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STABILITY ASPECTS OF PREFORMULATION AND FORMULATION OF SOLID PHARMACEUTICALS

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INTRODUCTION

The scientific discipline of formulating drugs into commercial delivery systems places a great deal of emphasis on accelerating physicochemical changes through high stress, short-term situations. Such predictive measures become increasingly more risk-oriented the higher the stress employed, and this "need-to-know" urgency is largely dependent on the time pressure exerted to progress the drug rapidly towards an NDA. In the majority of cases, the time taken to conduct normal stress long-term studies is unacceptable to an industrial profit-making environment.

There is at this time, however, simply no other way to gain confidence in the long-term stability behavior of a product than to have gone through the rigors of accelerated stability testing. This testing ranges from (a) preformulation screening of compatibility of components, (b) formulation screening where short-term comparative

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physical and chemical testing are used in the selection of a suitable formulation (or suitable container/closure system), and (c) final formula evaluation of laboratory lots, clinical supplies, scale-up lots and full scale production batches. Expiration dating based on such predictions should be considered tentative at best because too often high stress conditions induce reaction rates, mechanisms and by-products which are different from those perceived under normal stress conditions. For example, some prostaglandins are more unstable in the solid state than in the liquid state, beta-lactam side chains are known to isomerize in the solid state but not in the solution state, crystalline transformation resulting in greater thermodynamic reactivity can occur at high temperatures, melting of one ingredient may cause another to dissolve and degrade much faster than it would otherwise in the crystalline state, and physical processing (such as drying, mechanical grinding, or compression) may induce formation of highly reactive paracrystalline/mesomorphic forms. It is therefore understandable that regulatory authorities question the validity of accelerated data and demand substantial real-time data under normal storage conditions before approval of NDA's is granted.

A further complication is the so-called inertness of pharmaceutical adjuvants. Excipients are, in general, quite reactive towards drugs, and it is necessary for the research pharmacist to study and comprehend these effects in order that formulation stability can be manipulated. Intent of this article is to discuss the factors which influence stability of solid dosage forms.

FACTORS AFFECTING STABILITY OF SOLID DOSAGE FORMS

A. Moisture and pH

Moisture is perhaps the single most important factor affecting stability of dosage forms. Direct adsorption of water molecules onto the drug surface might easily induce hydrolytic decomposition. By adsorbing onto a drug-excipient interface, water can ionize either or both of the potential reactants to bring about an interaction that otherwise would not have occurred. Dry compression, hermetically sealed containers, the inclusion of a desiccant (or even molecular sieves) in the final package, microencapsultion with wax-like moisture barriers, and formulation of the drug with excipients having high critical relative humidities are just several of many approaches to minimizing the deleterious effects of moisture on a dosage form.

The effect that moisture exerts on stability depends on its strength of association - whether it is "free" water or "bound" water. Free or peripheral water is titratable in the washings collected from rinsing the solid with a solvent in which it is insoluble, whereas "total" water can be titrated in the solution prepared by dissolving the solid to release its water of crystallization. Bound water is calculated by difference. Generally, degradation arises as a function of the amount of free -- not bound water. For example, ascorbic acid decomposes on silica gel to an extent directly proportional to the amount of free water present.[1] Contrasting behavior, however, was observed in the case of thiamine hydrochloride adsorbed onto an excipient matrix in the presence of added

moisture,[2] where the extent of degradation, whose pattern resembled that of an equilibrium exhibited a clear maximum in the presence of 5% water. The water-soluble drug apparently competed actively with the water molecules for available excipient sites, and only a monolayer of solubilized, adsorbed drug underwent rapid degradation. Provided there was sufficient moisture present to form that monolayer, an equilibrium situation developed in which adsorbed drug beyond the monolayer degraded very slowly.

Recent evidence would suggest, however, that excipients themselves are inert per se, and it is indeed the water adsorbed onto their surfaces which is the reaction component.[3] When decomposition rates of nitrazepam adsorbed onto a wide variety of excipients exhibiting a wide range of surface area were compared, no correlation with surface area was found. Rather, it was the nitrogen adsorption energy (BET measurement) of each excipient which could be related to a linear decrease in hydrolysis rate (Figure 1). This observation strongly suggests that the water available for reaction on the excipient surface is the primary determinant of relative "inertness" of the excipients examined.

Simple drug hydrolysis in the solid state requires the actual solubilization of surface drug molecules in an adsorbed layer of water. When a relatively insoluble drug that degrades only in aqueous solution dissolves to a limited concentration in surface moisture, the total amount of drug subject to hydrolysis, i.e., total amount dissolved, depends only on the volume of water in the surface film. Assuming that the total volume of water added to the reaction system is directly proportional to the amount adsorbed on

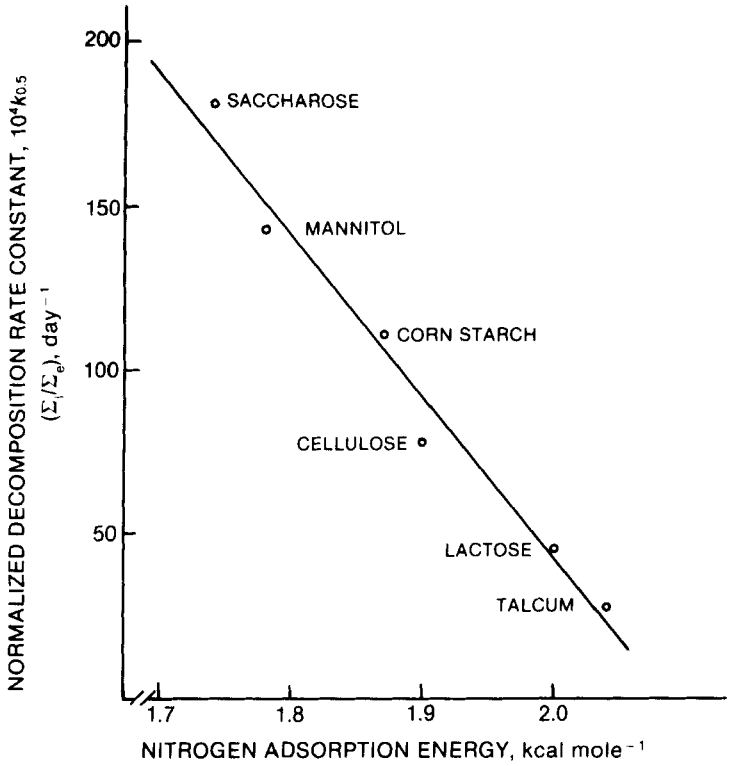


FIGURE 1

Normalized decomposition rate constants of nitrazepam in relation to the nitrogen adsorption energy of various excipients. Reprinted from Ref. 3, p. 1073, by courtesy of the author and Journal of Pharmaceutical Sciences.

the drug surface, the rate of hydrolysis will follow zero-order kinetics and is directly proportional to the volume of water added to the reaction system. A more soluble drug will behave in just the same manner, provided there is not enough free water present to completely dissolve the drug. Once the drug is totally solubilized, normal first-order kinetics prevail.

The practical value of this concept was demonstrated in a study conducted to evaluate the effect of various excipients on the sta-

bility of aspirin in the presence of moisture.[4,5] The formulated drug was suspended in varying amounts of water, and its stability was monitored as a function of time. Interestingly, extrapolation of the apparent zero-order rate constant to "zero percent" water at different temperatures correlated well with the rate constants obtained from long-term solid state studies at elevated temperatures.

Not infrequently, a drug whose hydrolytic degradation correlates directly with moisture content will exhibit an unexpected level of degradation at zero percent moisture. In a study of vitamin A degradation[6] in which previously collected data[7] was retreated to yield the graph shown in Figure 2, the sum total of vitamin A lost at all temperatures was plotted as a function of water concentration. In the absence of water, significantly more drug loss was observed than that predicted by extrapolation to zero percent water. Furthermore, stability of the drug remained at that level with the addition of up to 0.5% water. This behavior was attributed to simultaneous solid state oxidation of the relatively insoluble drug. Where oxidation is occasionally inhibited by moisture, its presence in such low levels resulted in a rise in oxidation that offset the decreased hydrolysis. With the addition of water in excess of 0.5%, however, total degradation increases linearly with water concentration, indicating that the contribution of solid state oxidation decreases and hydrolysis predominates.

One of the more significant means by which moisture influences solid state degradation is its ability to alter the microscopic pH environment of drug and excipient surfaces. Although measurement

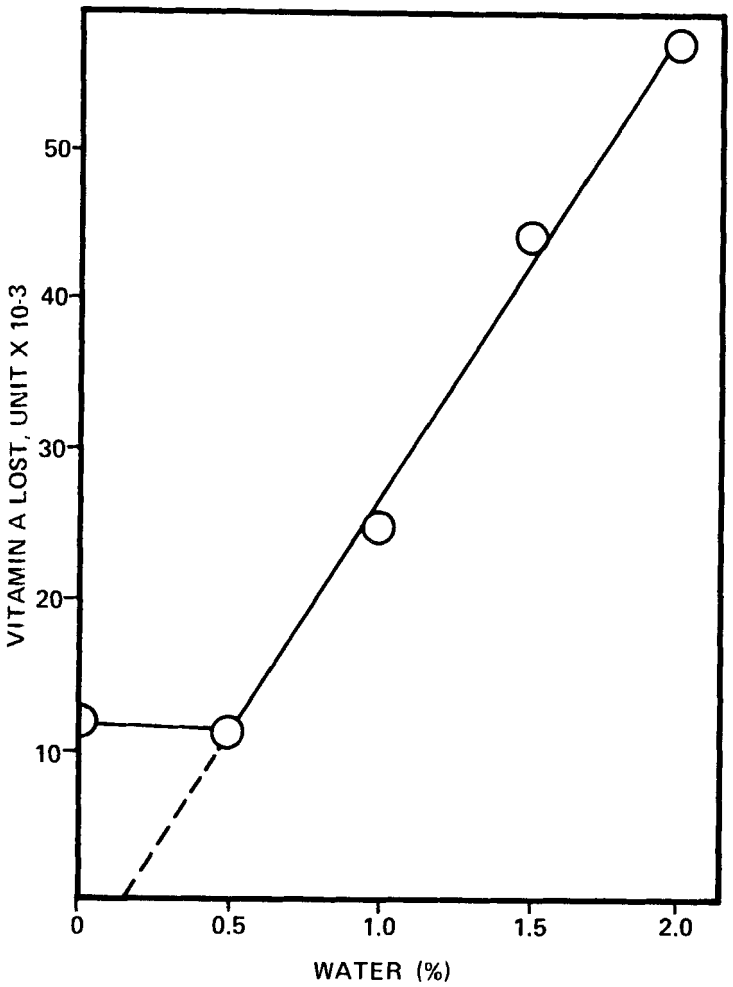


FIGURE 2

Plot showing the effect of water concentration on the stability of vitamin A acetate in a solid system. Reprinted from Ref. 6, p. 1859, by courtesy of the author and Journal of Pharmaceutical Sciences.

of microscopic pH is not directly possible, the pH of an aqueous slurry of excipient generally reflects the value of surface pH. In addition, an estimate of "dry" pK_a of surfaces can be obtained by observing the colors assumed by suitable Hammett-type indicators allowed to adsorb onto the formulation particles. The acid strength of a solid surface, defined by Walling[8] as "the ability of the surface to convert an adsorbed neutral base to its conjugate acid," has great implications for chemical stability. Any one of several factors can easily alter these characteristics. The ionization of excipients, drug, or degradation products in the presence of varying amounts of moisture all influence surface pH. Yet it can be successfully regulated by the judicious selection of additives. For example, both polyethylene glycol 4000 and triethanolamine have been used to prevent the isomerization of vitamin D_2.[9] In a study designed to stabilize aspirin, hexamic acid was added to an alkali stearate establishing a buffer system which successfully regulated the formulation pH to a value at which minimum aspirin hydrolysis occurs.[5] Addition of glyceryl monostearate or stearic acid to formulations containing lactose in the presence of an amine salt has been a successful means of preventing the discoloration caused by the interaction between these ingredients.[10] Acidic excipients were found to stabilize molindone hydrochloride over basic excipients.[11]

If a drug is moisture sensitive, then the degree of moisture protection provided by the packaging is key to its shelf-life. To determine this, it is prudent to first understand the relationship between temperature and humidity and the rate of decomposition.

Such a study was conducted by Genton and Kesselring[12] who examined a 1% nitrazepam dispersion on microcrystalline cellulose at four temperatures and six relative humidities. By means of an empirical three-parameter regression equation,

$$X_1 = a + bX_2 + cX_3 \qquad \text{(Eq. 1)}$$

where X_1 = log K, $X_2 = 10^3 T^{-1}$, X_3 = relative humidity, a = constant, b = partial regression coefficient of log K on T^{-1} (at constant RH), and c = partial regression coefficient of log K on relative humidity (T = constant), it was possible to correlate quantitatively a plane of regression for rate, temperature and relative humidity (Fig. 3). Having defined this plane, the rate

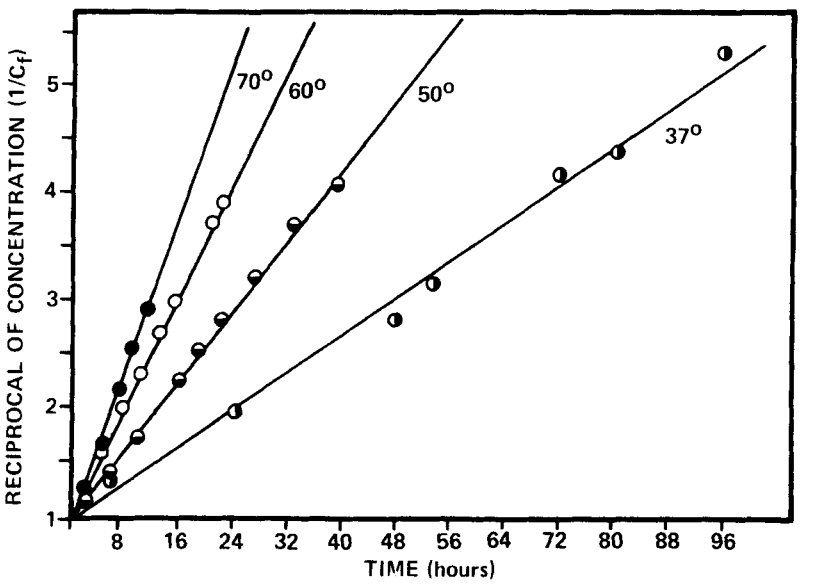


FIGURE 3

Variation of log K as a function of relative humidity and reciprocal temperature. Reprinted from Ref. 12, p. 679, by courtesy of the author and Journal of Pharmaceutical Sciences.

of decomposition at any temperature and relative humidity conditions could be easily ascertained by visual inspection.

Once the degree of protection required is determined, various packages with known moisture transmission rates can be rationally selected -- e.g., polyvinyl chloride is ≈12 fold more moisture permeable than an equal thickness of a triple laminate of low density polyethylene/polyvinylidene chloride/cellophane. Permeability also increases with a rise in temperature ($E_a \sim 3 - 8$ Kcal/mole), so that in a tropical climate where varying temperature and humidity pose a formidable driving force toward moisture penetration, the degree of protection needed is greater than in a temperate region. Generally, if the dosage form is processed with a very low moisture content and is packaged in a multi-laminate under low humidity conditions, the shelf-life can be considerably extended, e.g., bendroflumethiazide can form up to 16% of undesirable "free amine" within three months when exposed to 37% RH/40°C and packaged in PVC; when carefully prepared and packaged at low humidity in an Aclar laminate, the amount of decomposition under a similar harsh exposure was limited to 0.5%.[13] Predictive measures by an iterative calculation procedure using a mathematical model based on the moisture permeabilities of the packaging material and kinetic parameters have been described by Nakabayashi et al.[14]

B. Oxygen

Many drugs, especially those containing thiol, amine or aldehyde functionalities or centers of unsaturation, are subject to oxidative degradation on exposure to dry heat. For example, both

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

SCHEME I

polyene antibiotics, fumagillin and filipin, can be thermally destroyed as solids in the presence of air. Loss of spectral absorbance of each compound upon oxidation, illustrated for filipin in Scheme I, follows apparent second order kinetics. The oxidation is thought to proceed via a two-step mechanism: initially, an adduct of oxygen and the polyene molecule is formed reversibly, followed by the irreversible reaction of the activated oxygenated polyene with an adjacent polyene to produce an oxygenated product. If the rate constant governing the second step, k_2, is rate-determining and steady state conditions where O_2 concentration is constant, then

$$\frac{1}{[F]} = kt + \frac{1}{[F]_o} \qquad \text{(Eq. 2)}$$

where $[F]_o$ is the initial concentration of filipin. Figure 4 illustrates the typical second order behavior exhibited by filipin upon solid state oxidation.[15]

Many other pharmaceuticals readily undergo air oxidation or other chemical reactions in the presence of oxygen. Ascorbic acid oxidizes in the solid state according to pseudo-first order kinetics.[16] Oxygen plays a less direct role in other types of reactions such as the decarboxylation of aminosalicylic acid.[17] In this case, the rapid initial rate was followed by a decelera-tory period, resulting from an oxidative surface reaction which

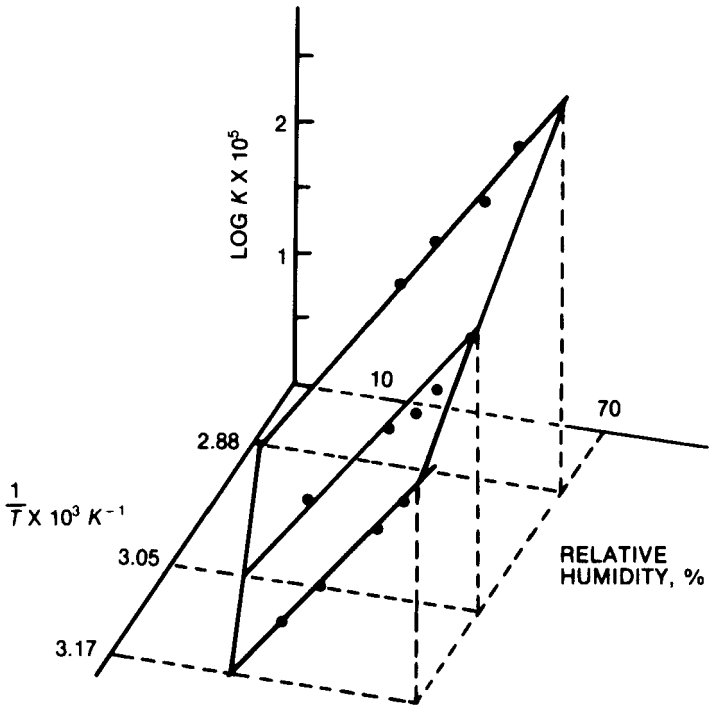


FIGURE 4

Plot illustrating the second order thermal degradation of crystalline filipin in the presence of air. The reciprocal of C_f is plotted against time in hours for several temperatures. Reprinted from Ref. 15, p. 355, by courtesy of the author and Journal of the American Pharmaceutical Association, Scientific Edition.

eventually retarded propagation. There are many methods by which oxidation and concurrent degradation can be inhibited in a formulation. Flushing the head space of containers with an oxidatively inert gas such as nitrogen or argon limits oxygen uptake. Another common method of stabilizing drugs prone to oxidation involves the inclusion of antioxidants in the formulation in order to scavenge oxygen from entrapped air or from the air admitted on removal of a dose. Presence of chelating agents to remove catalytic metal ions may also be beneficial.

Despite the earlier comment that water retards oxidation, there have been a number of recent examples where the presence of moisture accelerated reactions with molecular oxygen. For sulfhydryl compounds -- glutathione[18] and captopril,[19] the rate of decomposition is markedly enhanced by an increase in temperature and relative humidity. In the former case, the oligopeptide decomposes autocatalytically, and it was rationalized that glutathione decomposed in a saturated solution on the crystal surface. The rate was proportional to about 3 to 5 powers of humidity. In the latter case, rates of decomposition of captopril were zero order, and the postulate of solution degradation on the crystal surface was once more invoked.

The initial rate of decomposition of sulpyrine at 80°C under oxygen gas also depended on water content.[20] When the amount of water present was insufficient to dissolve all the sulpyrine, the rate was zero order; in the presence of a large amount of water, the rate was first order. The rate was also first order in the partial pressure of oxygen.

Solvates or hydrates are usually more chemically stable than their parent anhydrates because the solvent or water stabilizes the crystal lattice and results in a higher melting (or desolvation) point. However, the case of dialuric acid is atypical[21] -- it is unstable in solutions exposed to air and exhibits a half-life of 30 seconds at room temperature. In marked contrast, desolvated crystals require 60 days at 76°C for complete oxidation, whereas for the hydrate, the reaction begins at several nucleation sites and is nearly complete within two hours at room

temperature and high humidity. The anhydrate has approximately the same crystal structure as the monohydrate (pseudomorphism) and contains voids previously occupied by water molecules. Surprisingly, these voids do not facilitate oxidation, thus suggesting that there are factors other than the ability of oxygen to permeate the crystal lattice which affect solid state oxidation reactions. Clearly, exposure to high humidity appears to be one of them.

C. Light

There are many pharmaceutical compounds, such as vitamins A, B, C, D and E, morphine, phenothiazine derivatives, sulfonamides, antibiotics, local anesthetics and steroids, that are subject to photolytic deterioration. This type of degradation, normally auto-oxidative in nature, is often catalyzed by metals, mediated by free radicals, and is readily affected by conditions of pH and moisture.

One simple mechanism for photolytic degradation was illustrated by Eble and Garrett[22] for the reaction in Scheme II where molecule A absorbs a quantum of light energy to form an excited species A* with a rate constant k_1. The photolytically activated molecule A* may either return to the ground state with a rate constant k_2 or react with a second molecule and decompose into products (P) with a rate constant k_3. In the steady state condition, $dA^*/dt = 0$ and

$$k_1 \cdot I_{abs} = (k_2 + k_3 A)A^* \qquad \text{(Eq. 3)}$$

where I_{abs} is the intensity of light absorbed. The rate-

determining step may be the step in which the activated molecule reacts with, or transfers its energy to, another molecule in the crystalline lattice. The probability of deactivation occurring increases as the number of reacted molecules adjacent to the activated molecule decreases, since

$$-\frac{dA}{dt} = \frac{dP}{dt} = k_3 \cdot AA^* \qquad \text{(Eq. 4)}$$

Substitution of the value of A* from Equation 4 gives

$$-\frac{dA}{dt} = k_1 \cdot I_{abs} \cdot \frac{A}{A + \frac{k_2}{k_3}} \qquad \text{(Eq. 5)}$$

If the mechanism is valid, first order kinetics result when $k_2 >> k_3$, i.e., when the rate of deactivation greatly exceeds the rate of product formation. Conversely, zero order kinetics prevail when $k_3 >> k_2$.

Photolysis of fumagillin proceeds at about the same rate in the presence of air as in its absence.[22] Since its reaction products are highly susceptible to oxidation, however, the photolytic activation step must be rate-determining. The free radicals produced by chain activation become entrapped in the crystalline lattice and retain their integrity until scavenged. Activation takes place primarily on the crystal surface, only

$$A + h\nu \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A^* + A \xrightarrow{k_3} P$$

SCHEME II

as far into the crystal as light can penetrate. Therefore, the extent of photolytic degradation is limited and fumigillin is observed to remain largely intact.

Interesting kinetic profiles have been observed when the color of dyes in solid dosage forms changes on exposure to high intensity light.[23-25] The degradation pattern given in Figure 9 (see previous paper) determined by reflectance spectroscopic analysis, consists of three consecutive first-order decays. The changes in slope were not attributed to three different mechanisms with different rates, but rather to a probable alteration in tablet surface which allowed the fading of subsequent layers. On the premise that photolysis is a surface phenomenon, it was not unexpected that the fading rate was greatest during the initial stage of irradiation. Accordingly, the interior of the tablet was unaffected. Generally, the thickness of the faded layer was observed to reach a maximum, at which time the tablet surface appeared white, and further exposure induced no additional degradation.

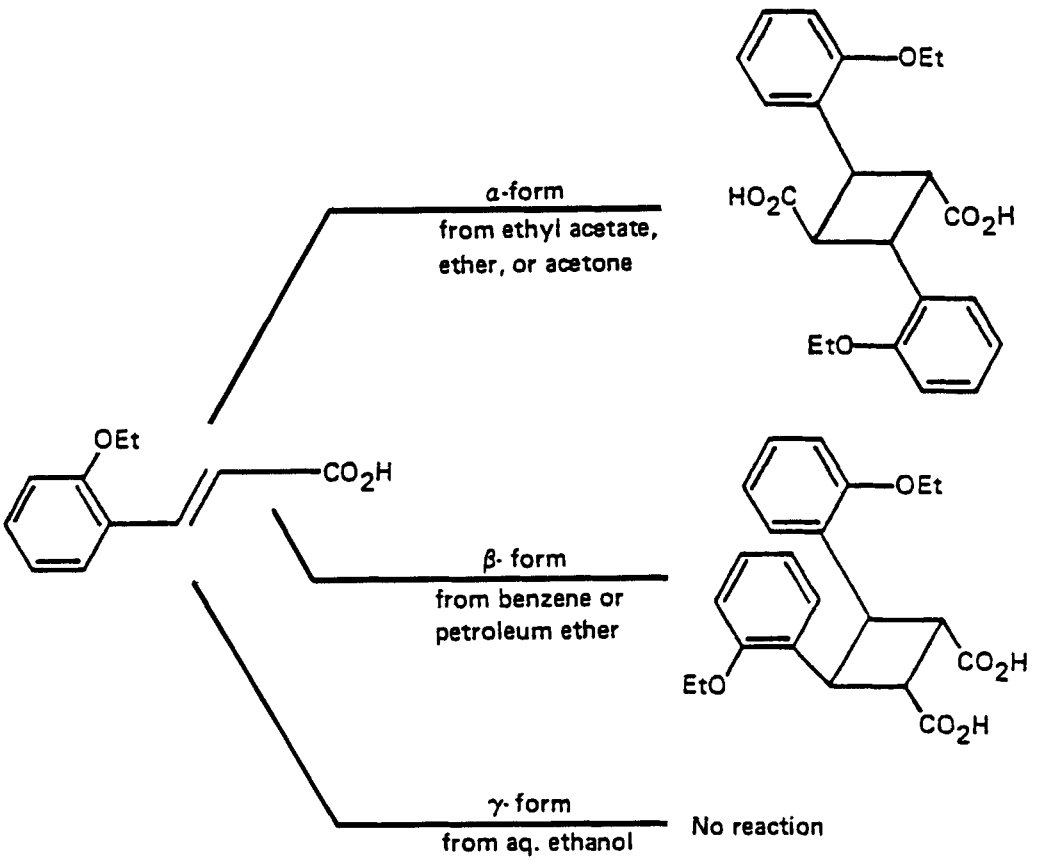
Both intensity of illumination and spectral character of radiation determine the effect light exerts on drug stability. Even though ultraviolet light is of lower energy than X- and γ-rays, it often inflicts as much photolytic damage. A quantum of ultraviolet light (e.g., at 253.7 nm, one quantum = 5 eV) contains energy sufficient to cleave a C-H bond of 3-4 eV bond energy. A UV-sensitive formulation can be very effectively protected against light degradation simply by packaging in amber bottles which restrict the transmittance of any incident energy

below 470 nm. An alternative approach that has met with very limited success involves the addition of an excipient which possesses high absorptivity and good stability in the desired UV region where the drug absorbs the damaging radiation. Applying a thick polymer film containing a high concentration of UV-absorber is an alternative approach. Of course an opaque capsule shell would be just as effective.

D. Crystalline State

Many crystalline organic compounds can exist as more than one polymorphic structure. If the molecules of such a compound assume a different relative geometry by breaking old or forming new bond associations during transformation from one polymorph to another, the transformation can be considered to be a solid state chemical reaction. Accordingly, the reactant polymorph and product polymorph might exhibit very different chemical behaviors. Scheme III[26] illustrates the contrasting products that arise from the (2+2)photocycloaddition of three polymorphic forms of o-ethoxy-trans-cinnamic acid.[27] Here the stereochemistry of the product (head-to-head vs head-to-tail) is determined by the spatial orientation and distances separating the overlapped double bonds of the molecules in the crystal lattice. Irradiation of the compound in solution produces only trans-cis isomerization with no dimerization.

The variation in light sensitivity exhibited by the anils (salicylidineanilines) has actually been used to classify their polymorph types.[28] Many anils undergo a reversible first-order change in color upon ultraviolet irradiation. The α-anils are



SCHEME III

photochromic and change color only upon irradiation, independently of temperature. The β-anils are thermochromic, however, changing color only as a function of temperature, and not from exposure to light. Such differences in behavior between polymorphs of the very same compound support the concept that only minimum atomic or molecular movement is necessary for the reaction to proceed. More specifically, the photochemical reactivity of a compound is directly dependent on the geometrical

relation between the nearest neighbor molecules in their crystal lattice.

Despite certain problems introduced by variations in crystalline form, such as bulk drug batch reproducibility, etc., these properties can actually be exploited by the pharmaceutical chemist. For example, exposure of methyl prednisolone to high temperatures and/or humidity brings about its fairly rapid, though limited, degradation. Although the extent of degradation plateaued in all cases, the Form IIb crystal form, a tert-butyl alcohol solvate, plateaued at a slightly higher level of degradation than either its desolvate Form II or its polymorph Form I.[29] Yet only its most stable crystal need be chosen for formulation. Furthermore, crystalline compounds are generally more chemically stable than their amorphous or glass counterparts. Crystalline potassium penicillin has been observed to withstand dry heat for several hours without significant degradation, while its amorphous form under the same conditions loses considerable activity.[30] Thermal decomposition rates for amorphous samples of penicillin G potassium, cephalothin sodium, cefamandole sodium, and cefamandole nafate were found to be at least one order of magnitude less stable than their corresponding crystalline form.[31] Absorbed water generally increased both the number of decomposition products and the net decomposition rate. Also, the degree of crystallinity of cephalothin sodium, as determined by solution calorimetry and X-ray diffraction, was found to correlate closely with stability.[32]

If the anhydrous form of a compound is either non-crystalline or is crystalline with a low melting point, sometimes it is advantageous to form a hydrate, providing the water of hydration is tightly bound. However, if the hydrate crystal lattice becomes ruptured, the water molecules either leave behind hydrophilic voids which are easily accessible by humidity, or they themselves become more reactive by reason of their mobility and spatial orientation. Therefore if a hydrate is employed, its phase transformation must be controlled by appropriate retardant excipients or by constant exposure to high humidity. However, the latter is unacceptable because if the temperature conditions are cyclical, chemical degradation of the anhydrate will undoubtedly occur.

Crystalline form of the monobactam, aztreonam, provides an excellent example of how polymorphism affects solid state stability.[33] Samples initially obtained were needle-like (α-form) and in the presence of high humidity (37°C/75% R.H.) decomposed via β-lactam hydrolysis, exhibiting a half-life of only ∿6 months. These crystals were harvested from an alcohol/water mixture, and it was postulated that during solvent removal, aqueous pores were formed which allowed facile, reversible expansion of the lattice to accommodate several molecules of water when re-exposed to moisture. By excluding moisture from the crystallization solvent, dense spherical crystals (β-form) were obtained which exhibited a remarkable resistance to water vapor absorption and thereby substantially increased the shelf-life to several years.

Abstracting water from the solvent may not, however, always nucleate a more stable form. For instance, the cephalosporin, cephradine, is a porous crystalline material which is extremely susceptible to oxidation (forming cephalexin) especially in the presence of moisture and has to be processed under a dry inert atmosphere and stored in tightly sealed containers. On the other hand, when isolated from an aqueous solvent, the higher melting crystalline dihydrate form is obtained which is exquisitely stable to moisture and oxygen and requires no special handling.[34] It becomes readily apparent from these two examples that knowledge of the effect of solvent of crystallization can have substantial implications towards the commercialization of a drug product.

E. Particle Size and Shape

Predictably, topochemical degradation reactions proceed faster if exposed surface area increases, as with smaller particles. In fact, the correlation between particle size and rate of dehydration of kaolinite has been shown to be linear over the first half-life.[35] The nonlinearity observed thereafter is attributable to total dehydration of the smaller particles occurring in the presence of only partially dehydrated large particles. Larger crystals are also less reactive in nucleation-controlled reactions, presumably because fewer nuclei exist to propagate the reaction. Anomalies in DSC data of hydrates can be attributed to nonhomogeneous samples. Smaller particle sized samples dehydrate faster than larger sized ones, sometimes leading to a bimodal thermogram. Therefore it is important that particle size

of the samples is well characterized. Of course if the heating rate is very slow, these differences will disappear.

Reactions involving grain boundary diffusion, however, offer an apparent anomaly to the general cases discussed above. In such reactions the rate constant is directly proportional to the square of the particle radius[36] and, therefore, larger particles exhibit greater reactivity. This can be attributed to the relative ease with which reactant can pass through a sample comprising larger particles.

Another instance in which smaller particles were less reactive than larger particles was reported for aspirin anhydride.[37] This result was explained by the fact that larger particles contained trapped solvents which liquefy and dissolve more solid to hasten the decomposition. This explanation was later challenged[38] because when these larger crystals were evacuated overnight at 85°C to remove any entrapped solvent, the decomposition profile did not change. Microscopic examination of half-reacted acetyl-5-nitrosalicylic acid showed that the larger crystals were completely covered with product whereas the smaller particles were only partially covered, thus suggesting that the reaction nuclei were not uniformly distributed throughout, and that smaller particles seemed to contain fewer nuclei. Large particles of captopril in the presence of excipients also undergo oxidation to the disulfide faster than smaller particles.[19]

Crystal habit in addition to size can also affect the reactivity of solids. Two morphologically different crystals,

column-shaped and ramified, were sorted under a microscope from a recrystallized batch of acetyl-5-nitrosalicylic acid.[39] The reactivity of the ramified crystals after exposure to humidity was about 5 times greater than that of column-shaped crystals. The difference in rate of decomposition was explained by the fact that the more reactive crystals when examined under a polarizing microscope exhibited many more cracks, grain boundaries and defects on their surface which provided regions for growing product nuclei. The contributions from surface area and polymorphism were effectively ruled out and since the energies of activation for the two rates were the same, the explanation for the rate differences seems to be consistent with morphological character.

F. Mechanical Manipulation

Although manufacturing of most solid dosage forms requires compression forces at some stage, very little is known about the interactions that can occur between ingredients during, and just after, such compression. Nevertheless, much evidence exists to prove that solid-solid interactions, even polymorphic transformations, can arise upon mechanical handling.[40-42] The amount of pressure and the duration for which it is applied, as well as the number of compressions to which a formulation is subjected, are all factors which contribute significantly to the extent of ingredient modification and interaction. If water molecules preferentially exit from ends of crystals, then mechanical handling which breaks the crystals longitudinally

will accelerate dehydration by reducing the length of the tunnels through which the molecules have to negotiate to escape.[43]

The presence of moisture serves only to enhance the effect of mechanical handling. Techniques such as DRS and DSC reveal a linear relationship between the force of compression and the rate of degradation induced by the solid-solid interaction of ingredients in a formulation containing p-aminobenzoic acid, oxalic acid and water.[42] Similarly, the rate of inactivation of alkaline protease has been shown to have a direct dependence on the compression parameters used in tabletting the enzyme.[44]

For the reaction between succinic acid and paranitraniline, the conversion to the addition product decreased with increase in compaction pressure. This implied that pore surface diffusion was significant because bulk or volume diffusion involves an increase in conversion with a decrease in the porosity of the mixed powder system.[45] The phase boundary controlled reaction model for the sphere reacting from the inward surface fit the data quite reasonably.

Grinding conducted at high amplitude in a vibratory ball mill and compression at high pressures on a tablet die were shown to cause interconversion and desolvation of several phenylbutazone polymorphs.[46] The effect of mechanical manipulation on the solid state properties of powders in the formulation and processing of solid dosage forms was reviewed by York.[47] Crystal growth can also be induced by compression. For instance, the growth of "whiskers" on the surface of caf-

feine anhydride and ethenzamide tablets could be increased simply by increasing the compression force.[48] Apparently, compression shatters crystal integrity and creates many new surfaces, thus exposing screw dislocations and other defects. These areas are particularly susceptible to super-saturation in a humid atmosphere and therefore they become the source of nuclei for whisker growth.

For solvates or hydrates, grinding can cause the compound to become more chemically unstable. The bonding force between the water of crystallization and the drug molecule within the hydrate is weakened by grinding, thus liberating water molecules which can then participate in hydrolysis reactions.

There are several approaches to minimizing the degradation that many formulations will incur upon processing. The frictional forces of grinding can be avoided by using a wet granulation process, as long as the granulation solvent itself does not induce polymorphic changes. Alternatively, since more severe compression is necessary to prepare a tablet, encapsulation might provide a suitable alternative for a pressure-sensitive formulation. In the case of a formulation that is also moisture-labile, however, the advantages of this latter approach must be weighed against the stabilizing effect a hard tablet can offer by retarding moisture penetration.

If a reversible reaction occurs and a gas is one of the reaction products, the rate of reaction can be markedly reduced by pelletization or by increasing the mass of the sample. Re-

tardation is accomplished through increasing the partial pressure of the gas developed within the powder compact. Such behavior was observed for the isothermal decomposition of barium carbonate (phase boundary controlled) and strontium carbonate (diffusion controlled).[49]

G. Complexation/Excipient Interactions

Drugs can interact with excipients or other drugs via a number of bonding mechanisms as previously discussed. Such interactions can cause considerable differences in dissolution rates, equilibrium solubilities, partition coefficients, etc., as well as in chemical stability.[50] And these changes can be either beneficial or detrimental to the formulation. Consider, for instance, the "protective shield" offered by the macromolecules cyclodextrin, hydroxypropylmethylcellulose and polyvinylpyrrolidone, which can improve via complexation the solid state stability of such reputedly labile compounds as the prostaglandins.[51] (Note that the isomerization of Prostaglandin A_1 is actually catalyzed by cyclodextrin.[52]) Similarly, benzocaine hydrolysis can be minimized by surrounding the drug molecule by cyclodextrin[53] or by the addition of caffeine with which the drug forms favorable hydrogen bonds.[54] Stabilization of vitamin D_3 is considerably enhanced by complexation with β-cyclodextrin.[55]

Too often, however, these interactions promote degradation. In such cases, the complexing agent should be either replaced or separated from the active compound. This can be

achieved by coating either of the interacting ingredients or by preparing some kind of partitioned dosage form. Thermal analysis is particularly useful in detecting such interactions, since the phase diagrams that can be constructed from thermal data will indicate the tendency of a multicomponent system to form a molecular compound upon melting.[56] If an interaction is so observed, this in turn implies that a similar interaction might easily occur in the solid state with the same stoichiometry, particularly under the stimulus of heat generated on compression or mixing. Studies to determine the effects of the interaction on solid state stability should then be conducted. Examples in which ingredient interaction is known to accelerate decomposition include dicloxacillin in the presence of stearic acid[57] and aspirin in the presence of its degradation product, salicylic acid.[58]

Drug-excipient interactions can be efficiently screened using DSC. Generally, any aberration in the thermogram raises concern over the potential use of any excipient. If a drug is moisture sensitive, addition of a weighed quantity of water to the drug-excipient mixture, followed by a sealing of the crucible, reveals a depression in the melting point of the drug proportional to the amount of water added, but dependent on the absorption capacity of the excipient. Direct compression excipients for the formulation of captopril tablets were chosen in this way.[59]

For antibiotic powders which are to be employed parenterally, use of a soluble salt is desirable. If, however, the

salt is hygroscopic or the resulting lyophile is amorphous and therefore chemically and physically unstable, then a physical mixture of the crystalline drug and an alkanizing agent can solve the problem. Selection of the best excipient for cephradine was accomplished through DSC studies of mixtures of the drug with meglumine, tromethamine, anhydrous sodium carbonate and trisodium phosphate dodecahydrate.[60] The only mixture which exhibited similar thermograms to the original individual components was the one containing sodium carbonate, and this excipient was selected for the commercial dosage form. Similar studies were employed for the selection of arginine as the preferred excipient for aztreonam.[61] In this case, sodium carbonate was also compatible, but the volume of carbon dioxide released upon reconstitution and subsequent reaction with the strong acid group of the aztreonam molecule was excessive and for this reason use of this excipient was precluded.

Two particularly reactive silicate surfaces which interact with drug molecules are colloidal silica and montmorillonite. In the former case, hydrophobic drugs adsorbed onto the hydrophilic silica surface become susceptible to hydrolysis because of the hydrogen bonding between the adsorbant and the adsorbate. In the latter case, drugs interact by ion exchange and penetrate into the interlayer space of the clay. Decomposition of the drug depends on its molecular dimensions and orientation of the reactive group vis a vis the surface of oxygen atoms of the silicate. These types of interactions are usually studied using X-ray diffraction and IR spectroscopy techniques.

Reactions can also occur between metallic adjuvants and certain drugs. A study of the interaction between magnesium oxide and isoniazid[62] led to the conclusion that a metal-ion complex was formed via chemisorption. Other drug-metallic excipient interactions that have been reported include those of oxytetracycline, anthracene, phenothiazine, or hydrochlorothiazide with magnesium oxide, magnesium trisilicate or magnesium hydroxide.[41] Tetracycline, bishydroxycoumarin, and methantheline have also been shown to interact with a wide range of metallic excipients.[63]

Non-metallic surfaces can influence the course of a solid state reaction. For instance, when heated in the presence of microcrystalline cellulose, alkoxyfuroic acids produce carbon monoxide, whereas when the neat solid compound itself is heated, only carbon dioxide is formed. The former reaction is facilitated by the compound dissolving in its own decomposition product. By spreading out onto the excipient it produces many more contact points.[64]

Even though an excipient itself may prove inert to the active component of a formulation, it may still have some surface impurities, such as unreacted metals or residual solvents, whose origin lies in the processing of the excipient. These impurities can then react and/or degrade the drug, particularly in a sorbed moisture layer, and reduce its activity. For example, surface ferric ion in certain clays has been shown to accelerate oxidative degradation of hydrocortisone. Occasionally, traces of formaldehyde can be found in starch, and traces of heavy metals can be found in talc. Providing that the impurities are not catalytic,

however, and their reaction with the drug requires a definite stoichiometry, the degradation should effectively cease once the impurity has been consumed. If the drug form proves to interact with all excipients, then an alternative isomer, polymorph or salt form which exhibits a higher melting point or is less hygroscopic (and less soluble) should be sought. Salt forms suitable for drugs have been previously described.[65] In general, calcium salts are less hygroscopic than sodium potassium or amine salts. The nafate salt of propoxyphene has been used to avoid an incompatibility with aspirin and codeine, and tylosin phosphate is used in pelletized animal feeds rather than the corresponding tartrate salt. Excipients may be used to prevent two drugs from interacting, but if this concept fails, means to accomplish total separation can be utilized, i.e., a multilayered tablet or a tablet within a capsule. A commercial example of the latter is the propranolol-bendroflumethiazide capsule, inside of which is a mini-tablet of bendroflumethiazide surrounded by sustained release propranolol pellets.

THE PHYSICAL PHARMACY STABILITY SCREEN

No new drug enters the marketplace without accruing a lengthy history of development. Its course has been plotted by a multidisciplinary team that strives to make the progress of a promising candidate as efficient as possible. Once it has been established that the pharmacological profile of a compound is desirable, it begins its journey to the clinics. Important physicochemical data must be collected and a basic dosage form chosen. The physical pharmacist must then evaluate the inherent stability

of the compound and be able to predict with some accuracy its stability under conditions of formulation. This could involve a multitude of stability tests; however, only small quantities of drug are usually available at this stage of development. The scope of such testing must therefore be determined judiciously, so that minimal amounts of both drug and time will be consumed in obtaining a maximum amount of information valuable to the formulation chemist. Challenging the compound with a "physical pharmacy stability screen" is one very efficient way to gather this information, which is to be used as a guide in formulating clinical supplies.

Firstly, the stability screen evaluates the stability of the pure drug under a variety of conditions. The compound is subjected to storage under air and nitrogen, to high-intensity light, and to moisture, all at several temperatures. The effect of compression is evaluated by comparing the stability of loose powder to that of a compressed disc. If the drug proves sensitive to moisture, compression may provide some protection. If the drug reacts adversely to compression, grinding or mechanical shear, lyophilization or wet granulation from a volatile solvent should be considered. The hygroscopicity of the drug is also evaluated.

Solvolysis often occurs within a solid, most frequently in the moisture adsorbed on excipient surfaces. It can also result, however, from the residue of a granulation solvent or from entrapped solvent of crystallization. Both hot-stage

microscopy and TGA are helpful in determining the presence of such solvent molecules and their possible role in catalyzing decomposition. Routine solution stability studies are also conducted. If the drug is ionizable, its stability is measured on either side of its pK_a, hopefully to assist in the identification of decomposition products. Solutions of the drug in the granulation fluid are also monitored for stability in case an interaction can occur, such as transesterification with alcohols.

Many analytical procedures can be used to implement the screen, e.g., TLC densitometry, DRS, DSC, TGA and hot-stage microscopy. With these methods of analysis, the major portion of the screen can be conducted with as little as 1 g. of material.[50,66-70]

Should quantitation of the reaction rate (e.g., fraction reacted, weight gain or loss as a function of time) be available at the early stage, it is advantageous to attempt to linearize the data. This can be accomplished by computer fitting the data to the kinetic models described earlier -- power law, contracting geometry, 2D diffusion controlled, Jander, Prout-Tompkins, second order, first order, etc., when n can vary from 3, 2, 1, 1/2, 1/3, 1/4, etc. It is possible that more than one equation will fit the data, and it becomes difficult to choose the correct one. By least squares fit at several temperatures, the best model can be selected. The rate constants can then be treated in the Arrhenius fashion to extrapolate the rate constant to room temperature. Such an

exercise is acceptable only for making predictions in the early stage; later on in the development sequence, it is important to understand why a law is obeyed and to have knowledge of the underlying assumptions and implications in applying these models.

The physical pharmacy stability screen provides a logical, organized approach to characterizing the stability and compatibility of the drug prior to evaluation in humans. It assists in establishing an adequately stable, basic formulation for clinical trials. More subtle modifications of the formula, for the purpose of enhancing bioavailability or further increasing stabilization, can be made at a later stage. These might include complexation, microencapsulation, film-coating, preparation of a two-layer tablet, excipient substitution or special packaging. If it is necessary to change functional groups or salt forms, the screen will hopefully indicate this early in the drug's development. With the information derived from the screen, a compound should progress smoothly through clinical trials, without encountering delays caused by uncharacterized problems of stability.

SUMMARY

This article summarizes the scope of the area of solid state stability of formulations. It is clear that this is a broad, relatively unexplored discipline that needs a more fundamental approach than simple reporting of potency retention after stressing mixtures of drugs and excipients. However, if a basic understanding is achieved, there are a

multitude of strategies that can be employed in manipulating drug stability. The high cost of clinical trials precludes unnecessary delays, drug modification, or formulation changes during development. The physical pharmacy stability screen provides at least a systematic procedure to evaluate physico-chemical properties of a new drug entity and reveals in advance any undesirable drug-excipient interactions that, if left undetected, could severely impede its progress towards commercialization.

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