in the formulation is necessary for the darkening of such tablets. For the browning reaction of the isoniazid-lactose system, the presence of isonicotinoyl hydrazones of lactose and hydroxymethylfurfural has been confirmed.[7] The proposed degradative mechanisms are shown in Scheme III. Similar examples include reactions of dextroamphetamine sulfate with lactose[8,9] and haloperidol with hydroxymethylfurfural.[10]



SCHEME III

A non-classical addition reaction might include the formation of inclusion compounds from the reactions of amines with β-cyclodextrin or desoxycholic acid[11,12] and of fatty acids with cyclodextrins.[13]

2. Exchange Reactions

$$A_{(s)} + BC_{(s)} \rightarrow AB_{(s)} + C_{(s)} \qquad \text{(Eq. 2)}$$

$$AB_{(s)} + CD_{(s)} \rightarrow AD_{(s)} + BC_{(s)} \qquad \text{(Eq. 3)}$$

Unfortunately, no attempt has been made to characterize the movement of the reaction interface in exchange reactions, despite the numerous examples of this behavior reported. For example, the breakdown of aspirin in tablet formulations containing phenylephrine[14] has been found to result in a concurrent loss in phenylephrine activity (Fig. 1). At room temperature, the primary degradation pathway is acetylation of the secondary amine function of phenylephrine. At elevated temperatures, however, acetylation was found to have progressed to the drug's phenolic and alcoholic groups. Other instances

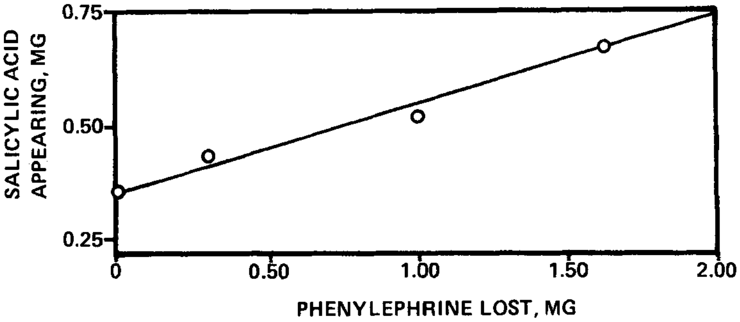


FIGURE 1

Decrease in phenylephrine activity plotted against increase in free salicylic acid for a multi-ingredient tablet containing phenylephrine hydrochloride and acetylsalicylic acid with storage at 70° for 4 weeks. Reprinted from Ref. 14, p. 377, by courtesy of the author and Journal of Pharmaceutical Sciences.

where transacetylations have been reported include the degradation of codeine-aspirin tablets[15] and of aspirin anhydride tablets.[16] In the latter case, transacetylation occurred between the anhydride degradation products. While acetaminophen and aspirin apparently do not undergo exchange,[17] aspirin will exchange anions with calcium stearate:[18]

$$2\ \text{Aspirin} + \text{Ca (Stearate)}_2 \rightarrow \text{Ca (Aspirin)}_2 + 2\ \text{Stearic Acid} \qquad \text{(Eq. 4)}$$

The accelerated breakdown of aspirin formulated with calcium stearate might be attributable to a destabilizing rise in pH (to ∿4.0) effected by the buffering action of solvated aspirin and calcium aspirin.

SOLID-GAS REACTIONS

$$A_{(s)} + B_{(g)} \rightarrow C_{(s)} \qquad \text{(Eq. 5)}$$

$$A_{(s)} + B_{(g)} \rightarrow C_{(s)} + D_{(g)} \qquad \text{(Eq. 6)}$$

Except for oxygen and carbon dioxide, most gases common to the atmosphere are fairly unreactive. Although nitrogen itself is essentially inert, certain of its oxides, as well as oxides of sulfur, can be acidic in the presence of water vapor. Moisture generally will enhance the reaction if it occurs readily in the solution state. The presence of moisture may sometimes antagonize oxidation reactions because the water tends to adsorb on the surface of the solid where oxidation is likely to occur.

Despite its obvious significance, very little work has been carried out on solid-gas reactions between a drug and water vapor. It is difficult on a practical basis to separate the effect of water vapor from the effect of adsorbed moisture, since under normal conditions both are abundant. It is generally assumed, however, that adsorbed water layers exist on the surface of most drug particles, allowing surface particles to dissolve and decompose hydrolytically, much as they might in saturated aqueous solution. The adsorbed water molecules are then assumed to have the ordinary properties of solvent and reactant.

The double dehydrobromination of solid meso-dibromobutane derivatives provides an interesting example of the difference in behavior between the reaction of amines with a compound dissolved or in the crystalline state. The stereochemistry of products arising from attack by gaseous ammonia is dictated by crystal packing (signifying topochemical control) whereas in solution, a mixture of isomers is obtained.[19]

Examples of oxidation include that of ascorbic acid,[20] fumagillin[21] and filipin.[22] Also, Rastogi[23] has proposed that some addition reactions, e.g., picric acid with naphtols, occur in the vapor state since reaction products are observed even when the solid reactants are physically separated.

SOLID STATE TRANSFORMATIONS

1. Polymorphic Transitions

$$A_{(s)I} \rightarrow A_{(s)II} \qquad \text{(Eq. 7)}$$

Polymorphic transitions occurring within the solid state are governed by the free energy of the phases. At any given temperature and pressure, the phase with the lowest free energy is the most stable. The compound, therefore, tends to exist in this phase. If the temperature and pressure are changed, the condition of minimum free energy may require the compound to undergo transition from one phase to the other. If these transformations are to be predicted and controlled, the transition temperature must be determined.

Although polymorphic transitions are not strictly chemical reactions, polymorphs often exhibit different chemical stability; it is important that their presence be detected and characterized. Those transformations requiring only slight changes in crystal symmetry usually proceed at a rate much faster than those demanding a considerable change in structure -- and it is possible for the same crystal to exhibit both kinds of transformations. Implicit in the earlier statement is that a change in molecular structure does not occur. An example wherein such a phenomenon could have been mistaken for polymorphism was described by Borka[24] -- the spasmolytic substance baclofen melts at 205°C and instantly resolidifies upon cooling to a white, crystalline mass melting at 117°C. What actually occurred was not polymorphism, but a thermal arrangement to a γ-lactam structure and release of a molecule of water.

Thermally catalyzed polymorphic transformations are best studied 10-20° below the melting point. Their energy of activation is usually quite large, ∿50-100 kcal/mole. The thermally induced transformation of sulfamethoxydiazine[25] is shown in Fig. 2 and a similar transformation of chloramphenicol palmitate[26] is given in Fig. 3. The lag period observed in the

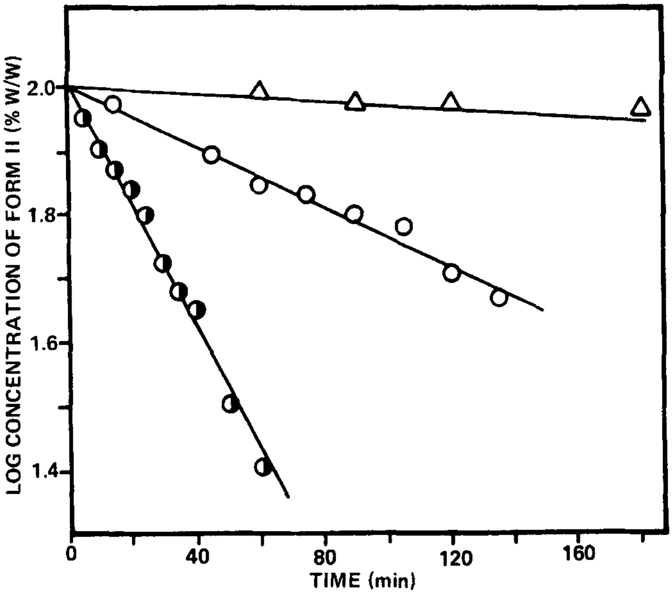


FIGURE 2

Transformation of sulfamethoxydiazine Form II to Form I in the solid state at various temperatures. Δ - Δ 100°, O - O 105°, ◑ - ◑ 110°. Reprinted from Ref. 25, p. 923, by courtesy of the author and Journal of Pharmacy and Pharmacology.

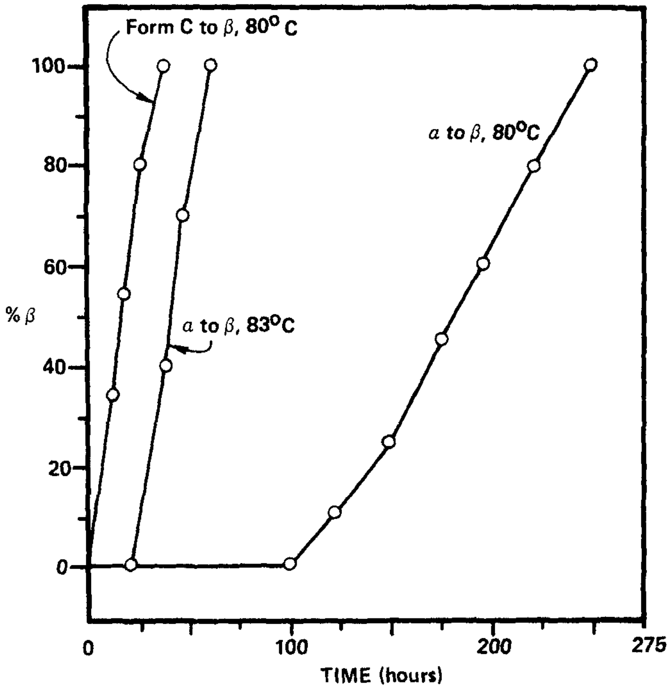


FIGURE 3

The velocity of solid phase transformation of the α-form and form C of chloramphenicol palmitate to the β-form at different temperatures. Reprinted from Ref. 26, p. 368, by courtesy of the author and Acta Pharmaceutica Suecica.

latter figure is probably a measure of the time needed to produce an adequate number of nuclei for the transformation to occur under steady state conditions. These transformations can also exhibit diffusion-controlled kinetics as reported for sulfathiazole.[27]

In the presence of water vapor, transformations can occur more readily. Condensation of a monolayer of water on the crystal surface allows facile recrystallization of the required number of catalytic nuclei, and the energy of activation is decreased to the order of ∿20 kcal/mole. It follows then that certain polymorphic transformations can be greatly retarded simply by abstracting water from the drug environment.

An alternative means of minimizing polymorphic transformations involves the doping of a drug sample with a structurally related compound. The ease of fit of these "aberrant" molecules to growing sites on nuclei explains their effectiveness as retarding agents. For example, chloramphenicol stearate has been used to stabilize chloramphenicol palmitate,[28] sodium cholate for cholesterol,[29] and cortisone alcohol for cortisone acetate.[30] A less elegant, but just as effective way of retarding transformation is to use polymeric additives which preferentially adsorb at the growing crystal surface of the stable form. Some agents such as sodium carboxymethylcellulose, pectin, acacia and gelatin were found to retard the overall transformation of the β-form of chlortetracycline hydrochloride crystals[31] and polyvinylpyrrolidone was found to inhibit crystallization of the amorphous form of nabilone.[32] In the latter case, hydrogen bonding of the drug with the polymer was postulated to prevent intermolecular hydrogen bonding necessary for crystallization.

2. Rearrangement

$$A_{(s)} \rightarrow B_{(s)} \qquad \text{(Eq. 8)}$$

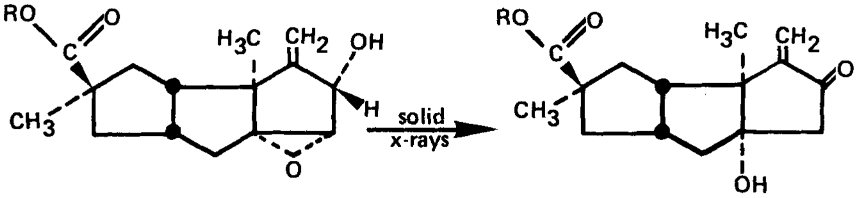
Rearrangement reactions in the solid state are usually catalyzed by heat or light. Isomers are compounds which have the same chemical structure but melt at different temperatures. They are, therefore, sometimes confused with polymorphs, but the melted state of isomers is different, and this distinguishes them from polymorphs. However, the same principles apply -- those isomers which are crystalline and exhibit a high melting point are nearly always more chemically stable than their corresponding racemate mixture. The isomerization reactions of such pharmaceuticals as vitamin D_2 and ℓ-hyoscyamine[33,34] and the epimerization of β-lactam antibiotics fall into this category.

The solid state rearrangement of the p-bromophenacyl ester of the epoxy alcohol, hirsutic acid to the corresponding isohirsutic acid as shown in Scheme IV (R = p-bromophenacyl) has been reported[35] to occur upon induction by X-rays through migration of two hydrogen atoms. This solid phase transformation occurred without disruption of the crystal packing and with only a slight change in the position parameters of the two oxygen functions. A chain reaction involving a chemically active propagating species was proposed as the mechanism of reaction. Other rearrangements were extensively discussed by Byrn.[2]

3. Sublimation

$$A_{(s)} \rightarrow A_{(g)} \qquad \text{(Eq. 9)}$$

If a substance loses weight before it melts, this process



SCHEME IV

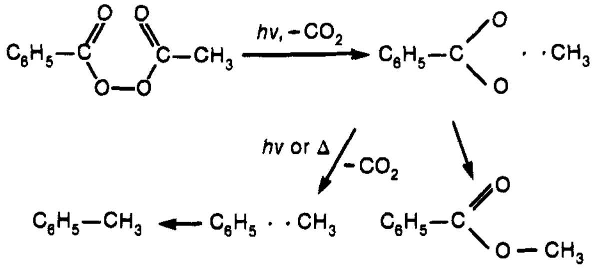
is known as sublimation. If it continues to lose weight from the melted state, then vaporization is occurring. Examples of solids which sublime include camphor, naphthalene, ethyl carbamate and anthraquinone. If the solid vaporizes and the gas phase decomposes, then the rate of reaction would be essentially zero order because the vapor pressure is constant at constant temperature.

When solid state decompositions are studied at high temperatures under vacuum, the solid will frequently sublime and deposit on cooler parts of the apparatus if its temperature is not well controlled. Any decomposition which might occur in the gas phase could easily lead to misinterpretation of results. For instance, the content of salicylic acid formed upon the decomposition of aspirin may not provide a reliable basis for judging stability of aspirin tablets.[36] The loss of salicylic acid upon sublimation is appreciable under accelerated stability testing conditions, and, if left unrecognized, the measure of degradation product could yield an assay with a high bias.

4. "Type I" Reactions

$$AB_{(s)} \rightarrow B_{(g)} + C_{(s)} \qquad \text{(Eq. 10)}$$

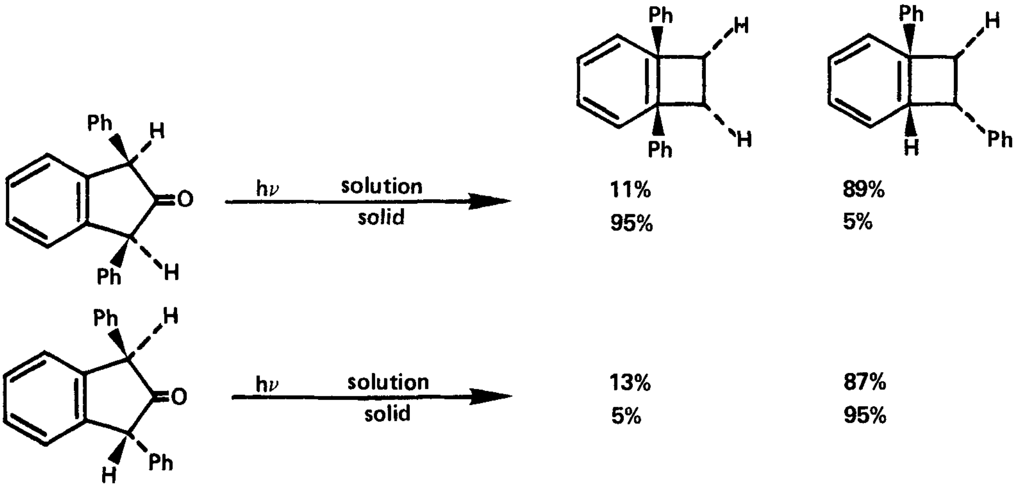
Reactions of this type include solid state decarboxylation, dehalogenation, dehydration and desolvation. The photolysis of crystalline acetyl benzoyl peroxide yields methyl benzoate, toluene and carbon dioxide (Scheme V), whereas thermolysis or photolysis of the melt leads to a host of aro-



Scheme V

matic products. Whereas deuteration studies ruled out intermolecular processes, X-ray and electron paramagnetic resonance (EPR) spectroscopy revealed that the methyl radical is capable of discriminating between the two oxygens of the benzoyloxy radical. The reasons for this discrimination were only partially found in the analysis of crystal packing, however. The search for an escape path for carbon dioxide was found to be more important.[37] Similarly, Cohen and Green[38] also remark that the reaction products observed during the photodecarbonylation of cis- and trans-1,3,-diphenyl-substituted 2-indanones[39] show a striking change in stereoselectivity between the solid isomers, but no difference in their solution behavior (Scheme VI). The crystalline phase appears to be a suitable medium for photoelimination as it allows entry of light and escape of gaseous products.

Dehydration or desolvation has been shown to follow either zero-order kinetics, such as griseofulvin chloroformate[40] and ampicillin trihydrate,[41] or first-order kinetics as with theophylline monohydrate.[42] For hydrated ampicillin, the dependence of the reaction rate on the shape of the particles



SCHEME VI

has been demonstrated.[41] Pure crystalline needles of ampicillin trihydrate obey an apparent zero-order rate as in Fig. 4, while spherical, commercial samples containing small amounts of excipients dehydrate at a different rate, as shown in Fig. 5. According to the "contracting sphere model," discussed in detail in the section on Kinetic Features, the difference in dehydration rates was consistent with the geometric shape of the crystals. Even more different were the dehydration profiles of glucuronamide hydrates[43] shown in Fig. 6. These were observed to be asymptotic, consistent with a diffusion-controlled reaction in which anhydrous material accumulates at the surface to impede the release of water vapor.

5. "Type II" Reactions

$$AB_{(s)} \rightarrow B_{(\ell)} + C_{(g)} \qquad \text{(Eq. 11)}$$

In Type II reactions the liquid (molten) decomposition

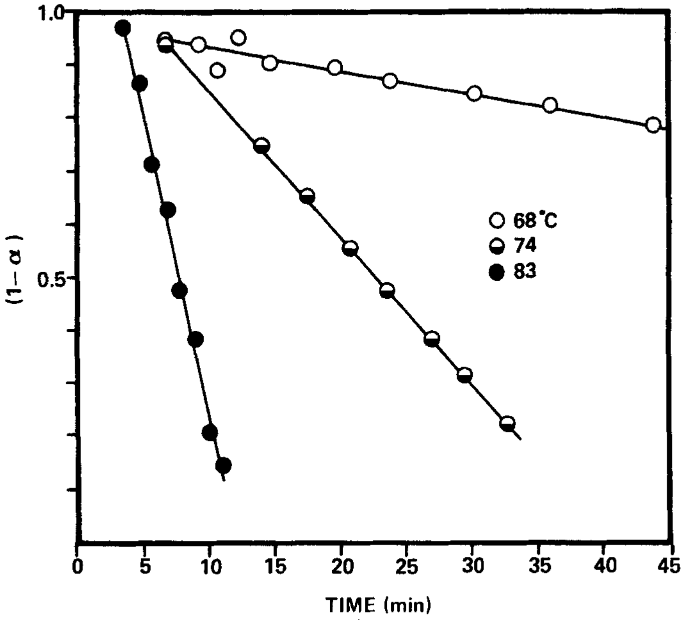


FIGURE 4

Fraction of crystalline ampicillin trihydrate remaining in heated sample as a function of time. Reprinted from Ref. 41, p. 793, by courtesy of the author and Journal of Pharmaceutical Sciences.

product dissolves part of the solid while the decomposition proceeds as two parallel reactions: (a) normal solid state decomposition, and (b) decomposition of a saturated solution of compound in its decomposition product (the amount of which changes with time). When the liquid layer is present on the surface of the solid, molecules at energetic sites dissolve first. No longer can the decomposition be expected to occur as a function of nucleation. Rather, the solid decomposition process is more likely to be surface-controlled, and hence resembles a first-order process. The thermal decomposition of substituted benzoic acids,[44] substituted salicylic acids,[45]

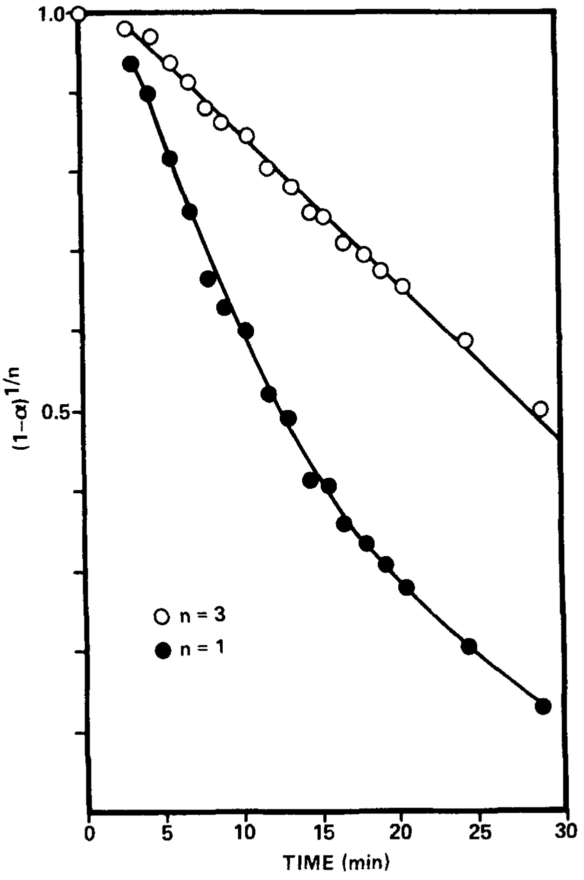


FIGURE 5

Fraction of ampicillin trihydrate present in the capsule formulation (1-α) at various times at 74.5° (plotted in two ways). Reprinted from Ref. 41, p. 793, by courtesy of the author and Journal of Pharmaceutical Sciences.

cupferron tosylates,[46] and vitamin A derivatives[47] also fall into this category.

6. Miscellaneous Solid Decompositions

$$AB_{(s)} \rightarrow A_{(s)} + B_{(s)} \qquad \text{(Eq. 12)}$$

$$AB_{(s)} \rightarrow A_{(g)} + B_{(g)} \qquad \text{(Eq. 13)}$$

These two reaction types are not observed as frequently as

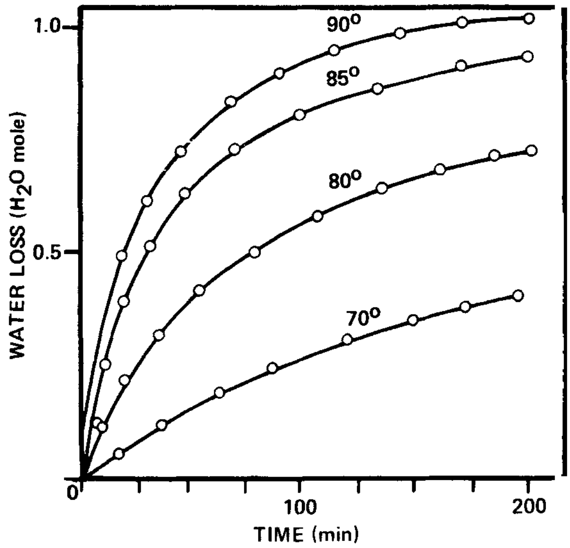


FIGURE 6

Dehydration curves of glucuronamide hydrate. Reprinted from Ref. 43, p. 320, by courtesy of the author and Yakugaku Zasshi.

those discussed previously. An example of reaction (Eq. 12), however is given by

$$AgI \rightarrow Ag + \tfrac{1}{2}I_2 \qquad \text{(Eq. 14)}$$

and an example of reaction (Eq. 13) is provided by the decomposition of another salt:

$$NH_4NO_2 \rightarrow N_2 + 2H_2O. \qquad \text{(Eq. 15)}$$

EXPERIMENTAL METHODS

The solid state kineticist is fortunate to have a variety of analytical methods at his disposal, many of which are unique to his discipline. The more familiar of these include thermal analysis, X-ray diffraction, microscopic examination, and infrared spectrophotometry. Conventional methods of separation and analysis common to solution kinetics, such as thin-layer and high performance liquid chromatography, require sample work-up; nevertheless they remain valuable because of their general applicability to most drugs. Depending upon the nature of the reaction, less familiar techniques such as dilatometry, gas pressure-volume measurements, conductivity, or magnetic susceptibility determinations might also provide a means of following the rate of degradation. More elegant techniques such as reflectance spectroscopy provide a rapid, specific assay for the drug in the presence of its formulation excipients.

The nature of the drug and of the reaction it undergoes upon degradation, however, dictates the methods of analysis available for studying a reaction system. If the drug is stable upon solubilization in an extraction solvent, conventional separation methods can prove successful in studying the kinetics of a reaction system. Quantitation using such techniques, however, naturally relies upon the efficiency and selectivity of the extraction procedure in releasing drug from its intimate contact with both excipients and degradation products, the latter often having similar solubility profiles. Assay of the drug once it is selectively solubilized is rarely precision-limiting since it can usually be accomplished by sensitive techniques such as UV, GC, HPLC, or quantitative TLC. Although some method of separation analysis can usually be employed to monitor drug retention, such analyses are often time-consuming and require relatively large sample sizes.

Ideally, an assay should provide a sensitive, nondestructive measure of drug in the presence of its formulation excipients and degradation products. Reflectance spectroscopy and various X-ray techniques can provide these advantages if the formulated drug is conducive to such measurement. These assays allow the rapid, quantitative analysis of many small samples (or repetitive analysis of a single sample) during a kinetic run. This is particularly important for studying a solid reaction system, since its intrinsic heterogeneity requires careful statistical interpretation of multiple analyses for assimilating accurate kinetic data. In solid state stability studies, it is in fact often difficult to discriminate between normal assay variation and incipient degradation. This further emphasizes the need for a sensitive, highly selective assay for intact drug. The accuracy with which one can measure initial degradation, i.e., less than 5%, can be increased, however, by characterizing and quantitating degradation products, as well as by monitoring loss of activity.

Vital to the success of a solid state kinetic study is the establishment of well-defined reaction parameters of the stability testing conditions, carefully chosen sampling intervals, and reproducible analytical methods. Solid systems are complex enough without introducing any unnecessary experimental variables. A case in point: separate reports from the same laboratory have been known to indicate contradictory kinetic behavior between two different samples of the same compound, analyzed by a common technique.[41,42] Such discrepancies might result from differences in sample particle size, particle shape, atmosphere, thermal lag in reaching equilibrium, analytical parameters, or sampling sequence. This and the many more uncited examples of contrasting data serve to emphasize the care which must be taken in studying a solid state reaction.

DIRECT SPECTROSCOPIC ASSAY METHODS

1. Diffuse Reflectance Spectroscopy (DRS)

Reflectance measurements are generally made by connecting a suitable attachment, comprised primarily of reflecting mirrors and an integrating sphere, to a standard UV spectrophotometer. Monochromatic light is directed onto a finely powdered sample, and the reflected radiation is collected by the integrating sphere and detected in the usual manner. Sample work-up is minimal, requiring only that the reference contain the same excipient material as the sample. It is often necessary to dilute the sample and the reference material with a common diluent if the drug is too concentrated to record an on-scale reflectance spectrum. In this manner the technique closely resembles that of UV spectrophotometry. Plotting reflectance *vs* wavelength then yields a spectrum similar to that of UV transmittance spectra.

Since DRS essentially measures the UV of drug molecules on the surface of an excipient, it is possible to qualitatively identify types of interactions from the magnitude of spectral shifts. Guidelines for characterizing these interactions are based on their associated bond strengths: van der Waals, 0.5 kcal/mole; hydrogen bond, 5-10 kcal/mole, and covalent bond, >40 kcal/mole. Thus physical adsorption involving van der Waals forces should result in spectral shifts of only 1-2 nm; those involving hydrogen bonding should display spectral shifts of 5-10 nm; and chemisorption of the donor-acceptor type can exhibit spectral shifts (mainly bathochromic) of 10 nm or more, and may be accompanied by a color change. Interactions of a wide variety of active medicinal agents with metallic and non-metallic excipients have been studied by Lach and coworkers.[48,49] Most of the spectral shifts they observed were attributed primarily to donor-acceptor chemisorption and, to a lesser extent, to physical adsorption.

DRS can be useful as a tool for choosing compatible excipients for drug formulation. Figures 7 and 8 show the reflectance spectra of phenylbutazone adsorbed on lactose and on magnesium carbonate.[50] The drug-lactose sample exhibits a peak at 240 nm which does not shift upon heating, indicating the presence of physical adsorption only. The drug-magnesium carbonate sample, however, shows a large peak shift from 225 nm to 267 nm upon heating, which has been attributed to the selective chemisorption of drug via an acid-base reaction on the adsorbing excipient surface. Stability data show that the drug remains stable in the presence of lactose but degrades when mixed with magnesium carbonate, supporting the conclusion that the strength of drug-excipient interaction is proportional to the destabilizing effect exerted by the excipient.

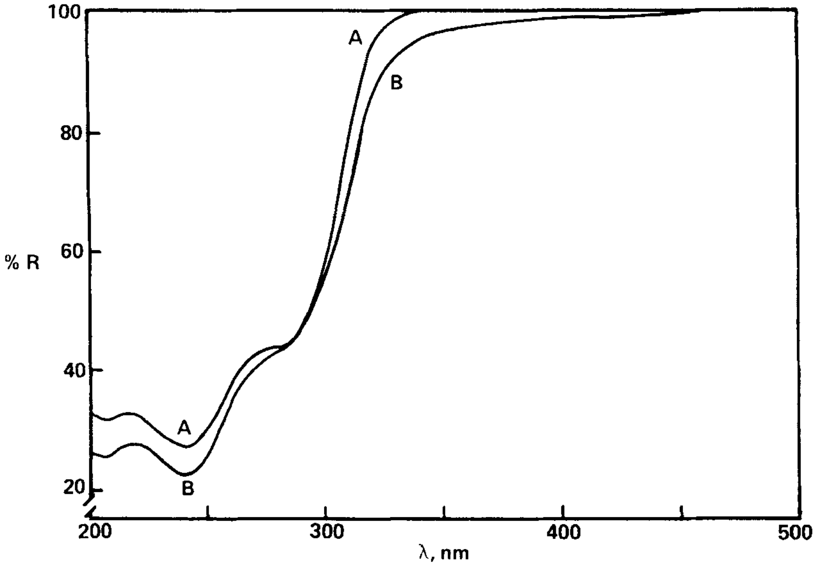


FIGURE 7

Reflectance spectra of phenylbutazone - lactose sample before and after heating. A, initial spectrum; B, after 214 hrs. at 70°C. Reprinted from Ref. 50, p. 31, by courtesy of the author.

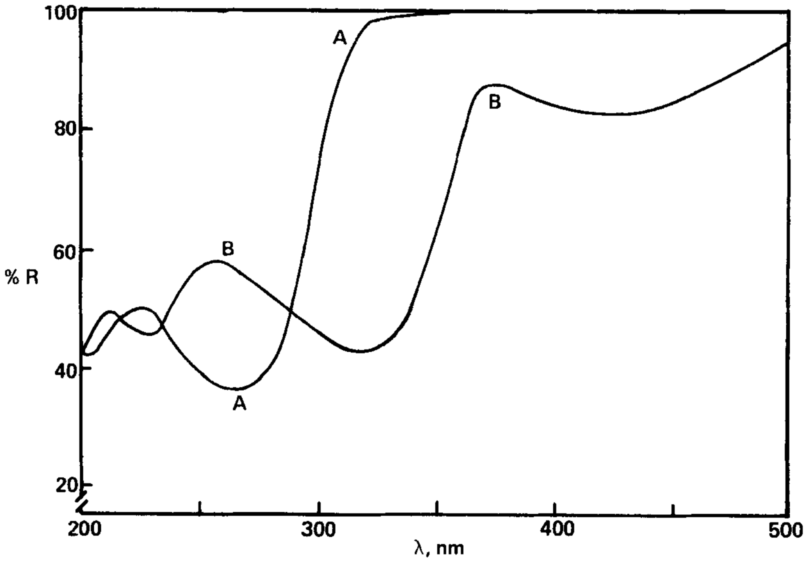


FIGURE 8

Reflectance spectra of phenylbutazone - magnesium carbonate sample before and after heating. A, initial spectrum; B, after 143 hrs. at 70°C. Reprinted from Ref. 50, p. 32, by courtesy of the author.

In addition to its qualitative utility, DRS can also serve as a reliable quantitative tool. Just as the measure of reflectance compares to transmittance in conventional UV spectroscopy, so also does log reflectance compare to absorbance, which is proportional to concentration. The apparent rate of the fading of dye on a tablet surface has been evaluated using reflectance spectroscopy.[51] Based on the log "absorbance"-time plot shown in Fig. 9, it was concluded that the fading followed successive first-order kinetics. The highest rate of degradation, observed during the initial stage of irradiation, was considered to indicate most accurately the rate of photodegradation on the tablet surface.

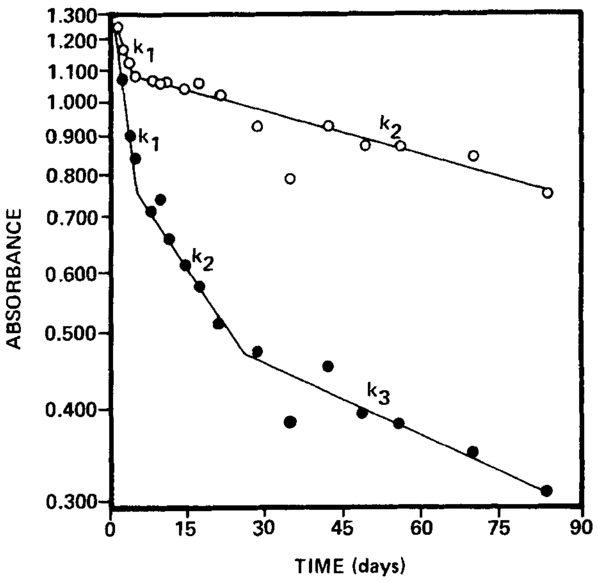


FIGURE 9

Influence of light intensity in the fading of the surface of tablets colored with D & C Blue No. 1 lake. O, ordinary light; ●, accelerated light. Reprinted from Ref. 51, p. 143, by courtesy of the author and Journal of Pharmaceutical Sciences.

Application of the Kubelka-Munk equation to reflectance data provides an alternative approach to the quantitative interpretation of reflectance behavior. The equation is given as

$$\Theta_t = \frac{(1-r_\infty)^2}{2r_\infty} \text{ or } f(r_\infty) = \frac{2.303\ \varepsilon c}{s} \qquad \text{(Eq. 16)}$$

where Θ_t is the Kubelka-Munk function, (i.e., ratio of absorbed light to scattered light at a given wavelength), r_∞ is the ratio between the absolute reflectance of the sample to that of the standard, $f(r_\infty)$ is the remission function, ε is the molar absorptivity, c is the molar concentration and s is the scattering coefficient.[52] If it is assumed that s remains constant (which is observed when the wavelength of incident radiation is smaller than the average dimension of particles), it becomes evident from Equation 16 that the remission function correlates linearly with concentration. Using this relationship, Pope[53] was able to follow the consecutive zero-order kinetics of acetaminophen degradation induced by excipients. The change observed in the DRS spectra of blends of acetaminophen with time is shown in Fig. 10. The technique was also proven valuable for analysis of whole acetaminophen tablets.

The Kubelka-Munk relationship can also be applied to the study of dye fading as a function of light intensity and time. Since fading is proportional to the product of

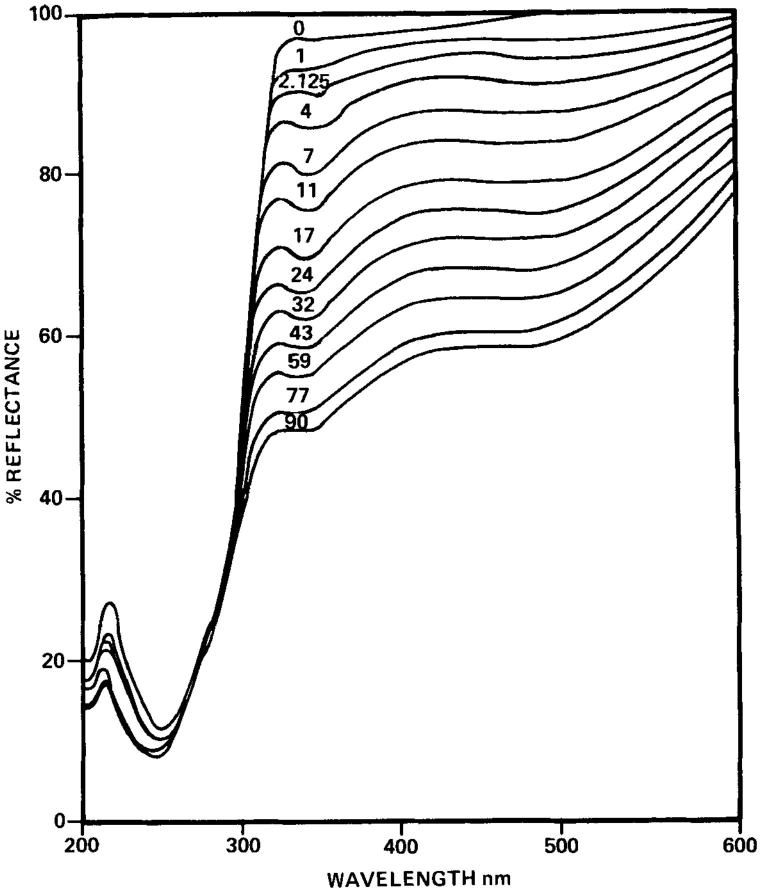


FIGURE 10

Diffuse reflectance spectral profile of acetaminophen-silicic acid equilibrated mix (8.18 mg per gm mix) heated at 100°C packed in reflectance cells. Numbers shown are time in days. Reference was similarly treated silicic acid. Reprinted from Ref. 53, p. 79, by courtesy of the author.

time, t, and intensity of light, I, one can plot the "fading function" ln Θ_t vs the product of time and intensity as illustrated by the example given in Fig. 11.[54] The independence of slope with respect to concentration indicates that the fading of the dye at the surface of the tablet is first

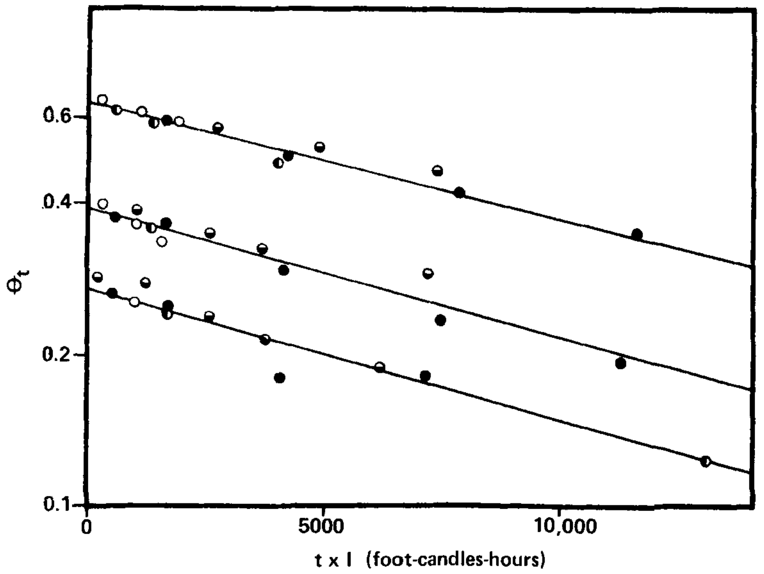


FIGURE 11

Plots of θ_t <u>vs</u> the product of time and intensity. ○, 11 foot-candles; ◓, 50 foot-candles; ●, 80 foot-candles; ◐, 655 foot-candles. Top line, 0.06% dye; middle line, 0.03% dye; bottom line, 0.015% dye. Reprinted from Ref. 54, p. 282, by courtesy of the author and Journal of Pharmaceutical Sciences.

order. The general first-order equation for the linear plots in Fig. 11 is

$$\ln \Theta_t = -kIt + \ln \Theta_{t_o} . \qquad \text{(Eq. 17)}$$

By determining the times at which objectionable fading takes place under high intensity, it is possible to calculate the time necessary for objectionable fading to occur under normal storage conditions.

2. Infrared Spectrophotometry (IR)

Infrared spectroscopy is another useful method for quantifying the rate of solid state reactions or transformations.

The solid cannot be prepared for analysis as a solution or KBr pellet since these preparations are likely to destroy, or at least modify, crystalline form. Measuring either the absorbance of a sample mulled in Nujol or the attenuated total reflectance (ATR) of a finely powdered sample, however, can yield acceptable quantitative data. The accuracy of such measurements requires that the sample have absorption bands that exhibit a constant absorbance ratio for a particular crystal form. This ratio must vary quantitatively with the concentration of the crystal form being studied. Reliability of the technique is greatly enhanced if an absorption band common to the original crystal and its polymorphs and/or degradation products can be identified, since this band can serve as an internal standard.

Examples in which this technique has been used successfully include examination of the interconversion of sulfamethoxydiazine crystal forms[25] and the pyrolytic breakdown of aspirin anhydride.[16] Figure 12 illustrates the use of three pertinent wavelengths in the spectral carbonyl region for the assay of aspirin anhydride in which the isosbestic point at 1,755 cm^{-1} serves as an internal standard.

3. X-Ray Techniques

Crystalline materials in powder form exhibit highly characteristic X-ray diffraction patterns in which the positions and relative intensities of peaks are well-defined and reproducible. From the 2θ values of these peaks, the spacing

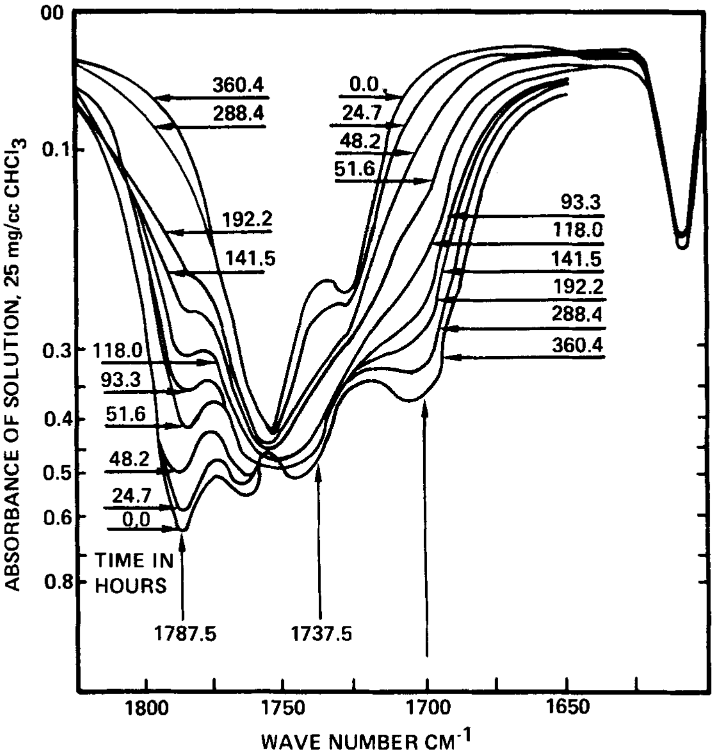


FIGURE 12

The carbonyl region infrared spectra of aspirin anhydride (lot I) degraded at 60° in "soft" glass vials. Reprinted from Ref. 16 , p. 685, by courtesy of the author and Journal of the American Pharmaceutical Association, Scientific Edition.

values (d distance) for the different planes of the crystal can be calculated using the Bragg equation, $n \lambda = 2 d \sin \Theta$, at any given wavelength of the X-ray source. The diffraction pattern of a crystalline powder is characteristic for the crystal lattices of that particular polymorph. By measuring the rate of disappearance (or appearance) of a peak unique to the reactant (or product), the kinetics of a reaction or transformation can be determined. This method has been used to follow the desolvation reaction of several crystalline hydrates.[41] Samples are placed into a heated sample holder and changes in their diffraction patterns are monitored at specified angles (2θ) as a function of time to measure the rates of hydrate disappearance and anhydrate appearance. A typical reaction profile is shown in Fig. 13.

A word of caution is necessary about the influence of crystal habit and particle size on the nature of diffractograms. If crystal faces of a compound are oriented in differ-

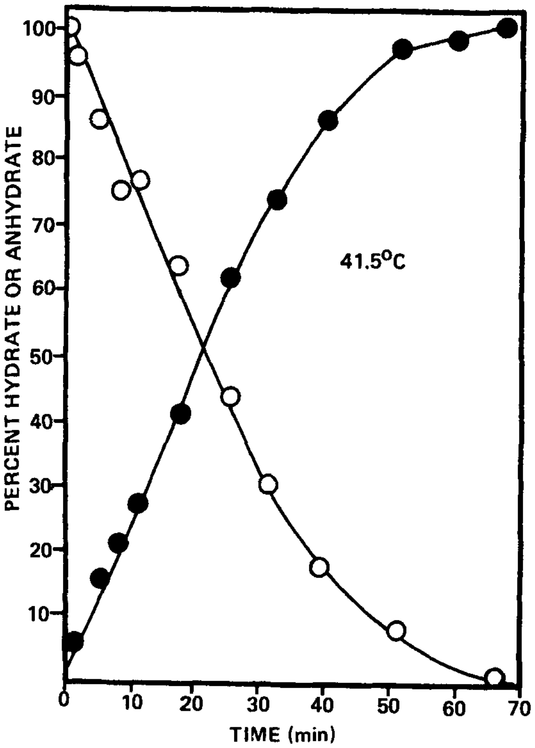


FIGURE 13

Fraction (in percent) of monohydrate (O) and anhydrous (●) forms in theophylline powder as a function of time. Reprinted from Ref. 41, p. 793, by courtesy of the author and Journal of Pharmaceutical Sciences.

ent ways such that the X-ray beam sees a different atomic array, then major intensity variations can be observed, even though on close examination the basic pattern is unchanged. Clearly then, sample preparation is a procedure which requires standardization for X-ray diffraction studies. One must also be careful that grinding does not reduce the crystallinity of the sample.

Since crystals serve as unique micro-reaction vessels, X-ray crystallography can often be used to determine the exact position of atoms as they re-orient themselves during a reaction. This can provide valuable information for the physical pharmacist as he attempts to chart, and ultimately to predict, the path followed by all atoms throughout the course of a reaction.

Since diffraction peaks are additive for mixtures of compounds, care must be taken to ensure that samples are pure if their transformations are to be studied by this technique. But this additive property can be helpful, however, in studying chemical decomposition. Although poorly crystalline intermediates appearing in the reaction mixture can hinder the detection of other intermediate phases by inducing heavy scattering and line broadening,[55] as illustrated in Fig. 14, these effects, if carefully interpreted, can be used to determine the direction of interface movement and the evolution of product nuclei. Because of the wealth of information offered by X-ray analysis, it can be expected to play an in-

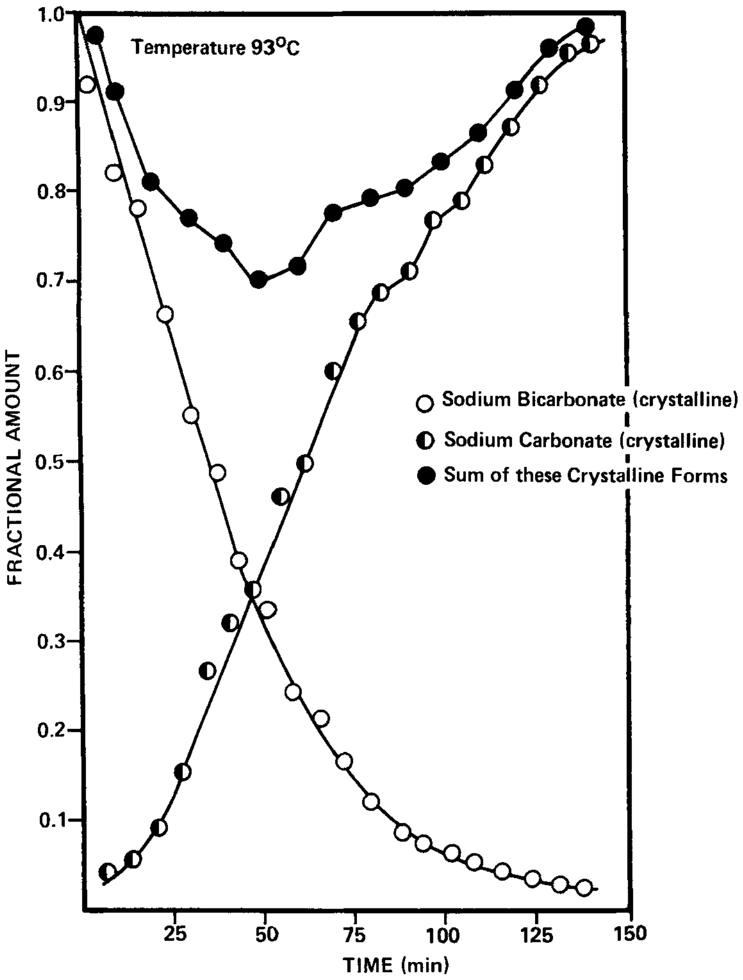


FIGURE 14

Decomposition of sodium bicarbonate at 93°C. Reprinted from Ref. 55, p. 33, by courtesy of the author and Drug Development Communications.

creasingly commanding role in solid state stability studies of the future.

THERMAL ANALYSIS

Thermal analysis measures the changes in a sample's physical or chemical properties as a function of temperature. Differential thermal analysis (DTA) records as a function of temperature the difference in temperature (ΔT) between the sample and an inert reference material. Differential scanning calorimetry (DSC) produces data similar to DTA, except that the area under the DSC curve is directly proportional to the total amount of energy (q) transferred in or out of the sample. The ordinate, therefore, is proportional to the rate of heat transfer (dq/dt) to the sample at any given time. The wide acceptance of DSC is based on its low sensitivity to sample geometry and rapid response to temperature alterations. Lastly, thermogravimetric analysis (TGA) measures the change in weight as a function of temperature, and differential thermogravimetric analysis (DTG) measures the change in weight as a function of temperature and is usually generated with an analog from the TGA signal.

Application of thermal analysis to solid state stability kinetics is valuable both qualitatively and quantitatively. DTA can be used to screen the compatibility of drugs with excipients: if the thermograms of drug-excipient mixtures show characteristic new peaks, it can be inferred that an interaction is occurring between the compounds and is likely to result in chemical incompatibility. When DTA was used to study mixtures of cephradine and of dicloxacillin with various excipients,[56,57] the relative stabilities predicted by the thermal data showed excellent correlation with actual stability results after 8-week storage at 50°.

DSC can be useful for determining the oxidative stability of drugs. The sample is first raised to an elevated temperature in an inert atmosphere. After equilibrium is reached, the atmosphere around the sample is rapidly changed from inert to oxidizing. The time between exposure to the oxidizing atmosphere and the onset of exothermic oxidation of the material relates directly to its oxidative stability.

1. Quantitation

Quantitative analysis of solid state stability can be achieved by examining thermal behavior under either dynamic or isothermal conditions. In dynamic analyses, in which the temperature is increased at a constant rate during sample analysis, the area under the DSC peak or the TGA weight loss is usually linearly related to the amount of solvate or hydrate remaining. Samples can be stored in constant temperature ovens, withdrawn at various intervals, and analyzed for loss of intact drug. Typical profiles resulting from such experiments are illustrated in Figs. 15 and 16. This method is, of course, only practical if the reactions are relatively slow such that no further decomposition occurs during actual sample analysis.

Alternatively, the stability of a sample can be studied under isothermal conditions. Changes in a sample's weight

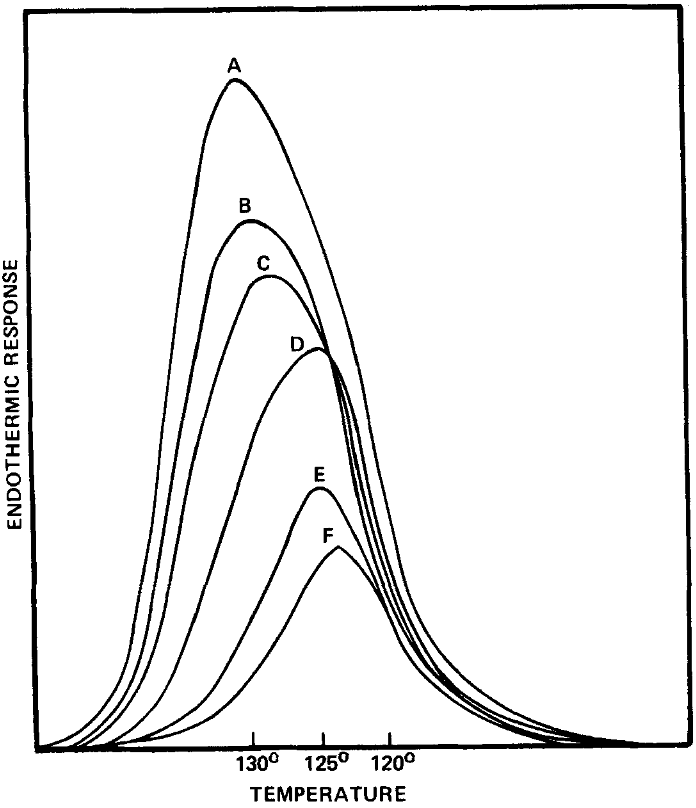


FIGURE 15

Plot illustrating the change in DSC desolvation endotherm with time for an experimental chloroformate at 70°C. A, 2 hrs; B, 8.4 hrs; C, 12 hrs; D, 21 hrs; E, 26 hrs; F, 36 hrs.

(TGA) or temperature (DSC) are monitored as a function of time as the sample remains at constant temperature within the furnace of the instrument. The sigmoidal profile obtained by TGA, an example of which is shown in Fig. 17, provides quantitative information about the amount of intact drug. Some data manipulation, however, is required to interpret the DSC scan given in Fig. 18. The areas under the isothermal thermogram must be integrated over several increments of time as measured from

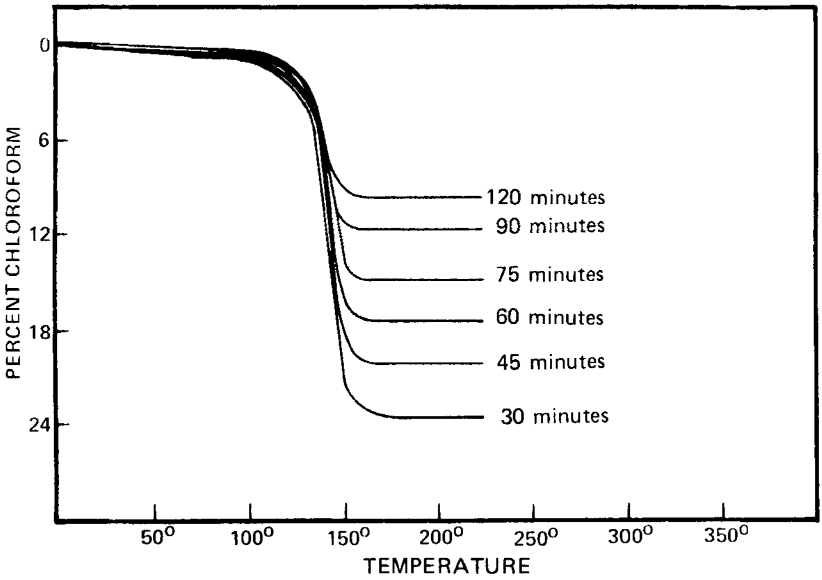


FIGURE 16

Plot illustrating the TGA isothermal weight loss with time for an experimental chloroformate at 100°C.

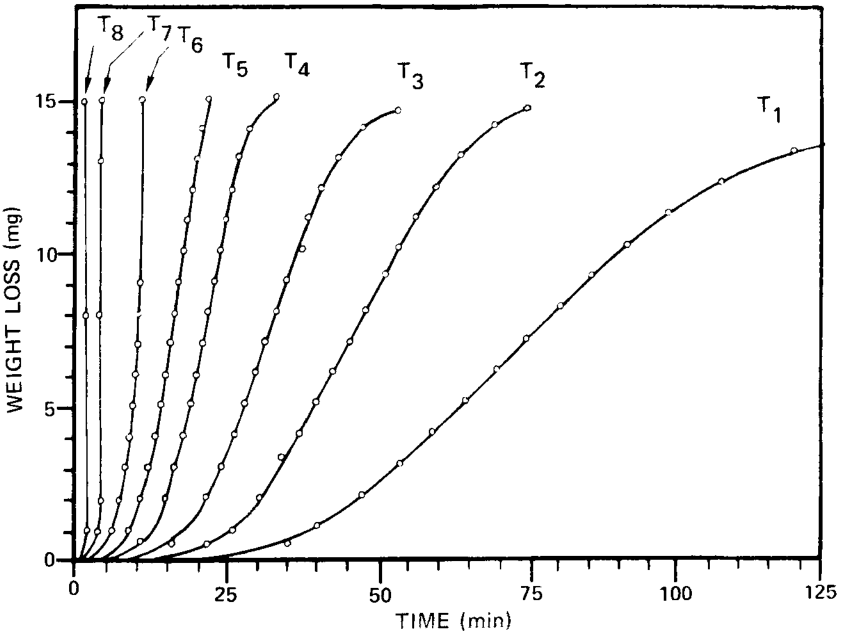


FIGURE 17

Typical isothermal weight loss curves at various temperatures in a flowing inert atmosphere.

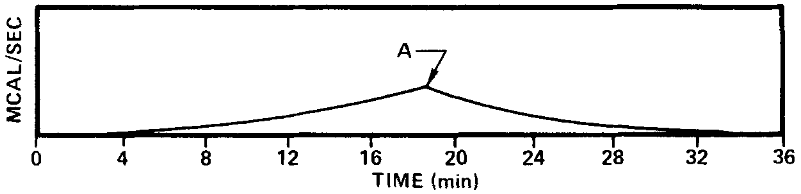


FIGURE 18

Isothermal thermogram of cupferron tosylate obtained at 114°C. Point A is point of maximum deflection. Reprinted from Ref. 46, p. 254, by courtesy of the author and Analytical Chemistry.

successive times "t" to the time of reaction completion. Dividing the area of each time increment by the total area under the curve yields the fraction of intact drug remaining at that time t. The decomposition kinetics are then examined by plotting the fraction of drug unreacted vs time, as shown in Fig. 19.

Many semi-empirical methods have been developed to estimate energies of activation (E_a) thermoanalytically. The derivation of these relations, however, requires that certain assumptions be made: (1) the order of reaction remains constant; (2) changes in the atmosphere have no effect on the reaction; and (3) the temperature remains constant throughout the sample, i.e., no thermal gradient exists throughout the sample (independent of sample size and heating rate). The assumptions, of course, do not always hold true. But if these empirical methods are used in the light of their potential shortcomings, they can often provide a rapid method for determining E_a without the volume of experimental data required by the isothermal approach. (If the volume change is negligi-

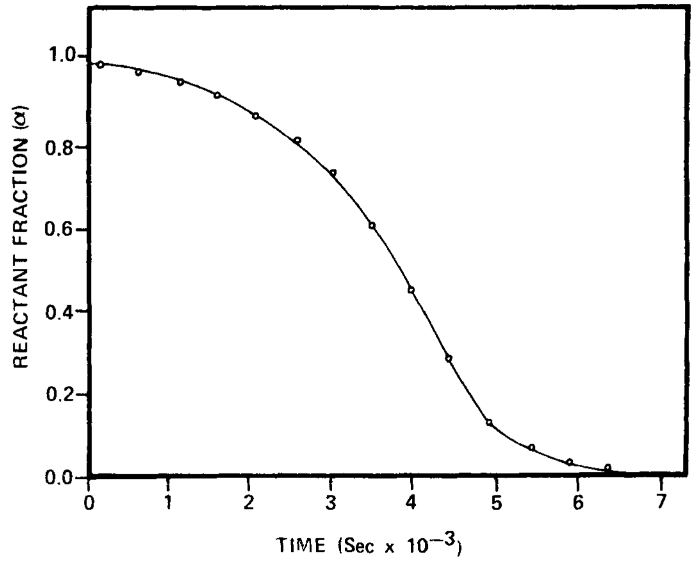


FIGURE 19

Decomposition history of cupferron tosylate at 103°C. Reprinted from Ref. 46, p. 254, by courtesy of the author and Analytical Chemistry.

ble, then heat of activation, ΔH_a, and energy of activation, E_a, can be considered equivalent.) For the first of these methods, Freeman and Carroll[58] have developed an Arrhenius relation for dynamic TGA in which $dw/dt = kW^n$, where W is the weight of reactant and n is the order of reaction. Combining this with the Arrhenius equation, they conclude that a plot of

$$\frac{\Delta(\frac{1}{T})}{\Delta \log W} \quad \text{vs} \quad \frac{\Delta \log (\frac{dw}{dt})}{\Delta \log W}$$

should yield a linear plot with a slope of $-E_a/2.303$ R and an intercept of n. Figure 20 illustrates the use of this relation.[59] This method was also recently applied to the deamina-

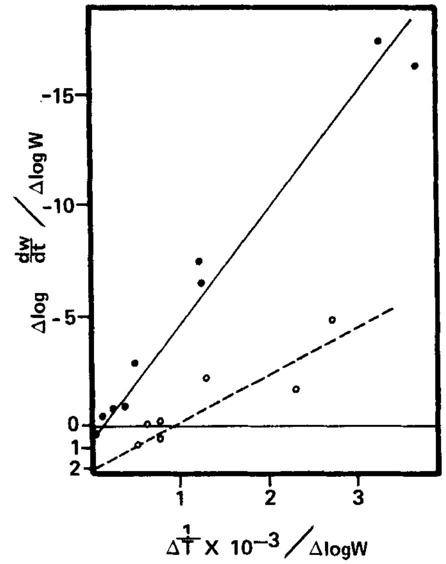


FIGURE 20

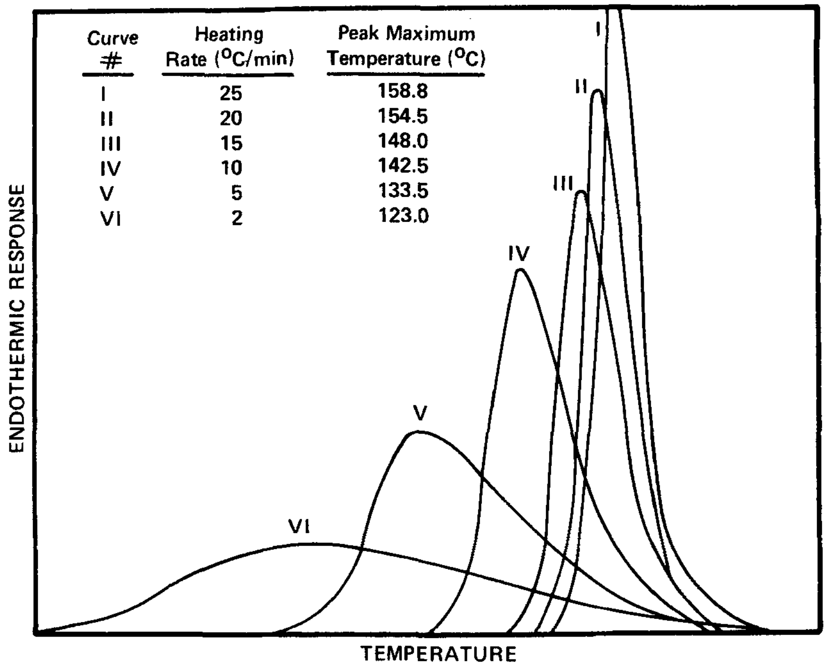
Kinetics of dehydration (heavy magnesium oxide in RH 40%). Reprinted from Ref. 59, p. 700, by courtesy of the author and Yakugaku Zasshi.

tion of the complex between theophylline and benzylamine in the solid state.[60]

A second treatment related to the shift in exo- or endotherm temperature as a function of heating rate was derived by Kissinger.[61] By assuming that the peak in the DTA deflection must occur at the moment of maximum rate of reaction, he developed an expression that relates the magnitude of this shift at various heating rates to the energy of activation required for the transformation to occur:

$$\frac{d\left(\frac{\ln \Phi}{T_m^2}\right)}{d\left(\frac{1}{T_m}\right)} = \frac{-E_a}{R} \qquad \text{(Eq. 18)}$$

where Φ is heating rate and T_m is the peak maximum temperature corrected for instrumental thermal lag. (It should be noted that for fast reactions the corrected peak temperature is unrealistic, since the center of the sample might not reach this temperature until the reaction is nearly complete.) A typical profile generated by this form of data treatment is shown in Fig. 21. Activation energy for the dehydration of tulobuterol hydrochloride hydrate was recently studied using this methodology.[62] This technique was also employed to characterize the thermal decomposition of alkali metal salicylates (lithium, sodium and potassium) and pharmaceutical dosage forms containing them.[63]



Curve #	Heating Rate (°C/min)	Peak Maximum Temperature (°C)
I	25	158.8
II	20	154.5
III	15	148.0
IV	10	142.5
V	5	133.5
VI	2	123.0

FIGURE 21

Effect of heating rate on the peak maximum temperature for the desolvation endotherm of an experimental chloroformate.

2. Atmospheric Effects

The kinetic behavior of a solid sample changes considerably if the surrounding atmosphere is altered. This is particularly true for a solid that loses weight reversibly during decomposition. For a given sample geometry, the atmospheric effect will depend upon whether the surrounding gas is static, flowing or dynamic. The most significant influence occurs, of course, when the atmosphere itself is involved in the reaction under investigation. For instance, a dehydration reaction can be affected markedly if studied under conditions of high humidity. Even ambient air contains sufficient water vapor to affect the rate of dehydration, e.g., at 25° a change from 40% to 80% R.H. signifies a large rise (10 mm Hg) in absolute humidity. As the sample is heated, water will continue to diffuse out of the particles only if the temperature remains high enough to vaporize the water in the presence of extant partial pressure. The dehydration rate therefore will be effectively zero, regardless of temperature, when the equilibrium vapor pressure of the sample falls equal to or below that of its surroundings.

Decarboxylation is similarly affected by the partial pressure of CO_2 in the sample atmosphere. The decomposition of $CaCO_3$ at various pressures of CO_2, as shown in Fig. 22, indicates that the rate of reaction is indeed decreased by an increased partial pressure of CO_2.[64]

Obviously, the partial pressure of gases such as O_2, N_2, CO_2 and H_2O must be considered when studying the degrada-

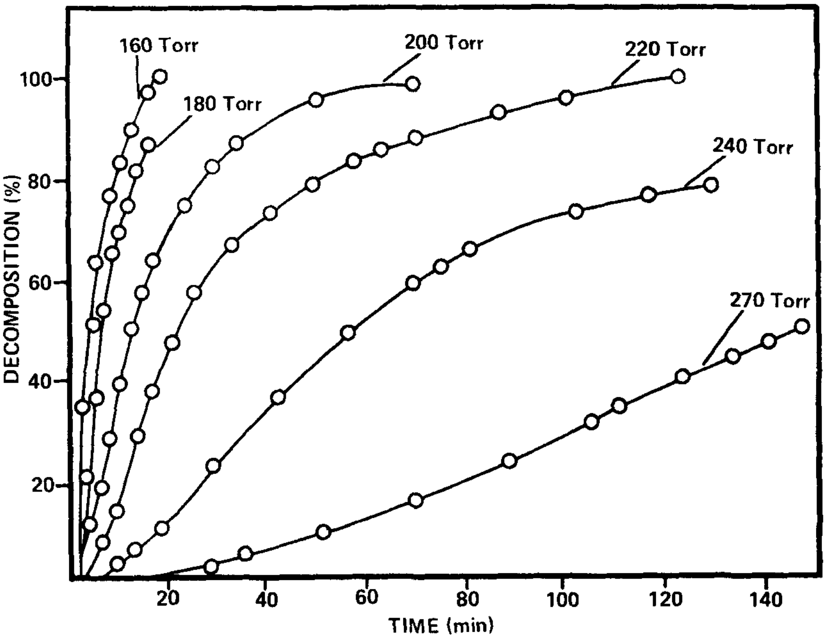


FIGURE 22

Decomposition of calcium carbonate at 850°C at various pressures of carbon dioxide. Reprinted from Ref. 64, p. 297, by courtesy of the author and Academic Press.

tion of drugs. The rate of desolvation of organic drug solvates, however, should remain independent of ambient air effect, since the partial pressure of the solvent common to the solvate is normally negligible. This is especially true if nitrogen is allowed to flow over the sample during analysis. If necessary, the effect of atmospheric gases on decomposition reactions can be essentially overcome by placing the sample under high vacuum.

The extent to which the atmosphere affects a sample is naturally controlled to a large degree by the exposed surface area of the sample. Likewise, the release of vapor from within a decomposing solid is also dependent upon surface area. Therefore.

sample thickness and particle size are major factors in determining a sample's thermal behavior. An examination of the rates of dehydroxylation of kaolinite prepared as discs of varying thicknesses reveals an interesting relationship.[65] When w/w_o, the fraction of weight loss, is plotted as a logarithmic function of time, as shown in Fig. 23, the resulting plots indicate initial first-order kinetics. These rates are extrapolated to determine the theoretical reaction rate of a disc of "zero thickness." Arrhenius plots of the resulting data, however, were linear only for the "infinitely thin" discs, indicating the strong dependence

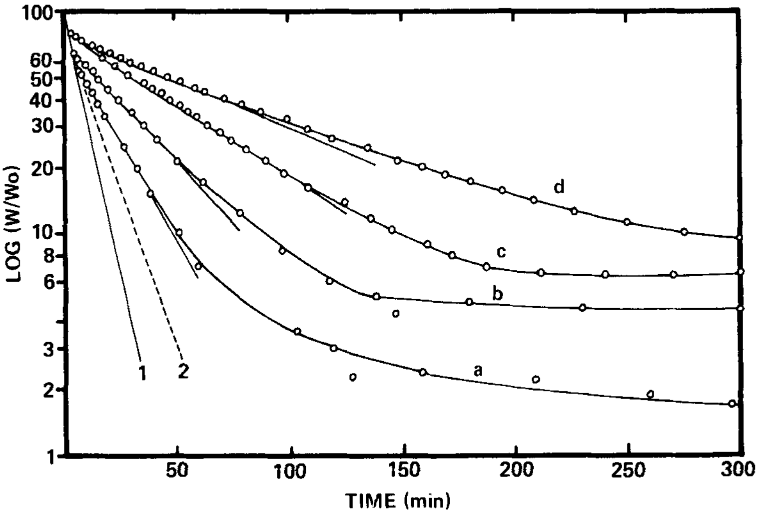


FIGURE 23

Variation of log (w/w_o) with time for kaolinite disks heated at 497°C; (w/w_o) is expressed as a percentage of total weight loss by dehydroxylation. Curves a, b, c, and d correspond to disks of thickness 0.38, 0.83, 1.55, and 2.68 mm, respectively. Curve 1 is the extrapolated curve for an infinitely thin disk and curve 2 corresponds to a very thin layer of uncompacted powder. Reprinted from Ref. 65, p. 347, by courtesy of the author and Journal of American Ceramic Society.

of the reaction rate on the distance over which the vapor must travel to diffuse out of the crystal. This emphasizes the consideration that must be given sample geometry in interpreting solid stability data.

If two or more gaseous products are produced, the use of thermal analysis for studying the mechanism of these reactions becomes quite complicated. In these cases, it is advantageous to combine conventional thermal analysis simultaneously with evolved (or effluent) gas analysis techniques, such as mass spectrometry or gas chromatography. Complementary methods for identifying the remaining solid, such as X-ray analysis, can also be performed. For example, a two-step decrease observed by TGA analysis of magnesium hydroxide was attributed upon X-ray diffraction to the initial liberation of a single absorbed water molecule of hydration, followed in the second step by liberation of a water molelcule related to the magnesium oxide crystal structure.[59] Laser Raman spectroscopy can also be used to observe changes in lattice structure as the solvent molecule escapes.[66]

Whether or not thermal methods should be used in conjunction with other simultaneous measurements depends largely on the physical chemistry of the reaction and the extent of information sought. In any event, the complete characterization of a material and its reaction behavior can only be performed by using several techniques, singly or in combination as each case dictates.

Recently, a significant advance in this arena has been achieved in that many of the previously mentioned drawbacks and assumptions have been overcome by Abou-Shaaban and Simonelli[67-71] by taking advantage of data obtained from simultaneous DTA, TGA and DTG. This technique records the weight as a function of temperature, the change in weight as a function of temperature, and also the temperature difference between the sample and an inert reference substance as a function of temperature at constant heating rate.

For the simple sublimation case -- see Equation 9, the rate of weight loss is

$$\frac{d\,(W^t_{obs})}{dt} = -\,k\,(W^t_{obs}) \qquad \text{(Eq. 19)}$$

where k is the specific rate constant, and W^t_{obs} is the weight of the remaining solid $A_{(s)}$ at any time t.

For <u>non-isothermal</u> runs, the heating rate dT/dt is considered by converting the time derivative of the weight of $A_{(s)}$ to a temperature derivative by dividing both sides of Equation 19 by dT/dt or "a":

$$\frac{-d\,(W^t_{obs})}{dT} = \frac{k}{a}\,(W^t_{obs}) \qquad \text{(Eq. 20)}$$

By incorporating the Arrhenius expression and taking logarithms, the following expression is obtained:

$$\log\left[\frac{\left[-d\,(W^t_{obs})\right]/dT}{(W^t_{obs})}\right] = \log\left[\frac{Z}{a}\right] - \frac{\Delta H}{2.303\ RT} \qquad \text{(Eq. 21)}$$

A plot of the left hand side of this equation versus $1/T^{o}K$ yields a linear function of slope equal to $-\Delta H/2.303\ RT$ and an intercept of $\log\,[Z/a]$. ΔH is the heat of activation, $d(W^{t}_{obs})/dT$ is the instantaneous first derivative of the weight observed with respect to temperature, "a" is the heating rate and Z is the pre-exponential factor in the Arrhenius equation.

For <u>isothermal</u> runs, the integral form of Equation 19 is

$$\int_{W^{o}_{obs}}^{W^{t}_{obs}} \frac{d(W^{t}_{obs})}{(W^{t}_{obs})} = -k \int_{0}^{t} dt \qquad \text{(Eq. 22)}$$

$$\therefore \quad \log\,(W^{t}_{obs}) = -kt/2.303 + \log\,(W^{o}_{obs}) \qquad \text{(Eq. 23)}$$

where W^{o}_{obs} is the initial weight of $A_{(s)}$. From Equation 23, a plot of $\log\,(W^{t}_{obs})$ versus time should produce a straight line with a slope of $-k/2.303$ for each of the temperatures studied.

This basic approach was extended to a number of fundamental types of solid state reactions which lose weight as a function of time and temperature, and the corresponding mathematical analyses can be found in references 67-71. The technique requires that a simultaneous thermogravimetric trace containing both the integral and first derivative weight loss as a function of temperature be available or calculable. A typical trace is shown in Fig. 24 for the phase transformation of theophylline monohydrate and its relative data analysis as shown in Fig. 25. Note that the weight of the reacting solid as a function of time is monitored at a single heating rate and that the furnace atmosphere

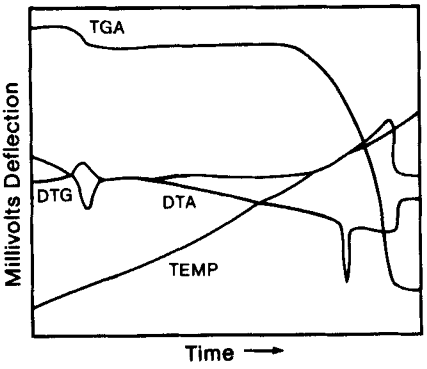


FIGURE 24

Simultaneous TG-DTG thermograms for theophylline monohydrate phase transformations, in nitrogen atmosphere obtained from 8.1 mg as stated in the experimental conditions. Reprinted from Ref. 69, p. 117, by courtesy of the author and Thermochimica Acta.

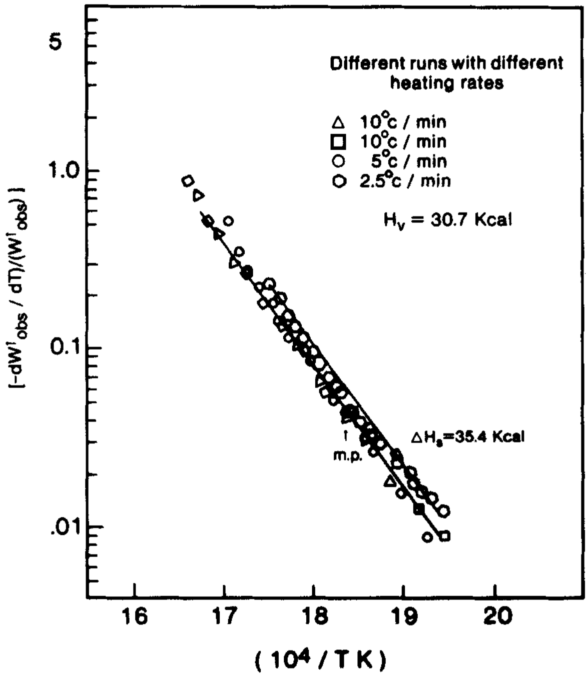


FIGURE 25

Non-isothermal plots for anhydrous theophylline phase transformations, obtained from different runs with the same sample size but with different heating rates. Reprinted from Ref. 69, p. 117, by courtesy of the author and Thermochimica Acta.

must be dynamic to remove the gaseous product. The value of ΔH so obtained is essentially independent of sample size and heating rate. The non-isothermal technique requires only a single experiment to obtain the kinetic parameters in sharp contrast to the more tedious, time-consuming isothermal approaches mentioned previously. This technique is also applicable for elucidating complex reactions which involve multiple steps and mechanism changes, each having its own heat of activation, e.g., multi-step desolvation, dehydration followed by sublimation, dehydration followed by decomposition, sublimation followed by vaporization, and transformation followed by degradation.

MICROSCOPY

Use of a hot stage is a very useful adjunct technique available to the physical pharmacist. Accurate melting points can be obtained under controlled heating rates and desolvation or dehydration can be observed (by the generation of visible bubbles) if the compound is mounted in silicone oil. Crystals in the dry state also turn opaque under dehydration and the movement of the boundary interface is often characteristic, e.g., the anisotropic behavior of caffeine monohydrate suggests water molecules preferentially exit along tunnels parallel to the long axis of the crystal.[72] Observations characteristic of each compound can be made as the substance melts or cools. These include refractive index of the melt, tendency to sublime, rate of growth of crystals as a function of temperature, form of crystal front and polymorphism. Degree of crystallinity can be estimated from extent of birefringence. A hot stage was used to detect the presence of liquid crystals of cromolyn sodium as a function of temperature and relative humidity.[73] Drug-excipient interactions can also be studied by simply mixing drug crystals and excipient together and cycling heating and cooling on a hot stage. Observation of melt-zone at the boundary interface can detect eutectics, addition compounds, solid solutions or other incompatibilities.

The most efficient way to determine which of two forms is stable at a given temperature is to observe the relative solubilities of the two in a solvent. This is best and most rapidly done by observing crystals of both together in a drop of saturated solution under the microscope. The less soluble form will grow, and the more soluble will dissolve. This is called a solution phase transformation, and it progresses more rapidly the higher the solubility and the greater the difference in solubility of the two forms. The transition temperature is then the temperature at which the solubilities are equal and at which the transformation rate in either direction is zero. Above the transition temperature, one form grows at the expense of the other, and below that temperature the reverse is true. By approaching the transition from both sides, the exact temperature can usually be determined to within a few tenths of a degree. This can often be done if equilibrium is established rapidly.

Solid state transitions can be qualitatively and reproducibly studied using the hot-stage microscope equipped with a video tape recorder. Quantitation of change in color, optical rotation or index of refraction is effectively obtained if a photocell in the eyepiece is connected to a recorder. Preferably, the instrumentation should integrate the photovoltmeter optics and temperature state to optimize light intensities. Use of circular polarized light will eliminate sample orientation effects. The polymorphism of aspirin has been studied using thermal optical techniques.[74]

When extra surface relief detail is required, scanning electron microscopy (SEM) is the technique of choice. Proper utility of SEM allows distinct identification of such morphological textures as grain boundaries, lattice defects, and screw and edge dislocations. (The compound is attached to a copper cylinder by application of PVC/acetone mixture; the system is evacuated and a thin coating of gold-palladium (60/40 alloy) is applied for about three minutes.) The major drawback to this technique is the use of a high vacuum for preparation of the specimens. Inclusion of solvents in the crystal lattice and tendency to sublime therefore cannot be observed, as in the normal hot stage method. Presence of craters and voids where solvent has escaped, however, is usually discernible.

DILATOMETRY

Most compounds, especially fats and oils, change in volume upon undergoing polymorphic transformations. In such cases, it is possible to carry out precise kinetic measurements using a dilatometer. The volume (height) of mercury displaced by the solid within a small bore (2 mm) tube is measured as a function of temperature or time. Using this technique, it was discovered that by adding minor amounts of chloramphenicol stearate to the palmitate derivative of the drug, the rate of polymorphic transformation of the palmitate could be markedly retarded.[28] Results of this study are shown in Fig. 26. It is postulated that the impurity interacted with the crystal lattice in such a way as to delay formation of nuclei of the new polymorph.

GAS PRESSURE-VOLUME DETERMINATION

When gaseous products are formed during a reaction, the rate of reaction can be followed at increasing time intervals by measuring the volume or pressure of the gas generated. Vacuum racks of various levels of sophistication have been designed for such

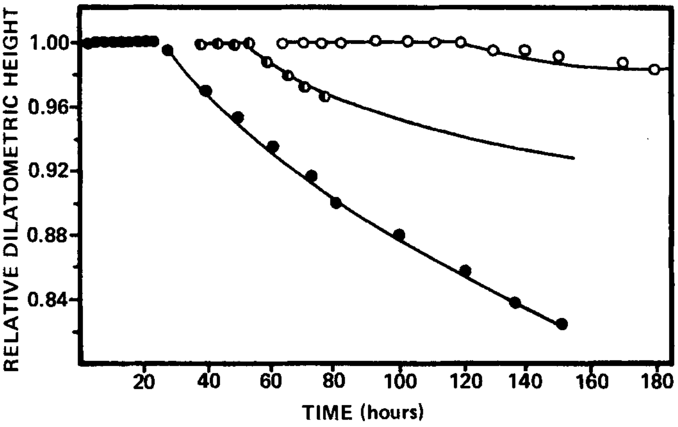


FIGURE 26

Plot showing the effect of adding 1, 2 and 3% chloramphenicol stearate on the transformation rate of Polymorph B to A of 99.9% chemically pure chloramphenicol palmitate. Key: ●, 1%; ◐, 2%, O, 3% chloramphenicol stearate added. Reprinted from Ref. 28, p. 965, by courtesy of the author and Journal of Pharmaceutical Sciences.

studies.[75,76] Because these studies are usually conducted under high vacuum, solid samples often sublime during the reaction. Care must therefore be taken to minimize sublimation by precisely controlling the temperature of the reaction vessel. In addition, the number of moles of gas evolved must be correlated with the loss in titer of solid remaining. Gas evolution-time curves are usually sigmoidal in shape, a phenomenon which will be discussed in the section on Kinetic Features.

MISCELLANEOUS TECHNIQUES

Methods other than those discussed above can trace the decomposition or transformation of a solid reactant in the presence of its reaction products. These methods, applicable only if the measured property of the reactant is sufficiently different from that of the product(s), include electrical conductivity,[77] magnetic anistropy, dielectric constant, electron spin resonance (ESR), electron paramagnetic resonance (EPR), and solid-state carbon-13 nuclear magnetic resonance (NMR) spectroscopy.

Solution calorimetry can be used as a quantitative measure of degree of crystallinity. This method is based on the observation that, for many solids, the energy of the amorphous form is significantly higher than the energy of the crystalline form. The heat of solution, or calorimetric, percent crystallinity, P_c, is defined by:

$$P_c = 100\,\frac{\Delta H_s^o - \Delta H_a^o}{\Delta H_c^o - \Delta H_a^o} \qquad \text{(Eq. 24)}$$

where ΔH^{o}_{s}, ΔH^{o}_{c}, and ΔH^{o}_{a} are the heats of solution to infinite dilution of the sample, the 100% crystalline standard, and the 100% amorphous standard, respectively. Pikal et. al.[78] have used solution calorimetry to predict the relative stability of a number of β-lactam antibiotics. Highly sensitive solid state calorimetric methodology is also under development which can measure thermal power output of solid state reactions at or near ambient temperatures. When such equipment becomes available, the need to dissolve the sample will be precluded thus leading to a more accurate representation of reaction rates, even though they may be as low as 5% per year.

Laser Raman spectroscopy is convenient and versatile for investigating pharmaceutical solids -- spectra of both lattice vibrations and intramolecular vibrations in the same arrangement can be obtained. The spectra of lattice vibrations provide valuable information on crystalline interactions and can be used to characterize crystalline modifications, the effect of various perturbations on crystal structures, and desolvation processes. The study of intramolecular vibrations is used to examine both the specific nature of the solute-solvent interaction and the chemical stability of various forms. Solvates of griseofulvin were studied using this methodology.[66]

If the drug is degraded by an excipient via acid or base catalysis, the rate of degradation can be followed by monitoring the change in pH of a suspension of the ingredients as a function of time.[6,18] For a drug subject to photodegradation, electron spin resonance (ESR) spectroscopy can provide a means of determining the nature and quantity of the free radicals that are likely to be produced during the decomposition. If the drug absorbs at a selective analytical wavelength, simple UV spectroscopy can be used to follow degradation. An analysis of photodegraded fumagillin, solubilized and measured at a wavelength of 351 nm, was proven to degrade with first-order kinetics by this technique.[79]

A simple but unique method has been described for studying the kinetics of reaction between hydrocarbons and picric acid in the solid state.[3] The reactants are first packed into a glass capillary, and then movement of the colored interface of product material between the reactants can be observed visually. In particular, the change in thickness (ξ) of the reaction zone generated by the reaction between naphthalene and picric acid could be correlated with diffusion-controlled kinetics as shown in Fig. 27. For reactions producing colorless products, radioactive tracers can be used to assess movement of the reaction zone.

For the many drugs whose direct assay is precluded by interference from excipients, etc., some type of separation analysis is necessary. As discussed previously, the advantage of the wide applicability of separation techniques is often nearly outweighed by the disadvantage of excessive sample manipulation and assaying time. Although chromatographic techniques (liquid, gas, thin-layer) have simplified the monitoring of decomposition products once a solid sample has been appropriately prepared, their effective use in quantitative analysis requires some sophistication. Such innovations as gradient

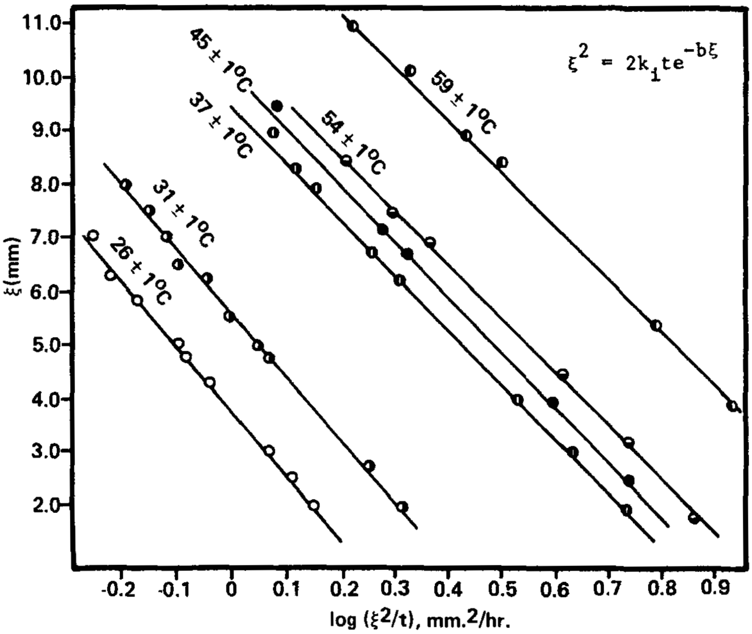


FIGURE 27

Kinetic treatment of the diffusion-controlled reaction between naphthalene and picric acid. Reprinted from Ref. 3, p. 2708, by courtesy of the author and Journal of Physical Chemistry.

elution, spectrodensitometry and electronic integration of peak areas help make chromatography one of the more versatile quantitative tools in the physical pharmacy laboratory. Depending on the reaction system and the detection methods to which the system responds, chromatographic techniques can be used to quantify degradation products to levels as low as 0.5%.

KINETIC FEATURES

KINETICS OF THE MOVING BOUNDARY

1. Topochemical Control

The geometry of the reacting particle(s) plays an important role in determining the rate of those solid reactions which originate at the surface and proceed as a moving, reacting interface. Given the simple case of a solid particle having a regular geometry and reacting with a surrounding gas, the surface reaction takes place at a rate dependent on surface area and propagates inwards as a moving boundary to the center of the crystal. Such "contracting geometry" reactions follow the general equation type:

$$1 - (1 - \alpha)^{\frac{1}{n}} = kt \qquad \text{(Eq. 25)}$$

where α is the fraction decomposed at time t, k is the decomposition rate constant, and n is an integer value which defines the particle geometry such that n = 1 for a flat surface, n = 2 for a cylinder, and n = 3 for either a cube or a sphere. This equation is derived on the assumption that the boundary moves with zero order kinetics.

For example, for a reacting sphere of radius r, there will be left unreacted at time t, a sphere of radius $r - k_o t$. Solving for the fraction decomposed,

$$\alpha = \frac{\frac{4}{3}\pi r^3 - \frac{4}{3}\pi (r - k_o t)^3}{\frac{4}{3}\pi r^3} \qquad \text{(Eq. 26)}$$

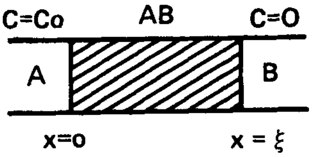
$$= 1 - \frac{(r - k_o t)^3}{r^3} \qquad \text{(Eq. 27)}$$

and therefore $(1 - \alpha)^{\frac{1}{3}} = 1 - \frac{k_o t}{r}$. (Eq. 28)

Just as the straightforward first-order relation, $1 - x = e^{-kt}$, approaches the expression, 1 - x = 1 - kt, for small values of kt, Equation 28 approaches a first-order relation when values of $k_o t/r$ are small. Carstensen postulated that this may account for the approximate first-order behavior exhibited by many solid state decompositions.[80] Topochemical control is generally reported, however, when n = 3, e.g., the sublimation of ammonium perchlorate[81] and nitronium perchlorate,[82] the reaction between succinic anhydride and p-nitraniline[83] and the dehydration of sodium bicarbonate.[55] The dehydration of a capsule formulation of equiaxial ampicillin trihydrate particles shown in Fig. 5, has also been reported to obey the diminishing sphere model, whereas needle-like crystals of pure ampicillin trihydrate have generally exhibited the zero-order decomposition illustrated in Fig. 4.

2. Diffusion Control

a. Solid-Solid Reactions. For the solid reaction between A and B to form AB, where reactants remain in direct contact, the reaction is considered to proceed along the direction of the x coordinate. If A is more mobile than B, the product moves toward B while the interface A/AB corresponds to x = 0. At any time t, the thickness of the product zone is ξ as illustrated in Scheme VII. Rastogi[23] provided a semi-theoretical justification by assuming that the reaction at the interface is instantaneous, so that the concentration of molecules A at the AB/B interface is always zero. Accordingly, the concentration of A at the A/AB interface always remains



SCHEME VII

equal to the initial concentration C_o. If m, the amount of A diffusing at any time t through the product layer, is proportional to ξ, then

$$\frac{dm}{dt} = \beta \frac{d\xi}{dt} = - SD \frac{\partial C}{\partial x} \qquad \text{(Eq. 29)}$$

where β is a proportionality constant, S is the area of cross-section through which A is diffusing, and D is the diffusion coefficient. For the particular case considered above in which the concentration gradient is linear, ∂C/∂x is just equal to C_o/ξ, so that

$$\frac{d\xi}{dt} = - \frac{SD}{\beta} \frac{C_o}{\xi}. \qquad \text{(Eq. 30)}$$

Upon integration by separation of variables, assuming that β is independent of ξ and using the boundary condition ξ = 0 at t = 0,

$$\xi^2 = 2kt \qquad \text{(Eq. 31)}$$

where k is the rate constant of diffusion, and $k = SDC_o/\beta$. Since $D = D_o e^{-E_a/RT}$, where D_o is a constant and E_a is the energy of activation, we have

$$2k = \frac{SD_o/C_o \exp(-\frac{E_a}{RT})}{\beta}. \qquad \text{(Eq. 32)}$$

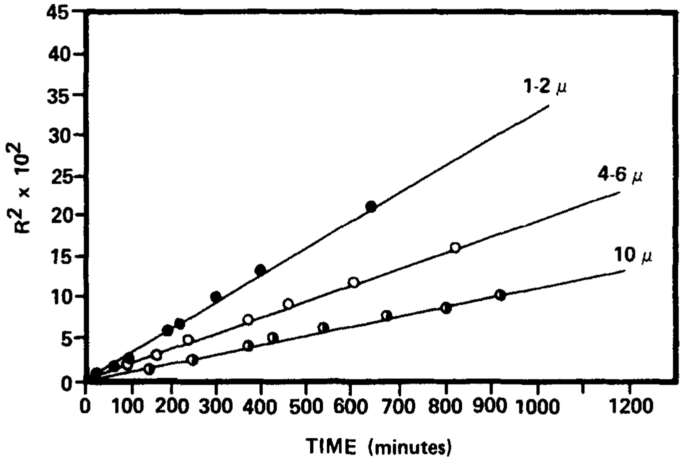


FIGURE 28

Parabolic plots for three size fractions of kaolinite at 400°C. Reprinted from Ref. 84, p. 134, by courtesy of the author and Journal of the American Ceramic Society.

The parabolic rate law (Equation 31) would be valid when the phase boundary reactions are very fast, as in the dehydration of kaolinite (Fig. 28), and rate is inversely proportional to the thickness of the dehydrated layer over a constant cross-sectional area S.[84] If there is a small time lag, the concentration of the reactant A at the interface where the reaction is occurring will not be zero. Assuming that the concentration of A at AB/B interface is C* instead of zero, then

$$\frac{dC}{dx} = \frac{C_o - C^*}{\xi} \qquad \text{(Eq. 33)}$$

The concentration would be zero, say at some distance greater than ξ given by $x = \xi + b$, where b is a constant, so that

$$\frac{dC}{dx} = \frac{C_o}{\xi + b} \cdot \qquad \text{(Eq. 34)}$$

By the same derivation as that used for Equation 30, the following is obtained:

$$\frac{d\xi}{dt} = - \frac{SDC_o}{\beta(\xi + b)} \qquad \text{(Eq. 35)}$$

which on integration yields

$$\xi^2 + 2b = \frac{2SDC_o t}{\beta}. \qquad \text{(Eq. 36)}$$

Rastogi[23] observed that the value of the parameter β would depend on the extent of the reaction inside the particles constituting the product layer zone, and its value would depend on the void volume, density, shape and size of the particles. Because diffusion-controlled reactions are also dependent on a change in shape, it is advantageous to examine the geometric implications on diffusion behavior. By combining Equation 28 with Equation 31, the diffusion-controlled rate of reaction of a spherical particle is described, where

$$\xi = r[1 - (1 - \alpha)^{\frac{1}{3}}] \qquad \text{(Eq. 37)}$$

and

$$[1 - (1 - \alpha)^{\frac{1}{3}}]^2 = \frac{2kt}{r^2} \qquad \text{(Eq. 38)}$$

in which characteristic root-time dependence is observed.

Equation 38 assumes that the sum of the volume of unreacted B and the volume of the reaction product AB is equal to the original volume of B. This assumption may not always be correct, however, since it depends on the restriction either that x = 0 or that the molar volumes of A and AB are equal. Nevertheless, the "Jander" equation has been successfully applied to the study of the dehydration of glucuronamide hydrate, shown in Fig. 29, and to the degradation of aspirin[85] as in Fig. 30. For the degradation of aspirin in the presence of magnesium stearate, a mathematical model based on cylindrical particles was employed.[86]

Developing the correct mathematical rationale for a diffusion-controlled reaction is not straightforward. Although the proper geometric model can often be determined by simple microscopic examination, the above equations assume uniform

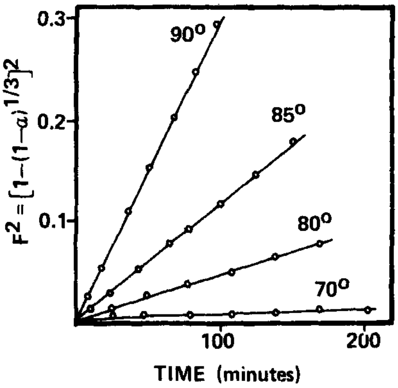


FIGURE 29

Relation between linear fraction of dehydration (F) and time for glucuronamide hydrate. Reprinted from Ref. 43, p. 321, by courtesy of the author and Yakugaku Zasshi.

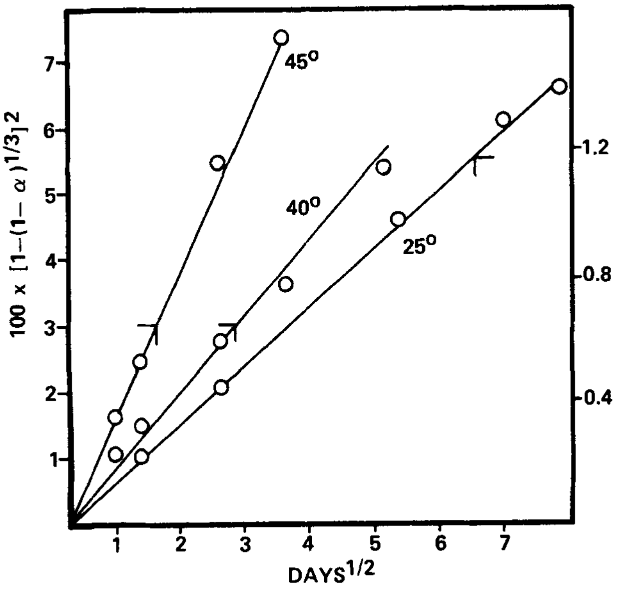


FIGURE 30

Topochemical decomposition pattern of aspirin. Reprinted from Ref. 85, p. 757, by courtesy of the author and Journal of Pharmaceutical Sciences.

particle size as well as shape. Smaller crystals would decompose sooner than larger ones, a situation which these equations cannot accommodate. Furthermore, the assumption that planar diffusion applies to a three-dimensional situation usually remains valid for only the initial part of the reaction. Despite the non-idealities with which the diffusion model must contend, however, the root-time dependence it predicts is generally observed over the major course of such reactions.

b. Solid-Gas Reactions. The kinetic treatment of solid-gas reactions, e.g., the tarnishing of metal, often assumes that diffusion of the reactant gas through the product layer is slow and rate-limiting while chemical reaction with unreacted solid at the moving boundary is instantaneous. Although this assumption is usually valid for solid-solid reactions as previously discussed, the contrasting mobility of gas must be considered. Gas diffusion might in fact be quite rapid through the many cracks and pores of the average pharmaceutical solid whose packing is not as compact as that of metal crystals. Furthermore, chemical reaction of the gas with drug might be far from instantaneous. Thus solid-gas reactions of pharmaceuticals might very well be controlled both by the rate of diffusion and by the rate of chemical reaction.

A model has been designed in which a "reaction zone" is substituted for a solid-gas interface.[20] In this model, the reactant gas can diffuse, without reacting, past a point in the solid where unreacted solid particles still exist. A concentration gradient of both solid reactant and gaseous reactant can then build up within the solid. Using this model, the following rate equation was derived to describe the air-oxidative degradation of a compressed mannitol conglomerate of ascorbic acid:

$$R = 1 - \frac{2(DC_o t)^{\frac{1}{2}}}{Y}\left[\frac{kC_o t}{3} - \frac{(kC_o t)^2}{10} + \frac{(kC_o t)^3}{42}\right] \quad \text{(Eq. 39)}$$

where C_o is the molarity of gas reactant in the solid at the interface, k is the rate constant for the chemical reaction, R is the residual ratio of the solid (1 - α), and Y is the thickness of the disc. In this model, the relative dependence of the overall rate of air oxidation on the two rate-controlling factors varies as a function of temperature. At low temperatures, the diffusivity of oxygen is small and the rate of gas diffusion is rate-limiting. At higher temperatures, however, the overall rate of degradation is controlled by the rate of chemical reaction because of the large increase in diffusivity of oxygen through the solid.

KINETICS OF SOLID DECOMPOSITION

Generally, when a solid decomposes, an S-shaped curve similar to that of Fig. 31 results from plotting the fraction decomposed as a function of time. These curves can usually be described by five characteristic features: an initial induction period (A-B), an acceleratory period (B-C) with an inflection point at C (x_i,t_i), a decay period (C-D), and a retention period (D-E) near the end of the reaction. Any one of these features,

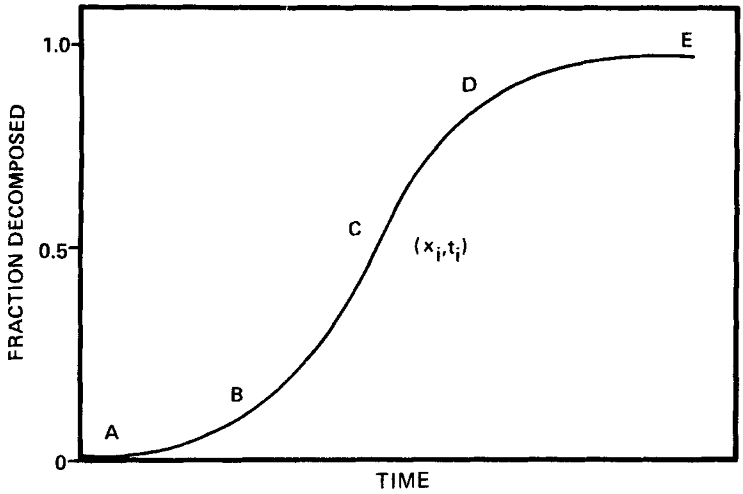


FIGURE 31

The generalized isothermal decomposition curve.

however, except for a point of maximum rate, might be absent in specific cases. The slow evolution of gaseous product limited to ∿0.1 to 5% typifies the induction period, which, if it is true induction, will invariably be succeeded by a period of acceleration which normally extends from 10 to 70%. The inflection point occurs at x ∿0.5. The decay period is both more difficult to analyze and less valuable to kinetic interpretation because the reaction is nearing completion, thereby increasing the dependence of rate on particle size and increasing the probability of sintering the particle surfaces. These factors, in addition to the possible deposition of product gas on the solid, all tend to reduce chemical reactivity and render the retention period irreproducible. If these effects can be eliminated, however, it is often possible to apply a first-order expression to the retention period.

1. Nucleation Control

Decomposition in the solid phase requires the initial formation of product nuclei on the surface of the degrading crystal. Since the activation energy of any reactant molecule located at a position of crystal strain is lower than that of more stable surrounding molecules, that molecule will decompose more readily. Thus, the initial product nuclei arise on or around lattice imperfections. It is reasonable to suggest that once an array of product molecules (which have a different unit cell from that of the intact solid) is established, further strains in the crystal surface are created. These strains are relieved by the formation of cracks which serve as new lattice imperfections. Decomposition is again favored at the mouths of the cracks and soon spreads down the crevices into the crystal. Any covering over the surface of a crack produces lateral strain which ultimately leads to further cracking from the inner surface. Thus a series of "branchings" occurs, and new planes of strain are generated. The deformation effect of the product on the electronic structure of an adjacent molecule of unreacted substance reaches a maximum along these planes, favoring even further decomposition. The chain reaction continues to develop until it encounters the interference of a plane of product molecules, at which time chain growth is halted. As could be expected from an accelerating-decelerating chain reaction such as this, sigmoidal volume-time curves are observed.

Clearly, the rate of product chain growth is a function of the extent to which the reaction has proceeded: as the network of chains builds in complexity throughout the solid, the probability of their termination also increases. Prout and Tompkins[87] assumed that there are initially N^* potential sites for nucleation and that the nucleation rate is proportional to N, the number of nuclei present at time t, i.e., $dN/dt = \alpha N$ where α is now the propagation probability. At a certain point in the decomposition, however, rows of product nuclei start merging such that a termination probability β must be associated with the rise in decomposition product. Thus

$$\frac{dN}{dt} = (\alpha - \beta)N \qquad \text{(Eq. 40)}$$

which cannot be integrated directly since α and β are functions of time.

Since these Type I decompositions exhibit sigmoidal profiles, Prout and Tompkins made a further basic assumption that the inflection point occurs at $x = 0.5$ and reasoned that α must equal β at this point. Assuming that $\beta = 0$ at $t = 0$ $(x = 0)$, α and β could be interrelated by the arbitrary function:

$$\beta = 2\alpha x \qquad \text{(Eq. 41)}$$

From the relation $dx/dt = k'N$, the equation for a sigmoid-shaped curve was derived:

$$\frac{x}{1 - x} = \exp[\alpha(t - t_i)] \qquad \text{(Eq. 42)}$$

where t_i is the time at which the inflection point occurs. An application of this equation to the decomposition of potassium permanganate[88] is shown in Fig. 32. The Prout-Tompkins treatment is not always applicable, however, especially when the inflection point does not occur at $x = 0.5$ such as in the data given in Fig. 33. It is generally observed that the rate of decomposition in the initial induction period is essentially zero order since the number of potential sites for nucleus formation approximates the number of sites created. External factors such as irradiation with γ-rays, grinding, crushing or scratching the crystal surface can reduce induction periods just as the method of preparation may ultimately affect thermal stability. Sigmoidal profiles

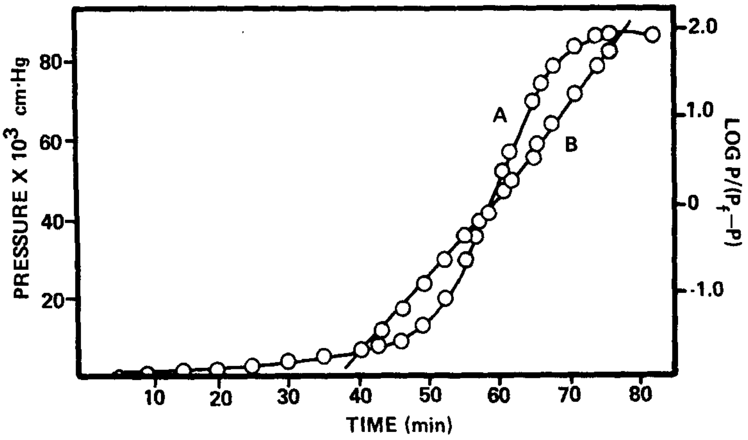


FIGURE 32

Curve A: pressure versus time plot for decomposition of a single crystal of $KmnO_4$ at 230°C. Curve B: plot for Prout-Tompkins equation. Reprinted from Ref. 88, p. 644, by courtesy of the author and Journal of Chemical Education.

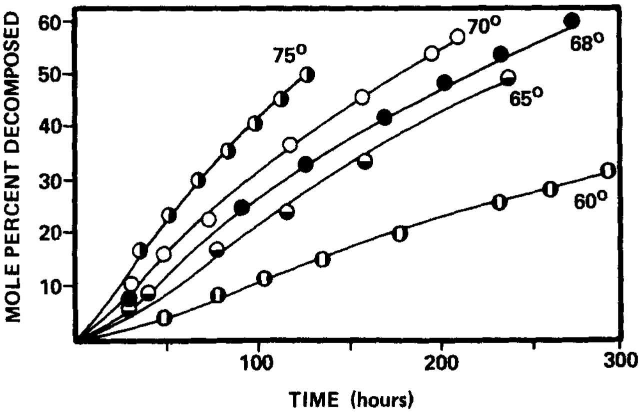


FIGURE 33

Solid-state decomposition of aminosalicylic acid at various temperatures. Reprinted from Ref. 76, p. 39, by courtesy of the author and Journal of Pharmaceutical Sciences.

have been observed in the pyrolysis of aminosalicylic acid[89] and aspirin anhydride,[16] and in the transformation of disopyramide polymorphs.[90]

Recently, Carstensen and Pothisiri[76] showed that first order kinetics can arise in special cases where N is proportional to the increase in BET surface area. They assumed that nucleation starts at some time $t_o > o$ with an assumed probability of $\alpha_o < 1$ and that $\alpha = \beta$ at $t = t_i$. At infinite time, the termination probability is $\beta = \beta_o$. By application of a functionality much more complicated than Equation 42, a first-order expression could be derived where

$$x = 1 - \exp[-\beta_o(t - t_o)],\ t \geqslant t_o. \qquad \text{(Eq. 43)}$$

Figure 34 shows that the use of this equation was successful

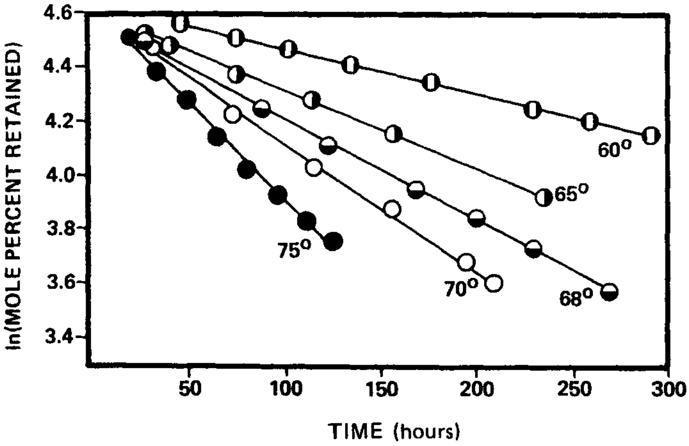


FIGURE 34

Data from Fig. 31 plotted as first-order kinetics. Reprinted from Ref. 76, p. 41, by courtesy of the author and Journal of Pharmaceutical Sciences.

in linearizing the data from Fig. 33. It should be recognized, however, that although complex expressions such as a Γ-function can be used to linearize the data points of a sigmoid, the redefinition of the profile does not usually aid in explaining the mechanism operating in the reaction.

2. Melting and Liquid Layers

As discussed previously, two parallel reactions occur during Type II decomposition: (a) normal solid state decomposition, and (b) decomposition of an increasing volume of saturated solution of the undegraded reactant in its liquid decomposition product. When the liquid product layer accumulates on the surface of the solid, reactant molecules will dissolve at various energetic sites. (In the Prout-Tompkins model, it was assumed that the reactant molecules were insoluble in their decomposition product.) The rate of such a reaction should not depend on nucleation, but rather on topochemical processes, approaching first-order kinetics.[80]

One treatment of Type II reaction kinetics was developed by Bawn.[91] Given that S is the solubility of the intact compound in its decomposition product in moles/mole and x is the number of moles of decomposition product found, then decomposition rate can be expressed as

$$\frac{dx}{dt} = k_s(1 + Kx) \qquad \text{(Eq. 44)}$$

where

$$K = k_\ell S - k_s S - k_s \qquad \text{(Eq. 45)}$$

and k_s and k_ℓ are the rate constants for decomposition of the solid and dissolved reactant, respectively. Integration of Equation 44 leads to the expression:

$$x = \frac{1}{K}[\exp(Kk_s t) - 1] \qquad \text{(Eq. 46)}$$

or

$$\ln [1 + Kx] = \alpha t \qquad \text{(Eq. 47)}$$

where

$$\alpha = Kk_s \qquad \text{(Eq. 48)}$$

Equation 47 describes an upwardly traced curve similar to that of segment AC in the sigmoid of Fig. 31. At one particular point (approximately corresponding to point C) all solid will have dissolved, and $x = x_i = 1/(1 + S)$ at $t = t_i$. Decomposition beyond point C follows solution kinetics and is represented by segment CDE in Fig. 31. Therefore, the S-shaped curves obtained in Type II reactions are actually a combination of two curves resulting from two different mechanisms. The value of K is found by treating the equation with adjustable parameters to impose linearity and zero intercept onto the data. The values of k_s and k_ℓ are then obtained by least squares iteration techniques. This kinetic treatment has been applied to the decomposition of benzoic acid derivatives by Carstensen and Musa[44] and more recently to the solid-state decomposition of alkoxyfuroic acids.[92] In the latter paper, the observed k_ℓ values are in good agreement with the calculated rates of decomposition in solution of the liquid parent alkylfuran. This data treatment further confirms the consistency of the model.

Liquid layers have also been implicated in the decomposition of a series of vitamin A derivatives. Guillory and Higuchi[47] empirically related the zero order rate constant k_A to the melting point T_M by the equation

$$\log k_A = \theta\left(\frac{1}{T_M}\right) + \sigma. \qquad \text{(Eq. 49)}$$

where θ is the characteristic slope for an homologous series. On this basis, one would expect the k_ℓ value as derived from the Bawn model to obey Equation 49. A similar inverse relationship between aspirin decomposition in aspirin-lubricant mixtures and the reciprocal of the melting point was recently confirmed.[86]

It has been reported that liquid layers might also be involved in the degradation of aspirin anhydride.[16] Sigmoidal behavior was characterized as an initial zero-order loss (linear) followed by a period of first-order loss (logarithmic). It was concluded that pyrolytic degradation started on the surface of the crystals and that the resulting surface layer of molten product lowered the melting point of the drug sufficiently to form a melt which degraded at a faster rate.

3. Moisture-Mediated Sigmoidal Profiles

Many compounds are relatively stable in the solid state until they are exposed to excessive moisture. The moisture-induced degradation of pure aspirin, observed to exhibit a sigmoidal profile of hydrolysis, was investigated in an attempt to define the mechanism of moisture adsorption and its participation in aspirin decomposition.[93] Interpretation of the data was based on two concepts: (1) water is rapidly absorbed onto the surface of aspirin, and (2) the water film becomes rapidly saturated with a portion of the solid aspirin. If monolayer adsorption occurs, each aspirin particle will be partially covered by a layer of water molecules. If multilayer adsorption occurs, each particle will be surrounded by a film of water. In each case the amount of water adsorbed is a function of vapor pressure. Decomposition proceeds for the most part only in solution, and, as a molecule of aspirin is removed from hydrolysis, it is instantly replaced by one from the solid.

Since the hydrolysis of aspirin produces acetic acid, the reaction is subject to acid catalysis, in which case $dC/dt = k_1AH^+$ where C is the concentration of salicylic acid, k_1 is the rate constant associated with the concentration of hydrogen ion and molecular aspirin, A is the aspirin concentration and H^+ is the concentration of hydrogen ion. By equating the concentration of acetic acid with C, which is a fair approximation, the ionization equation may be written, $K = (H^+)^2/C$.

Assuming that the volume of moisture adsorbed, V, follows a Freundlich isotherm equation, then

$$V = k'p^n \qquad \text{(Eq. 50)}$$

where k' is the proportionality constant, p is the vapor pressure, and n is the order of the sorption reaction with respect to p. After appropriate substitution and units manipulation, the rate of decomposition can be described by a complicated equation.

Recently, the original derivation of the sorbed-moisture model was challenged and a similar but more rigorous substitute offered.[94] Both analyses give linear plots indicating that the data is in agreement with the proposed model. The fact that the value of n = unity obtained from the mathematics suggests that aspirin degraded only in physically adsorbed water. This model, by accounting for degradation via solution kinetics in a saturated sorbed moisture layer, then serves as a foundation for predicting the stability of aspirin and likewise other medicinals which decompose in the presence of humidity and ionizable excipients.

Practically, however, drug within a dosage form normally experiences only partial coverage of adsorbed moisture. One might then expect the overall rate to vary as a function of the solid state rate constant (k_1) and the solution state rate constant (k_2). Using this model, Carstensen and Pothisiri[76] studied the decomposition of aminosalicylic acid in the presence of moisture for which the sigmoidal profile of degradation is given in Fig. 35. Starting with one mole of reactant at time zero, they defined A' as the number of moles of aminosalicylic acid left at time t. Assuming that the moisture adsorbed to the product m-aminophenol was not part of the "available" sorbed moisture layer, the amount of reactant

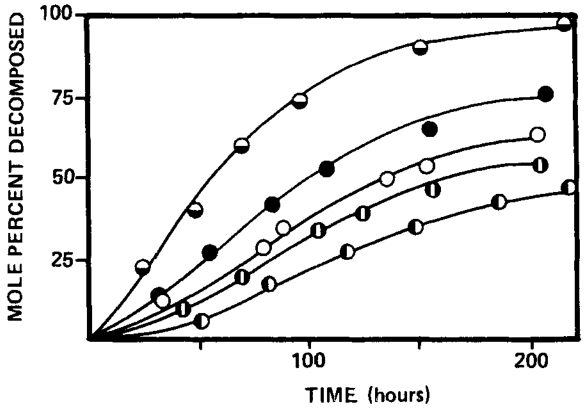


FIGURE 35

Solid-state decomposition of aminosalicylic acid at 65° in the presence of moisture. Key: ◐, 5.9 torr; ◑, 7.4 torr; O, 11.4 torr; ●, 17.6 torr; and ⊖, 23.8 torr. Reprinted from Ref. 76, p. 38, by courtesy of the author and Journal of Pharmaceutical Sciences.

in solution was equal to A'VS, where V is kilograms of water adsorbed per mole of solid (obtained from adsorption isotherms) and S is solubility of aminosalicylic acid in the liquid layers in moles per kilogram of water. The amount of solid aminosalicylic acid present was then equal to A' - A'VS, and decomposition rate could be expressed by the equation

$$-\frac{dA}{dt} = k_1(A' - A'VS) + k_2A'VS \qquad \text{(Eq. 51)}$$

whose solution yielded the expression

$$\ln A' = -k_1[1 + (\frac{k_2}{k_1} - 1)VS]t. \qquad \text{(Eq. 52)}$$

Treatment of the observed data according to the first order expression (Equation 52) is illustrated in Fig. 36.

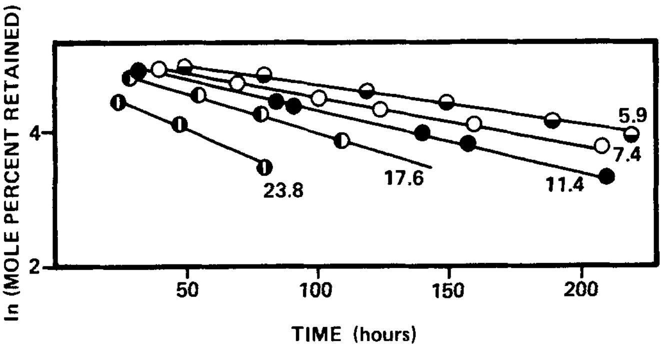


FIGURE 36

Data from Fig. 35 plotted by Equation 52. Reprinted from Ref. 76, p. 42, by courtesy of the author and Journal of Pharmaceutical Sciences.

TEMPERATURE DEPENDENCE

1. Arrhenius Plot

One of the most effective and widely used techniques for predicting long-term chemical stability is the construction of an Arrhenius plot and evaluation of activation energy. By measuring the dependence of reaction rate on temperature, the degradation of a stable compound stored at high temperatures over short intervals can be used to estimate the degradation that would be observed on lengthy storage under moderate conditions. Plotting the rates of the accelerated reaction as a function of temperature yields an Arrhenius plot from which suitable extrapolation leads to predicting the rate constant at room temperature. When constructing an Arrhenius plot, the rate of decomposition need not be followed for an entire half-life for reasonable accuracy. Linear regression analysis should be applied, however, to evaluate data resulting from kinetic studies at a minimum of four different temperatures. Regardless of their order, most reactions follow the Arrhenius relationship

$$k = Z \exp\left(-\frac{E_a}{RT}\right) \qquad \text{(Eq. 53)}$$

where Z is a proportionality constant and E_a is the activation energy. If the reaction is a simple equilibrium, such as $A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B$, then the rate constant for the reverse reaction is given by

$$k_r = Z_r \exp\left(-\frac{E_a + \Delta H}{RT}\right) \qquad \text{(Eq. 54)}$$

where ΔH is the enthalpy of reaction. The activation energy is a quantity that accounts for the fact that thermodynamically favorable reactions might not proceed spontaneously and speedily. It may be pictured as an energy barrier separating the stable reactant and product species such that a quantity of energy (E_a) must be added to either species to produce an activated complex which will then become either product or reactant as it releases energy. In a reversible reaction, a sufficient number of particles is supplied with this activation energy so that there is a recognizable tendency for interchange and consequent equilibrium.

The Arrhenius relation must be applied very carefully to a reaction, however, since its use implies certain necessary assumptions regarding the nature of the reaction. These include the assumptions that:

(1) E_a is temperature-independent. In most cases over a narrow temperature range this is at best a good approximation. In actuality E_a does vary slightly, depending on the partial heat capacity of all the molecules;

(2) the reaction mechanism remains the same at all temperatures. If two reactions of different activation energies can occur, the resulting Arrhenius plot will exhibit positive deflection in the region where the two rates are comparable. At higher temperatures the plot steepens as the reaction with the greater activation energy predominates, whilst at low temperatures only the reaction of low activation energy might occur. For example, in an alkaline environment, aspirin exhibits a temperature-dependent change in mechanism: at lower temperatures, the rate-determining step is diffusion-controlled, whereas at higher temperatures it is kinetically controlled;[85]

(3) the reaction system does not undergo physical changes such as precipitation, sublimation, melting, or vaporization. For instance, when aspirin hydrolyzes in the presence of adsorbed moisture, the salicylic acid thus formed remains in solution in the water layer until saturation is reached. At this point in the reaction, solid salicylic acid separates and can sublime as crystals on the dosage form or on the inside of the product container. The point at which this

occurs, however, is temperature-dependent, since solubility parameters change at higher temperatures [slope of Arrhenius plot equals $(\Delta H_{soln} + E_a)/2.303R$]. The overall kinetics of the reaction system might therefore change with temperature. Furthermore, only initial rate data can be plotted to determine the Arrhenius relation for a reaction that undergoes a phase change during its course. This technique has been successful in treating the decomposition of multivitamin products which show inordinate rate behavior after one half-life because of melting.

A change in temperature is often accompanied by more subtle changes in conditions, such as humidity. For some reactions such a change can be of critical influence on kinetics, in which case Arrhenius plot extrapolations are rendered useless and misleading. Consider, for instance, an encapsulated water-labile drug stored in either a water-permeable blister package or a sealed glass bottle. At high temperatures, the capsule can lose moisture through the blister film, but not from the bottle. Accordingly, the stability of the blister-packaged capsules will appear superior both by actual stability data and by extrapolation. At room temperature and 70% relative humidity, however, diffusion of water vapor might actually be reversed in the blister package, proving detrimental to the stability otherwise predicted. The capsules sealed in the bottle might in fact exhibit far greater stability under ambient conditions;

(4) no temperature-dependent equilibria occur in the reaction. In an equilibrium reaction, the activation energy is probably a composite function of several terms, each of which may be temperature-dependent. When equilibrium is involved, the rate of the overall reaction depends on the concentration of the product species formed in the equilibrium. If the equilibrium constant varies with temperature, a curved Arrhenius plot will result.

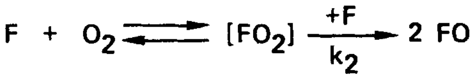
(5) the kinetics of the reaction are not governed by boundary migration. In phase boundary processes such as chemisorption, $\xi = kt$, where ξ is the thickness of the reaction product layer, the rate constant generally does not increase exponentially with temperature, invalidating the Arrhenius relation. However, if the velocity of the reaction is governed by a diffusion process, i.e., $\xi = kt^{1/2}$, k contains the diffusion coefficient which does increase exponentially with temperature. For such reactions an Arrhenius-type relation can be derived.

Obviously, use of the Arrhenius plot for prediction of stability must be considered in light of the controlling mechanisms of degradation. Not always can a reaction be satisfactorily accelerated. For solvolytic processes, $E_a \sim$ 10-30 kcal/mole, and the rate of reaction increases conveniently with a rise in temperature. If the rate-determining step involves diffusion or photolysis, however, then $E_a \sim$ 2-3 kcal/mole and only little advantage is gained by accelerated temperature studies. (Increases in pressure or light intensity are useful here.) On the other hand, pyrolytic reactions exhibit $E_a \sim$ 50-70 kcal/mole and the rates of degradation which may be significant at elevated temperatures may not be of any practical significance at the temperature of marketing and storage of the preparation.

The value of E_a obtained from Arrhenius studies can often be used as a diagnostic tool in the study of solid state mechanisms. For instance, when the values of E_a for k_1 and k_2 are equal, it is likely that the same mechanism is occurring over both parts of the reaction profile.[87] A study involving the decomposition of solid aspirin shows the calculated value of E_a to be equal to the E_a for solution hydrolysis of the drug, an observation which was used to strengthen the argument that aspirin degraded in a saturated sorbed moisture layer.[93] Other investigators have attempted to use the "linearity" of the Arrhenius plot to distinguish between zero and first order reactions.

2. Equilibria and the van't Hoff Relation

The degradation of pharmaceuticals often involves a condition of equilibrium brought on by forces of either chemical or physical origin. In such cases, one is likely to observe an asymptotic



$$F + O_2 \rightleftharpoons [FO_2] \xrightarrow[k_2]{+F} 2\,FO$$

SCHEME VIII

profile of drug loss. Both moisture and surface pH are two primary factors which, through their interaction, can induce chemical equilibria whose positions are temperature-dependent. Not all equilibria change as a function of temperature; however, an "apparent" equilibrium is observed when the supply of a reactive formulation impurity which causes drug degradation is exhausted. Similarly, a kind of physical equilibrium can be established when only a monolayer of drug degrades in the presence of an adsorbed excipient and subsequent multilayers remain intact. But once characterized, these latter types of equilibria are relatively simple to predict by the very nature of their temperature-independence. Since rate constants are meaningless in predicting the behavior of a chemical equilibrium reaction, however, some approach other than an Arrhenius study must be used to characterize temperature-dependent equilibria. The van't Hoff relation, applied here to solid state equilibria, provides a valid alternative approach.

Consider the simple equilibrium

$$A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B \qquad \text{(Eq. 55)}$$

where k_f and k_r are the forward and reverse first order rate constants, respectively. If B_t is allowed to represent the mole fraction of B at any time t such that $1 - B_t$ equals the mole fraction of A at time t, and B_∞ equals the equilibrium mole fraction of B, then the asymptotic rise in B can be described by

$$B = B_\infty(1 - e^{-kt}) \qquad \text{(Eq. 56)}$$

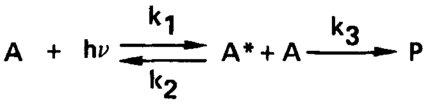
where $k = k_f + k_r$. By treating the data as an arithmetic series and choosing sampling intervals carefully, a good estimate of B_∞ can be obtained by iteration. While the values of the rate constant so obtained in this treatment are of little quantitative significance, the ultimate position of equilibrium is critical to observed stability. Therefore, several equilibrium values are determined in this manner (or by direct measurement if kinetically convenient) at various temperatures where

$$K = \frac{B_\infty}{1 - B_\infty} \qquad \text{(Eq. 57)}$$

These values are then plotted as a function of temperature according to the van't Hoff relation whose integrated form is

$$\ln K = -\frac{\Delta H}{RT} + \alpha \qquad \text{(Eq. 58)}$$

where α is a constant of integration. The value of ΔH calculated from the slope of the resulting graph can then be used to calculate (or graphically extrapolate to) the value of K (and hence B_∞) at temperatures where its direct measurement is inconvenient, such as at low storage temperatures.



SCHEME IX

The practical application of the van't Hoff equation is obvious. Suppose a solid drug hydrate exists in equilibrium with its dehydrated form:

$$D \cdot H_2O \rightleftharpoons D + H_2O. \qquad \text{(Eq. 59)}$$

If decomposition and recomposition proceed very rapidly, rate constants can be neglected. The equilibrium constant for this reaction is expressed as

$$K = \frac{[D][H_2O]}{[D \cdot H_2O]}. \qquad \text{(Eq. 60)}$$

If the hydrate and drug are both solids, their activities (or concentrations) are generally assigned the arbitrary value of unity, such that

$$K = [H_2O] \qquad \text{(Eq. 61)}$$

or

$$K = P_{H_2O}\,. \qquad \text{(Eq. 62)}$$

Therefore, the proportion in which the drug and its hydrate co-exist at any given temperature depends entirely on the vapor pressure of water over the system (excluding the effects of condensation, etc.), and if the existing humidity does not reflect the equilibrium vapor pressure, the reaction will proceed in the direction which will tend to bring about such equilibrium. For example, if the hydrate were subjected to a reasonably high temperature under vacuum, it might be expected to decompose completely. Once an atmosphere of water is supplied to it, however, it should remain intact as the hydrate, regardless of temperature.

Close examination of a typical van't Hoff plot such as that shown in Fig. 37 reveals several important considerations. If the material has an equilibrium pressure P_A at ambient temperature, while the ambient partial pressure of water vapor (humidity) is P_B, then the material is obviously stable. Heating the specimen to T_B might induce some dehydration, but only at the expense of raising the partial pressure of H_2O in the immediate vicinity of the drug which, in turn, exhibits the decomposition. If the water vapor is then allowed to diffuse away, the material will decompose as readily as the diffusion can occur. In general, the material will tend to dehydrate at any temperature to the right of that corresponding to the partial pressure of water vapor, actually

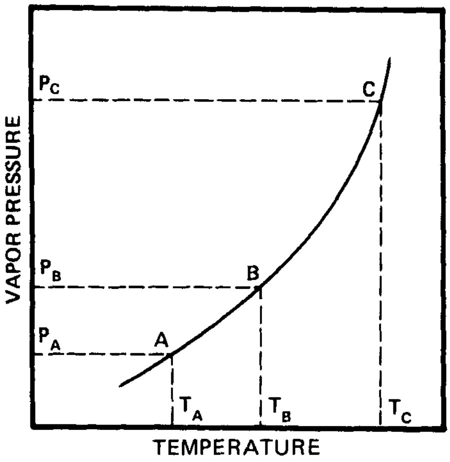
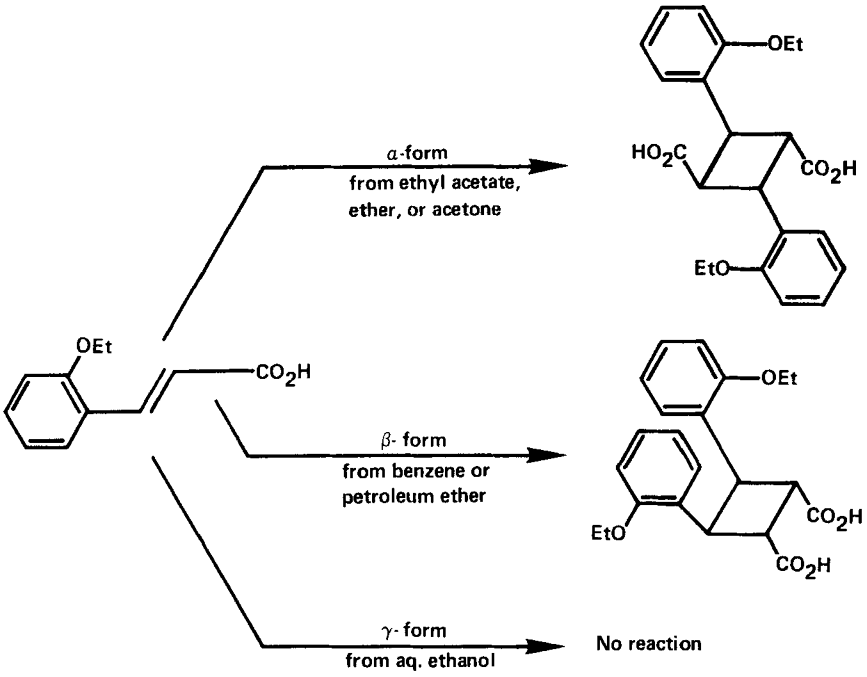


FIGURE 37

Typical van't Hoff plot for a reversible dehydration.

adjacent to the sample, and will tend to rehydrate at any temperature to the left. Therefore, if a drug hydrate is to remain stable in a dosage form, the difference between points A and B on the van't Hoff plot of the hydrate must be sufficiently large that normal changes in ambient storage conditions will not significantly affect its equilibrium.

If a drug substance does not form a hydrate but merely absorbs moisture, it is hygroscopic. The amount of moisture uptake depends on the surface area and the relative humidity. It is useful to determine the relative humidity at which the substance does not absorb moisture -- this is known as the critical relative humidity. This property can be determined



SCHEME X

dynamically by measuring the rate of uptake at higher humidities and extrapolating back to zero rate. Most pharmaceutical substances can be handled/processed if the critical relative humidity lies below 50%. An excellent historial review of the numerous approaches taken to characterize hygroscopic behavior and to quantify its effects was described by Van Campen et. al.[95] Also presented was an elegant experimental procedure which uses an adsorption apparatus to measure continuous weight gain as a function of vapor pressure. The kinetics of water adsorption onto hygroscopic choline halide salts were examined and found to obey their proposed model.

SUMMARY

Implicit in the successful design of a solid dosage form is the assumption that the pharmaceutical scientist has become fully acquainted with the fundamentals of solid state stability, The contents of this article were compiled to give the potential practitioner a grasp of how knowledge of solid state chemistry, experimental methods, and kinetics could facilitate studying factors affecting the stability of solid dosage forms in the broadest sense. Crucial to modern day drug development is the concept that dosage forms introduced to the clinic be commercializable from the beginning; false starts in a pivotal clinical program can be very costly. Therefore, for stable solid dosage forms to be developed in a rational, intelligent and streamlined fashion, application of the principles described herein is believed to be essential.

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