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EXPERT REVIEW

Impact of Excipient Interactions on Solid Dosage Form Stability

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ABSTRACT Drug-excipient interactions in solid dosage forms can affect drug product stability in physical aspects such as organoleptic changes and dissolution slowdown, or chemically by causing drug degradation. Recent research has allowed the distinction in chemical instability resulting from direct drug-excipient interactions and from drug interactions with excipient impurities. A review of chemical instability in solid dosage forms highlights common mechanistic themes applicable to multiple degradation pathways. These common themes include the role of water and microenvironmental pH. In addition, special aspects of solid-state reactions with excipients and/or excipient impurities add to the complexity in understanding and modeling reaction pathways. This paper discusses mechanistic basis of known drug-excipient interactions with case studies and provides an overview of common underlying themes. Recent developments in the understanding of degradation pathways further impact methodologies used in the pharmaceutical industry for prospective stability assessment. This paper discusses these emerging aspects in terms of limitations of drug-excipient compatibility studies, emerging paradigms in accelerated stability testing, and application of mathematical modeling for prediction of drug product stability.

KEY WORDS capsules · compatibility · degradation · dissolution · excipients · granules · impurities · mechanism · reaction · stability · tablets

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ABBREVIATIONS

Alu	aluminum
API	active pharmaceutical ingredient
ARP	Amadori rearrangement product
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
GC	gas chromatography
HCl	hydrochloride
HCTZ	hydrochlorothiazide
HDPE	high density polyethylene
HPLC	high performance liquid chromatography
HPMC	hydroxypropyl methylcellulose
HPO	hydroperoxide
ICH	international conference on harmonization
LC/MS	liquid chromatography tandem with mass spectroscopy
MVTR	moisture vapor transmission rate
NF	National Formulary
NMR	nuclear magnetic resonance (spectroscopy)
PEG	polyethylene glycol
pH_{max}	pH of maximum solubility
PVA	polyvinyl alcohol
PVP	polyvinyl pyrrolidone (povidone)
PhEur	European Pharmacopeia
PVP-VA	polyvinylpyrrolidone-vinyl acetate copolymer
PXRD	powder X-ray diffraction
SDMT	sorption desorption moisture transfer
ssNMR	solid state NMR
USP	United States Pharmacopeia

INTRODUCTION

Safety and efficacy are the main considerations in new drug research and development. To satisfy these requirements,

dosage forms are designed with an intent to provide adequate and reproducible bioavailability of the drug, while ensuring its physico-chemical stability over the designated shelf-life. While the chemical stability of a molecule is an inherent property governed by its chemical structure, a drug's stability in a drug product also depends on the dosage form-related characteristics—such as the presence of other components (excipients), manufacturing process, package, and storage conditions. Drug formulations are designed to maximize the physico-chemical stability of the drug contained therein, in addition to ensuring drug bioavailability and dosage form manufacturability. In this context, drug product instability is an area of continued research not only because of the diversity in molecular structure and formulation variables; but also to develop fundamental mechanistic understanding of its causes, which helps design mitigation strategies that form the cornerstone of successful drug product development and commercialization.

Physical instability refers to changes in the characteristics of a drug product that do not involve chemical bond formation or breakage in the drug molecule's structure. Physical instability can be exemplified by changes in appearance, drug release, polymorphic form, taste, odor, or tensile strength; or phenomena such as crystallization in amorphous systems, physical attrition, segregation, adsorption, and vaporization.

Chemical instability, on the other hand, refers to changes in the chemical structure of the drug molecule in the dosage form. These are related to drug degradation, resulting in reduced potency (drug content) and formation of other molecules (degradation products or degradants). Formation of degradation products is a toxicity or safety concern, while reduction in potency is an efficacy concern. Levels of degradants are closely regulated in dosage forms with well-defined detection, identification, and toxicological qualification limits based on their maximum permissible daily intake as clearly articulated in ICH guidelines.

Drug-excipient interactions can lead to both physical and chemical instability in solid dosage forms. These interactions could be due to interactions of drugs with excipients or reactive impurities in excipients (1). Early in drug product development, such instability in the dosage form is sought to be identified and avoided by prospective screening studies, such as excipient compatibility testing (2,3). Nevertheless, a thorough mechanistic understanding of the underlying causes of such instability is important in mitigating or minimizing their occurrence and the associated risks. This review will highlight some of these pathways of instability and recent developments in their mechanistic understanding and mitigation strategies.

GENERAL CONSIDERATIONS

Some of the common underlying mechanisms by which excipients affect drug stability in the dosage form are by altering moisture content in the dosage form, changing micro-environmental pH in the dosage form, acting as general acid/base catalysts, directly reacting with drug, or becoming source of impurities that can either directly react with drug substances or participate as catalysts in the drug degradation (2). Other changes that the excipients may cause to alter the physical and/or chemical form of the drug in the dosage form are mediated through mechanisms such as complexation, ion-exchange; polymorphic transformation of crystalline or amorphous forms; and the formation of eutectic or solid solutions.

Typical Aspects of Solid State Reactions

A common degradation pattern in the pharmaceutical systems is rapid initial degradation *via* first order kinetics, followed by progressive reduction in the rate of degradation (4). This is observed when the reaction is dependent upon a depleting constituent of the system, such as water or small quantities of reactive impurities in the drug or excipients. Slowing of first order degradation kinetics to a pseudo-equilibrium level is also observed in solid-solid surface reactions where impurity accumulation on the surface is responsible for the slowdown (2). For example, first order degradation kinetics with pseudo-equilibrium phenomena were reported for the degradation of thiamine hydrochloride (5) and ascorbic acid (6). The degradation pathways can be diverse, such as zero order degradation of aspirin in suspension (7); first order hydrolysis of triazolam (8); second order interaction of isoniazid with reducing sugars (9); consecutive first order degradation reactions of hydrocortisone hemisuccinate (10); and the reversible and parallel degradation pathways of pilocarpine solution in the neutral pH region (11).

Drug degradation pathways and patterns in solid dosage forms can differ from those in the liquid state due to the heterogeneity of the solid state and changes in physical state of the drug and other components with time (12). These differences lead to additional kinetic restrictions and modifications of reactions occurring in the solid state. Examples of such cases include (a) diffusion controlled reactions, (b) solid-state reactions rate limited by the formation and growth of reaction nuclei, (c) reactions that form a liquid product, and (d) reactions limited by amount of adsorbed water.

Diffusion Controlled Reactions

Diffusion controlled reactions are reactions of a solid reactant dispersed in another reactant, which is considered as a continuous medium. This mechanism is applicable to the reactions of solids with gases, liquids, or solids. The reaction product, solid or liquid, is deposited on the surface of the solid reactant as the reaction proceeds.

In a diffusion controlled reaction, the buildup of a layer of reactants and products on the surface of drug particles is a function of concentration, time, diffusion coefficient of reacting species, and the volume of the product already formed. Assuming spherical particles of uniform radii reacting throughout the surface with instantaneous surface nucleation and diffusion being the rate limiting step, the thickness of interface, x, that contains both the reacting components and the product is given by Eq. 1.

$$x^2 = 2D \times V_m \times C_0 \times t \tag{1}$$

where, D is the diffusion coefficient of the slowest transporting component, V_m is the volume of product formed from 1 mol of the slowest penetrating component, C_0 is the concentration of the penetrating species on the interfacial boundary, and t is time (13).

The isothermal rate of formation of the product, k, is inversely proportional to time, t, and a function of the fraction decomposed, α. Thus,

$$f(\alpha) = kt \tag{2}$$

A plot of *f(α) versus t* gives a straight line if the right reaction kinetics model is used, which depends on the underlying assumptions about the mechanism controlling the reaction and the size and shape of reacting particles. In a diffusion controlled reaction, *f(α)* is given by the parabolic Eq. 3 for a one dimensional diffusion process with constant diffusion coefficient, Eq. 4 for two dimensional diffusion controlled process in a cylinder, and Eq. 5 for a three dimensional diffusion controlled process in a sphere.

$$f(\alpha) = \alpha^2 \tag{3}$$

$$f(\alpha) = (1-\alpha)\ln(1-\alpha) + \alpha \tag{4}$$

$$f(\alpha) = \left[1 - (1-\propto)^{\frac{1}{3}}\right]^2 \tag{5}$$

Equation 5 was proposed by Jander (14) and has been used to describe the thermal decomposition of mercuric oxalate, thiamine diphosphate, and propantheline bromide (15).

Crystal Imperfections as Reaction Sites

Reactions of crystalline drug in the solid state can be limited to the imperfection sites in the crystal, that can act as sites where the drug preferentially reacts (2). Solid state reactions of this type limit the growth of impurity, x, by the presence and growth of crystal imperfections sites as given by Eq. 6.

$$\frac{dx}{dt} = k \times N = k \times t^n \tag{6}$$

where N is the number of crystal imperfections, n is a constant, t is time, and k is the rate constant. This equation was used to describe the initial hydrolysis rate of meclofenoxate hydrochloride (16), propantheline bromide (17), and aspirin (18).

Reactions That Form a Liquid Product

Reaction kinetics of solids leading to the formation of liquid products is complicated by reactions occurring in two media: the solid state and the liquid state (2). In this case, the overall reaction rate is obtained as a summation of the reaction rates in both states as per Eq. 7.

$$\frac{dx}{dt} = k_s \times (1 - x - Sx) + k_l \times Sx \tag{7}$$

where, S is the solubility of the drug in the liquid state formed, t is time, and k_s and k_l are the rate constants in the solid and the solution states, respectively. In this equation, *Sx* is the product of fraction degraded and the solubility of drug in the liquid phase, representing the molar fraction of drug in solution. Thus, *(1-x-Sx)* represents the molar fraction of the drug in the solid state. This equation can be integrated to a linear form Eq. 8.

$$\ln\left[1 + \frac{S \times (k_l - k_s) - k_s}{k_s}\right] = (S \times (k_l - k_s) - k_s) \times t \tag{8}$$

This equation, known as the Bawn equation, was used to describe the decarboxylation rate of benzoic acid and alkoxyfuroic acid derivatives (19,20).

Reactions Limited by Amount of Adsorbed Water

Reactions occurring in the adsorbed moisture layer are limited by the amount of adsorbed water. Drug degradation in such cases can be described by the following apparent or real zero order or first order Eqs. 9 and 10, respectively.

$$\frac{dx}{dt} = k \times V \times [H_2O] \tag{9}$$

$$\frac{dx}{dt} = k \times V \times [C] \times [H_2O] \tag{10}$$

where V is the volume of adsorbed moisture, *[H_2O]* is the molar concentration of water, *[C]* is the drug concentration, and k is the reaction rate constant. The term $V \times [H_2O]$ allows the calculation of amount of water. This model was

used to explain the degradation of aspirin (21), sulpyrine (22), and 4-aminosalicylic acid (23).

Model Independent Approaches

Model-fitting approaches involve the statistical analysis determination of best fit model for a given set of data. The use of statistical approaches to best fit the data to one of possible mechanistic models often leads to similar statistical fit to more than one kinetic model (24). In addition, solid-state reaction kinetics are not only inherently different from the kinetics of reactions in homogeneous phases, such as the solution state; but can also involve more than one rate limiting step. For example, the kinetics of loss of water involved in the dehydration of hydrates of drugs can include elements of both nucleation and diffusion controlled reactions. For crystalline drugs, dehydration usually begins at the sites of crystal defects, nucleation sites, where lattice strain leads to greater energy and molecular mobility of drug molecules in the immediate vicinity of the defect. This leads to the formation of a new solid phase, the dehydrated form of the drug, at the nucleation sites. Further progress of the reaction could involve the rate limiting steps of either the growth of nuclei or the diffusion of water. Further, the dimensionality of the diffusion of water depends on the crystal structure of the hydrate since water molecules tend to escape from the crystal lattice along certain directions, known as water channels. Thus, dehydration kinetics could involve different and/or sequential rate limiting steps depending on the nature of the drug hydrate crystal and experimental conditions. This was illustrated for the dehydration of nedocromil sodium trihydrate (25).

These considerations and limitations in model fitting lead to the use of model-independent or model-free approaches. An example of the model free approach is isoconversional analysis, which allows the calculation of the reaction activation energy, E_a, as a function of the extent of reaction and without assumption of a single reaction model. Thus, any variation in E_a from a constant value as the reaction proceeds could indicate a change in the rate limiting step of the reaction.

Khawam and Flanagan presented an example of the complementary application of both model-dependent and model-free methods of analyses of solid-state reaction kinetics (26). They applied these methods to the desolvation of sulfameter solvates with tetrahydrofuran, dioxolane, and dioxane, monitored by thermogravimetry. Using the model-based approach, the authors encountered difficulty in finding the best-fit reaction model for the kinetic data, since the statistical fit parameters for several models were similar. The application of the model-independent isoconversional analyses helped select the best-fit model. This example suggests that the application of model independent approaches may not be mutually exclusive of the model-dependent approaches, but the two may complement each other (25).

Role of Water (Moisture)

Most drugs and excipients contain water, which may be either bound or unbound. The bound water is the water of hydration or crystallization which is so tightly incorporated in the physical form of the material that it is practically immobile and is not available for reactions. This is exemplified by the stability of crystalline hydrates of hydrolytically unstable β-lactam antibiotics, wherein the water is incorporated in the crystalline matrix and is not available for reaction. As expected, the stability of these compounds is highly dependent on their crystallinity (27). In contrast, unbound water usually exists in equilibrium with the atmosphere in an absorbed or adsorbed state by the solid components and has higher molecular mobility. The variation in the content of water of an excipient with humidity reflects changes in the unbound water content.

Water activity is a direct indicator of the amount of free, mobile water in the system. Water activity in a solid is equivalent to the relative humidity in a closed environment produced in equilibrium with the solid excipient or drug-excipient mixture. Several authors recommend use of water activity determination for drug product stability correlation over total moisture determination by Karl-Fisher titrimetry and/or water uptake by weight gain (28,29). Thus, Burghart *et al.* correlated the water activity of solid oral dosage forms of levothyroxine and lyothyronine with their chemical stability (30).

Role of Water in Physical Instability

Slowdown of dissolution and disintegration of solid dosage forms on stability is often induced by moisture uptake in the tablets during manufacturing and/or storage. For example, Fitzpatrick *et al.* reported slowdown of dissolution and increase in the tensile strength of a tablet formulation containing povidone (polyvinyl pyrrolidone, PVP) as a binder, but not one containing hydroxypropyl cellulose (HPC) (31). These effects were attributed to moisture sorption by PVP causing depression of its glass transition temperature (Tg) to below the temperature used in accelerated stability studies. This transition from the rigid glassy to the relatively more mobile rubbery state was postulated to lead to increased tablet densification, reduced dissolution, and increased tensile strength. Nevertheless, the long term stability studies conducted at temperature below Tg did not induce dissolution slowdown. Also, in the authors' experience, the use of PVP as a binder did not show slowdown in dissolution stability for several drug products. Therefore, the

observation of dissolution slowdown with the use of specific binders or disintegrants is likely to be drug specific and also dependent on packaging and storage conditions.

Role of Water in Chemical Instability

The physical state of water in an excipient or the drug-excipient mixture determines its potential role in drug-excipient interactions. The water sorption–desorption properties of excipients are well documented (32,33). Presence of water in the solid-state systems has a significant impact on the stability not only in causing the hydrolysis of drugs, *e.g.*, of acetylsalicylic acid (34), but also its participation as a reaction medium and in increasing the plasticity and molecular mobility of the system. Excipients that strongly adsorb water may prevent drug degradation by scavenging water in a closed system, *e.g.*, colloidal silica (35) and silica gel (36), thus lowering water activity in the mixture. Excipients with higher adsorption energy, indicative of their higher bonding strength with water, can decrease the reactivity of water in the system compared to those with lower adsorption energy, as was shown in the case of nitrazepam (37). On the other hand, water in excipients such as microcrystalline cellulose is highly reactive because it is weakly adsorbed (38). This was the reason for the higher rate of hydrolytic degradation of aspirin in the presence of microcrystalline cellulose *versus* microfine cellulose (39).

Molecular mobility of drug and water molecules in the solid state directly correlates with their reactivity. The mobility of water molecules in a system can be directly measured by nuclear magnetic resonance (NMR) and dielectric relaxation spectroscopy. Mobility of water in the system have been correlated to drug stability in drug-excipient mixtures in several cases, *e.g.*, degradation of trichlormethiazide in gelatin gels (40) and of cephalothin in its mixtures with microcrystalline cellulose (41). Unbound, weakly adsorbed water contributes to molecular mobility within the system, which is a prerequisite for chemical reactions. Sorbed water plasticizes amorphous solids by reducing the glass transition temperature, Tg (42,43). The Tg of an amorphous solid represents transition from a highly rigid, less mobile, glassy state to a rubbery, mobile state with higher free volume. Water sorption leading to reduction in Tg is known in excipients such as starch, lactose, and cellulose (44), and amorphous drugs such as indomethacin (45).

A study of water sorption–desorption of a system as a function of environmental humidity at a fixed temperature (isotherm) can indicate the strength of sorption of water and its mobility within the system. The moisture sorption–desorption isotherms frequently present a hysteresis, which are indicative of the way water reacts with the system. Interaction of water with a solid phase can lead to formation of hydrate, adsorption of water on the surface of the solid, or absorption of water by the amorphous phase leading to the formation of a single phase (46). Cyclic exposure of a solid material to a given level of water in the environment (relative humidity) can change the affinity of the solid material to moisture. This is evident by the hysteresis loop in water sorption–desorption isotherms. For example, crystallization of amorphous material, such as spray dried lactose, during the sorption phase can lead to lower water content in the solid during the desorption phase, causing negative hysteresis (47). Alternatively, molecular reorganization of polymeric materials can make moisture sorption more favorable, thus leading to positive hysteresis.

Presence of hysteresis in pharmaceutical dosage forms can lead to differences in reactivity when a drug product is cycled between high and low humidities. Waterman *et al.* cycled a direct compression tablet of an investigational drug through high-low-high or low-high-low RH cycles at fixed humidity and determined the rate of formation of an RH-induced degradant (lactone) at initial and final humidity conditions (46). The authors observed that the degradant formation rate at high humidity condition was same for both phases of high-low-high cycle. In contrast, the rate of degradant formation was higher for the latter of the two phases of the low-high-low cycle. This study indicated that reactivity may not be dependent on the RH only but also on the humidity exposure history of the system. The authors hypothesized that this could be due to formation of solid-solution on the surface, alteration of mechanical properties of the surface to cause greater mobility, or alteration of the interfacial state such that higher amount of moisture was present at the interface even after drying (46).

Mitigation Strategies

Moisture-induced changes in physical properties of the dosage form can be mitigated by package design, such as the use of desiccants in high density polyethylene (HDPE) bottle packs or the use of moisture impervious aluminum-aluminum (Alu-Alu) blister pack. In addition, reformulation to reduce moisture sensitivity can help. For example, reformulation of ranitidine hydrochloride tablets in the presence of ion exchange resins, that reduce the equilibrium moisture content of tablets at same humidity, stabilized the tablets against changes in disintegration time and friability over storage (48).

Microenvironmental pH

Excipients can have an acidic or basic surface pH depending upon their chemical nature and composition. For example, Glombitza *et al.* measured the surface pH using pH indicator dyes and found that the surface of dicalcium phosphate was more acidic than that of microcrystalline cellulose (49).

For soluble excipients, the pH of the excipient solution is a simple indicator of the pH imparted by the excipients in solid state. For insoluble excipients, the pH of 5–20% excipient slurry in water could be used as an indirect indicator. The selection of excipients with compatible pH profiles, based on preformulation solubility and stability studies as a function of pH, is helpful in the design of excipient compatibility experiments. For example, acid labile drugs should not be combined with acidic excipients such as hydroxypropyl methylcellulose (HPMC) phthalate and HPMC acetate succinate. Similarly, magnesium stearate imparts a basic pH in its microenvironment and may contribute to the instability of base-labile drugs. Stanisz found that the chemical stability of quinapril HCl in binary drug-excipient mixtures was significantly better with acidic excipients than basic magnesium stearate (50). This study indicated that both the microenvironmental pH and humidity were significant factors in drug degradation. Thus, the presence of mobile water accelerates the surface pH effects of excipients by creating microenvironmental conditions of dissolved excipient on the interacting surfaces.

Most drugs are salts of organic acids or bases which may disproportionate to the free acid or base forms at acidic or basic pH, respectively, depending on the pH of maximum solubility (pH_{max}). Thus, pH modifying excipients may result in the formation of the free acid/base form of the drug. If the free acid/base form is more unstable than the salt form, this would lead to enhanced degradation. In addition, dissolution rate of the dosage form may be affected since free forms are usually less water soluble than their corresponding salts. The free form may also be volatile and be lost by sublimation from the dosage form, leading to mass balance issues in terms of loss of drug not being accounted for by the presence of degradation products (51,52).

PHYSICAL INSTABILITY

Organoleptic Changes

Changes in appearance (such as color or mottling on surface), taste, or odor sometimes becomes evident over storage, especially for some drugs with amine or sulfur groups. These changes are often associated with chemical changes in the dosage form, such as degradation of the drug or flavors. For example, reactions of reducing sugars, *e.g.*, lactose, with primary and secondary amine drugs *via* Maillard reaction followed by Amadori rearrangement can produce a multitude of colored products. The general mechanism of these reactions involves the reaction of the amine compound with the open form of the carbohydrate to form an imminium ion intermediate, that can either close to a glycosamine compound or deprotonate to form the enol version of the rearrangement product (53). Fluoxetine hydrochloride tablets can undergo Maillard reaction (Fig. 1) with lactose to form colored pigments (53). Also, some drugs, such as N-acetyl cysteine, can degrade into odorous chemicals. Stabilization strategies to prevent organoleptic changes often involve preventing drug degradation by changing the formulation to replace the reactive excipient(s) or by other means. For example, Murugesan *et al.* reported the use of antioxidants in the formulation of N-acetyl cysteine to prevent its oxidative degradation to an odorous product (54).

Changes in Drug Release

Physical instability in dosage forms is also encountered in terms of changes in drug release or dissolution. Significant changes in drug release during storage may impact its bioavailability. Factors that affect the dissolution stability of a product during aging include formulation components (active drug, excipients, and coating materials), processing factors, storage conditions, and packaging (55). Changes in the drug release are frequently a result of drug-excipient and excipient-excipient physico-chemical interactions in the dosage form. For example, dissolution slowdown of wet granulated tablets containing croscarmellose sodium was most pronounced in formulations containing lactose (56). These changes are often secondary to one or more primary mechanistic changes which involve phenomena such as changes in tablet porosity or density, change in the form of the drug substance (*e.g.*, polymorphism, hydrates, and salts), or reduced disintegration characteristics due to excipient interactions.

Presence or release of free formaldehyde in solid dosage form due to chemical degradation under stress conditions, such as high temperature and humidity, is well known to cause crosslinking of gelatin and reduce drug release from hard gelatin capsules. Crosslinking of gelatin shell can cause delayed drug release, which is dependent on dissolution conditions (57). The *in vivo* impact of delayed disintegration is likely to depend on the therapeutic window, inherent variability, and any site-specific absorption of the drug substance. For example, Digenis *et al.* reported bioequivalence of stressed and non-stressed hard gelatin capsules when amoxicillin was used as the drug marker (58). Using radiolabeled drug and GI transit monitoring using gamma scintigraphy studies, the authors observed delay in the onset of amoxicillin absorption, which was dependent on *in vivo* rupture of the hard gelatin capsule shell. This delayed absorption, however, did not affect the bioequivalence criteria of Cmax and AUC. Similarly, bioequivalence of stressed and nonstressed hard gelatin capsules was also observed using acetaminophen (59) and etodolac (60) as a marker.

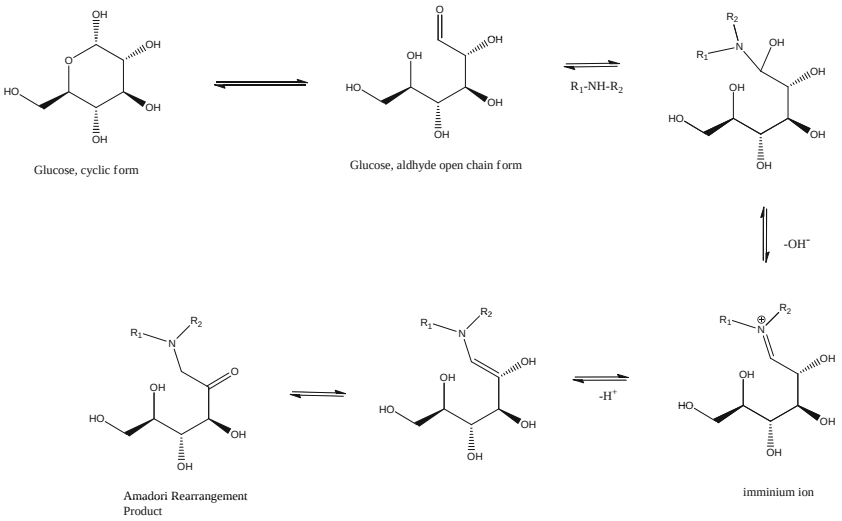

Fig. 1 Maillard reaction with Amadori rearrangement of secondary amine drugs with reducing sugars, resulting in the formation of imminium ion, which can deprotonate to form an Amadori rearrangement product.

Form Changes

Change in the form of the drug in a drug product is typically detected through its effect on one or more of drug product performance attributes—such as drug release or dissolution using a discriminatory method. For example, significant conversion of the higher solubility form II of the drug glimepiride to the lower solubility form I (61) and transition from a metastable to a stable form of theophylline on storage (62) in their tablet formulations could be detected using a discriminatory dissolution method. Changes in the polymorphic form of the drug can be investigated using one or more of X-ray diffraction (XRD); infra-red (IR), near-IR (NIR), solid state nuclear magnetic resonance (ssNMR), or Raman spectroscopy; solvent sorption isotherm; polarized microscopy; and hot stage microscopy.

Drug form changes can be a consequence of the interaction of the drug with another component of the formulation, such as an excipient or water. For example, grinding with colloidal silica led to the reduction in crystallinity and conversion of form B of chloramphenicol acetate to form A (63). The reduction in crystallinity by grinding with an abrasive excipient is suggestive of introduction of crystal defects during processing, that may then serve as sites of nucleation for polymorphic form conversion and/or reactivity of the drug with other components of the formulation ("Crystal Imperfections as Reaction Sites").

The effect of water on form conversion of a drug is usually observed during drug product storage, but can also occur during processing. The effect of moisture content of a formulation on its storage stability is a function of free rather than total water content of the drug product ("Reactions Limited by Amount of Adsorbed Water" and "Role of Water (Moisture)"). Thus, a film coated tablet formulation of a water sensitive drug showed greater instability at low total water content (by Karl Fisher titrimetry) but high water activity, than another formulation that had high total water content but low water activity (64). Similarly, storage of a drug product above a critical level of free water can lead to conversion between different hydrate forms of a compound. For example, nitrofurantoin exists in two anhydrous (designated α and β) and two monohydrous (designated I and II) forms. High humidity storage and processing conditions, *e.g.*, wet granulation, may lead to the conversion of the anhydrous to the monohydrate form, which can be detected by the appearance of a specific peak in the powder XRD (PXRD) spectrum that indicates the presence of the monohydrate form (65). Excipient interactions can also be useful to stabilize a drug against form conversion. For example, form transition from a metastable to a stable form of theophylline during wet granulation is inhibited by PVP. Higher molecular weight of povidone was more effective in inhibiting the transition than lower molecular weight (66).

Disproportionation of salts of weak bases due to moisture uptake and/or interaction with excipient(s) in the dosage form can lead to the formation or increased proportion of the free base form, which usually shows lower solubility, dissolution rate, and bioavailability. For example, Rohrs *et al.* reported dissolution slowdown of delavirdine mesylate tablets on stability, which was closely associated with the moisture content of tablets (67). This was attributed to the dual role of reduced solubility of the free base form of the drug and protonation of carboxyl sites on the croscarmellose sodium by the methanesulfonic acid (liberated by disproportionation of the drug). The propensity for disproportionation of a salt form of the drug depends upon solubility of salt, solubility of the free base, and the microenvironmental pH of the formulation relative to the pH of maximum solubility of the salt (pH_{max}) (68,69).

CHEMICAL INSTABILITY

Chemical instability in solid dosage forms is frequently a result of interaction between the drug and one or more

excipients or impurities in excipients. The most common reactions observed in pharmaceuticals are hydrolysis, dehydration, isomerization, elimination, cyclization, oxidation, photodegradation and specific interactions with formulation components (excipients and their impurities). The main factors that affect these reactions are temperature, pH, moisture in solids, relative humidity of the environment, presence of catalysts, light, oxygen, physical form, and particle size of the drug and excipients (2).

A brief review of excipient synthesis, isolation, and/or purification can give vital clues about their potential impurities and other characteristics that may pose problems in the formulation (Table I). However, due to their proprietary nature, the availability of this information is difficult to come by and restricted to informal vendor discussions and patent databases in most cases. Several examples of the presence and implication of reactive impurities in pharmaceutical excipients are known in literature (2).

Drug-Excipient Interactions

Solid dosage forms are usually less stable than the active pharmaceutical ingredient (API). Excipients in the dosage form typically catalyze the degradation of susceptible APIs. In most chemical reactions that involve excipients or components in excipients, drug degradation rate is usually proportional to its dilution. This is reflective of the diffusion controlled reactions ("Diffusion Controlled Reactions") wherein the drug particles are dispersed in the other solid components of the formulation. Excipients can enhance drug degradation rate through a chemical or a physical interactions. A chemical interaction refers to cases where the excipient reacts directly with the drug molecule, acts a catalyst for a chemical reaction that the drug molecule is susceptible to, or modifies the pH of the microenvironment such that the rate of chemical reaction is enhanced. A physical interaction describes scenarios in which the excipient does not directly affect the chemical reaction but rather modulate the physical state of the API such that rate of chemical reactions is increased.

Chemical Interactions

Chemical interaction of drug and excipient can involve direct reaction to form a covalent bond, catalysis, or pH modification effects.

Direct Reaction of the Drug and Excipient. Direct interaction of drug and excipient takes place when a functional group on the drug molecule is involved in reaction with a functional group on the excipient resulting in bond formation between the two molecules. The nucleophilic attack by the amine group of the drug molecule on the carbonyl group of reducing sugar is a typical example of this direct drug excipient reaction (70,71). The resulting hemiaminal intermediate is typically unstable and usually eliminates water to form imine or iminium ion. The reaction is referred to as Maillard reaction and is well known in food science literature. There are many examples in the pharmaceutical literature where amine drugs and lactose are involved in a Maillard reaction (53,72–79). The imine resulting from the initial reaction is in equilibrium with a glycosylamine (hemiaminal) formed by the addition of a hydroxyl group on the sugar molecule to the imine (Fig. 1). This is usually followed by Amadori rearrangement and then subsequent decompositon of the Amadori rearrangement product which leads to multiple products such as carbonyl compounds, furans, amide derivatives of the drug, pyrroles and other heterocyles (53). Some of those products have yellowish brown color and hence the Maillard reaction is known as the "browning reaction". Primary aliphatic amines are the most reactive in the Maillard reaction (72–75). However, secondary aliphatic amines have also been reported to undergo the Maillard reaction (53,76–78). Maillard reaction involving amino nitrogens in heterocyclic rings have not been reported in the pharmaceutical literature.

Maillard reaction between proteins and reducing sugars were also reported. The reaction involves condensation of the reducing sugar with the amino groups of the lysine and arginine residues in the protein to form glycosylamino derivatives. The glycosylamines may undergo rearrangement and further reaction to form multiple products. Aminocabonyl adducts formation by Maillard reaction on multiple lysine and arginine residues were reported in a lypohilized glucose formulation of the recombinant human relaxin (79).

Ester formation of hydroxyl containing drug molecules represents another type of direct drug excipient reaction. The ester can be formed by the reaction of the hydroxyl with a carboxylic acid group on the excipient or by a transesterification reaction of the drug hydoxyl group with an ester containing excipient. Reaction of carvedilol and 5-aminosalicylic acid with citric acid to form citrate esters in the solid state has been reported (80,81). The octanoate and decanoate esters of vitamin D3 were identified in a liquid formulation containing triglycrides (82). These esters are formed by a transesterification with the two major fatty acid esters (octanoate and decanoate) of the triglycerides present in the formulation. Drugs with alcohol groups can also undergo transesterification with the esters preservatives, methyl and propyl parabens.

A similar reaction which results in amide formation involves the reaction between an amine drug and carboxylic acids or their esters. Amines are less reactive towards carboxylic acids than alcohols (83). This was demonstrated by the interaction of citric acid with carvedilol which has both hydroxyl and amine groups (80). The higher concentrations

Table I The Method of Manufacture of Common Pharmaceutical Excipients and Their Potentially Reactive Impurities. Reproduced with permission from Narang et al. (2)

Examples of excipients	Method of manufacture	Potentially reactive impurities	Examples of known incompatibilities
Lactose	Lactose is a natural disaccharide consisting of galactose and glucose and is present in the milk of most mammals. Commercially, lactose is produced from the whey of cows' milk, whey being the residual liquid of the milk following cheese and casein production. Cows' milk contains 4.4–5.2% lactose and it is 38% of the total solid content of milk (32).	Lactose may contain glucose, furfuraldehyde, formic acid, acetic acid and potentially other aldehydes.	Maillard reactions, Claissen-Schmidt condensation reaction of its impurity - hydroxylmethyl-2-furfuraldehyde (127), and catalysis of hydrolysis (88,92).
Microcrystalline cellulose	Microcrystalline cellulose is manufactured by the controlled hydrolysis, with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad-size distribution (32).	The impurities in microcrystalline cellulose are glucose, formaldehyde, nitrates and nitrites.	Water sorption resulting in increased hydrolysis (39), Maillard reaction with residual glucose (169), adsorption of basic drugs (170), and non-specific incompatibilities due to hydrogen bonding capability (171).
Povidone and crospovi-done	Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acety-lene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone. Water-insoluble cross-linked PVP (Crospovidone) is manufactured by a polymerization process where the cross-linking agent is generated *in situ* (32).	Povidone and crospovidone contain significant levels of peroxides. Povidone may also contain formic acid and formaldehyde (124).	Oxidation attributable to peroxides (114), nucleophilic addition to amino acids and peptides(172), and hydrolysis of sensitive drugs due to moisture.
Hydroxypropyl cellulose (HPC)	HPC is a water soluble cellulose ether produced by the reaction of cellulose with propylene oxide (32).	HPC may contain significant levels of peroxides.	Oxidation of sensitive drugs due to residual peroxides.
Croscarmellose sodium	To produce croscarmellose sodium, alkali cellulose is prepared by steeping cellulose, obtained from wood pulp or cotton fibers, in sodium hy-droxide solution. The alkali cellulose is then reacted with sodium monochloroacetate to obtain carboxymethylcellulose sodium. After the substitution reaction is completed and all of the sodium hydroxide has been used, the excess sodium monochloracetate slowly hydrolyzes to glycolic acid. The glycolic acid changes a few of the sodium carboxy-methyl groups to the free acid and catalyzes the formation of crosslinks to produce croscarmellose sodium. The croscarmellose sodium is then extracted with aqueous alcohol and any remaining sodium chloride or sodium glycolate removed. After purification, croscarmellose sodium of greater than 99.5% purity is obtained. The croscarmellose sodium may be milled to break the polymer fibers into shorter lengths and hence improve its flow properties (32).	Monochloroacetate, nitriles, and nitrates. Monochloroacetate can react with nucleophiles.	Weakly basic drugs can compete with the sodium counterion, thus getting adsorbed on the surface of the disintegrant particles (173,174). Drug salt form conversion has also been reported (67).
Sodium starch glycolate	Sodium starch glycolate is a substituted and cross linked derivative of potato starch. Starch is carboxymethylated by reacting it with sodium chloroacetate in an alkaline medium followed by neutralization with citric, or some other acid. Cross linking may be achieved by either physical methods or chemically by using reagents such as phosphorus oxytrichloride or sodium trimetaphosphate.	Monochloroacetate, nitriles, and nitrates are potentially reactive impurities.	Adsorption of weakly basic drugs and their salts due to electrostatic interactions (175,176). In addition, the residual monochloroacetate may undergo S_N2 nucleophilic reactions.
Starch	Starch is composed of amylose and amylopectin, polymers of glucose connected by α 1,4 glycosidic linkages (in contrast to cellulose β1,4 linkages). Amylopectin has occasional branch chains connected by α 1,6 glycosidic linkages. Starch is extracted from plant sources through	Starch may contain formaldehyde, nitrites and nitrates.	Terminal aldehydes in starch react with the hydrazine moiety of hydral-azine HCl (135). Starch may also be involved in moisture-mediated reactions, may adsorb drugs, and may react with formaldehyde resulting in reduced functionality as a disintegrant (130,177).

Table I (continued)

Examples of excipients	Method of manufacture	Potentially reactive impurities	Examples of known incompatibilities
	a sequence of processing steps involving coarse milling, repeated water washing, wet sieving, and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations. Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available.		
Stearic acid	Stearic acid is made *via* hydrolysis of fat by continuous exposure to a counter-current stream of high-temperature water and fat in a high-pressure chamber. The resultant mixture is purified by vacuum-steam distillation and the distillates then separated using selective solvents.		Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents. Insoluble stearates are formed with many metals; ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts. A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs. Although such laboratory studies have suggested incompatibilities, *e.g.*, naproxen, they may not necessarily be applicable to formulated products. Stearic acid has been reported to cause pitting in the film- coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid. Stearic acid could affect the hydrolysis rate of API if the degradation is pH dependent. It could also potentially react with an API containing a primary amine to form a stearoyl derivative (178,179).
	Stearic acid may also be made *via* hydrogenation of cottonseed and other vegetable oils; by the hydrogenation and subsequent saponification of oleic followed by recrystallization from alcohol; and from edible fats and oils by boiling with NaOH, separating any glycerin and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid is then subsequently separated from any oleic acid by cold expression.		
Magnesium stearate	Magnesium stearate is prepared either by chemical reaction of aqueous solution of magnesium chloride with sodium stearate, or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures.	Magnesium oxide is a known reactive impurity.	Magnesium stearate can form hydrates with water and exists in four hydration states—mono, di and trihydrates (180). MgO impurity is known to react with ibuprofen (181). In addition, magnesium stearate provides a basic pH environment and may accelerate hydrolytic degradation (182). The magnesium metal may also cause chelation-induced degradation (183).
	The raw materials used in manufacturing of magnesium stearate are refined fatty acids, which is a mixture of palmitic and stearic acid with certain specifications. A fatty acid splitting (hydrolysis) process takes place first, where glycerin and fatty acids are separated. The fatty acids are then further refined to yield tallow acid. Magnesium stearate can be prepared through two processes: 1) Fusion - simple acid base interaction between tallow acid and magnesium hydroxide; or 2) Saponification - tallow acid is saponified first with sodium hydroxide, making a sodium tallowate (salt),		

Table I (continued)

Examples of excipients	Method of manufacture	Potentially reactive impurities	Examples of known incompatibilities
	then magnesium sulfate is added to the sodium tallow solution, followed by pH adjustment, dilution with water, wash and dry.		
Silicon dioxide	Colloidal silica is prepared by partial neutralization of an alkali-silicate solution, which leads to the separation of silica nudei. Size of the colloidal silica particles depends on the selection of pH and processing conditions. A pH stabilized colloidal suspension is then concentrated by evaporation of the liquid phase. Formation of silica gel or precipitated silica is associated with the use of acidic or slightly basic pH, respectively, causing fusion or growth of silica particles.	May contain heavy metal impurities.	May act as a Lewis acid under anhydrous conditions and may adsorb drugs (184,185).

of the carvedilol citrate esters compared to citric acid amides indicate that the known higher reactivity of alcohols is also manifested in solid dosage forms. Amines also have the potential to react with esters to form amides. Triacetin, a commonly used plasticizer in film coating formulations, is the triacetate ester of glycerol. Triacetin in the tablet film coat can potentially interact with amine compounds to form the acetamide derivative of the drug (84).

Ester formation can also take place by the reaction of drug molecules with carboxylic acid moiety and the hydroxyl groups of an excipient. Cetrizine sorbitol and glycerol esters were identified in oral liquid formulation of an antiallergic drug cetrizine, which were formed by the reaction of certrizine with glycerol and sorbitol in the formulation (85).

Drug interaction involving the maleate counter ion in a Michael addition reaction has been reported. Michael addition is a nucleophilic addition reaction of a nucleophile, such as a carbanion or a primary amine, to the α,β-unsaturated carbonyl compounds (Fig. 2). Michael addition reaction of phenylephrine hydrochloride with the maleate counter ion of dexbrompheniramine maleate was observed in common cold solid dosage forms (86). The nucleophile was the secondary amine of the phenylephrine which attacks the olefinic bond in the α,β position of the carboxylate group of the maleate. A similar reaction of the primary amine of seproxetine with its maleate counter ion was observed in capsule dosage form of seproxetine maleate (87).

Catalysis of Drug Degradation Reaction by an Excipient. In this scenario, the excipient acts a catalyst to increase degradation rate of the drug molecule but does not form lasting bond with the drug. Per definition of a catalyst, the excipient's role is to reduce activation energy of the reaction but is left unchanged at the end of the reaction. Solid state reactions in which excipients catalyze the degradation of a drug are a function of diffusion controlled collisions of reacting species and the catalyst ("Diffusion Controlled Reactions"), which can be facilitated by plasticization by adsorbed water ("Reactions Limited by Amount of Adsorbed Water" and "Role of Water (Moisture)"), and are generally initiated at the crystal imperfections that offer greater molecular mobility ("Crystal Imperfections as Reaction Sites"). These kinetic factors add to the difficulty in elucidating reaction mechanisms in solid state. Degradation mechanisms observed in solution state are in many cases applicable to degradation in the solid state, although kinetics are usually different. Since the solution system is simpler and lacks the complexity of the solid system, it is possible to decouple chemical and physical mechanisms that confound solid state stability studies. Solution studies are therefore more useful when the goal is to study underlying mechanisms for

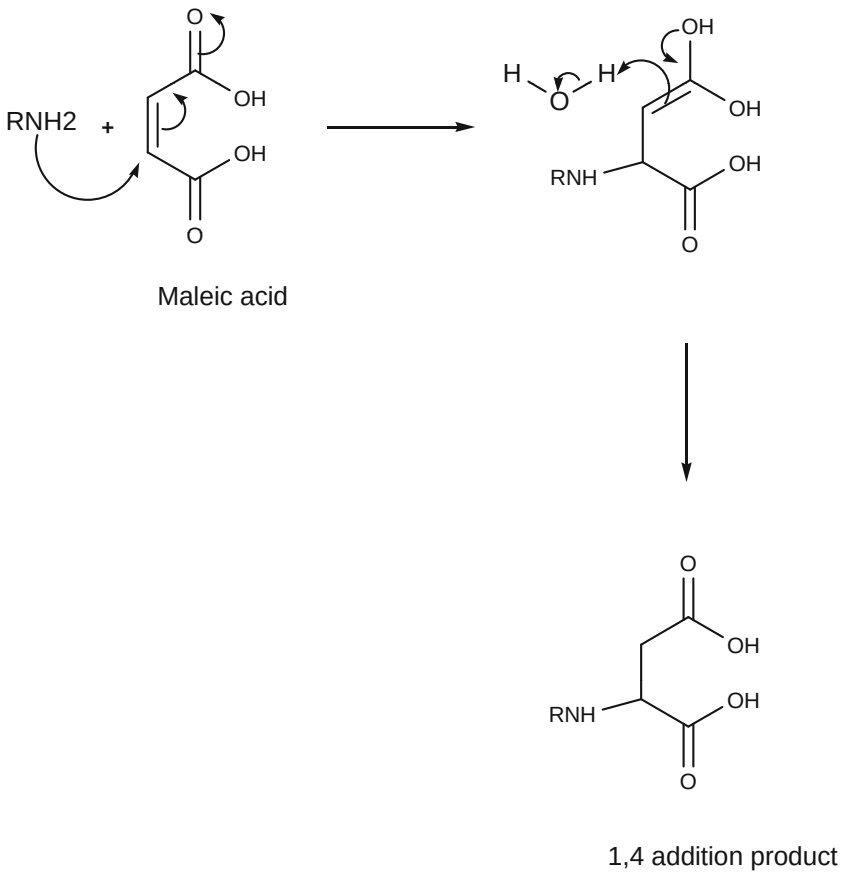

Fig. 2 Michael addition reaction of primary amines with maleic acid. Michael addition is a nucleophilic addition reaction of a nucleophile, such as a carbanion or a primary amine, to the α,β-unsaturated carbonyl compounds.

chemical reactions. For this reason, chemical stability is usually assessed first in solution studies to gain the understanding that supports subsequent solids state studies.

"Nucleophilic catalysis" by polyhydroxy excipients has been reported for ester hydrolysis. For example, hydrolysis rate of p-nitrophenyl esters in neutral to alkaline aqueous solutions was increased in the presence of dextrose, sucrose, sorbitol, and mannitol in a concentration dependent manner (88). Despite the high acidic pKa values for the polyhydroxy excipients used in the study, kinetic analysis showed that the catalytic species is the alkoxy anion. Thus, the catalytic effect of the polyhydric alcohol increased by the increase in solution pH and the associated increase in the alkoxy anion concentration. Degradation of β-lactam antibiotics was similarly enhanced in aqueous solutions of carbohydrates and polyhydric alcohols. Degradation of ampicillin in alkaline solutions was accelerated by glucose and dextrans (89). The first step of the reaction involves a nucleophilic attack by the alkoxy anion of the sugar on the β-lactam amide bond, eventually resulting in pencilloic acid and a piperazinedione derivative as the final products. Sucrose catalyzed hydrolysis of bezylpenicillin to bezylpenicilloic acid was also attributed to the nucleophilic mechanism (90). Cephalosporin undergoes a similar carbohydrate and polyhydric alcohol catalyzed reaction. The degradation rate of cephaloridine, cepahlothin, and cefazoline increased linearly with concentration of the polyhydric alcohol in solution (91). This rate accelerating effect by glucose on cephalosporin hydrolysis was directly proportional to the hydroxide ion concentration in the 6.5 to 11 pH range. The pH dependence was attributed to the increased fraction of the alkoxy anion in the solution as the pH increased.

An understanding of potential reaction pathways and kinetics in the liquid state can help delineate the stability observed in solid state. For example, hydrolysis rate of the methyl ester prodrug DMP-754 was substantially enhanced in binary blends with anhydrous lactose compared to the API. Since lactose also showed a concentration-dependent increase in rate of methyl ester hydrolysis in solution, a nucleophilic catalysis mechanism was proposed for the effect of lactose (92).

While kinetic analysis in solution studies suggested that the nucleophilic catalysis of ester and amide hydrolysis by polyhydroxy compounds is attributed to the more nucleophilic alkoxy anion (RO^-) rather than the less nucleophilic unionized hydroxyl group (ROH), studies showing further insight into the nucleophilic mechanism have not been reported. Some reports suggested that the nucleophilic mechanism proceeds *via* nucleophilic attack by the alkoxy ion on the ester or the amide resulting in the formation of

sugar ester intermediate that rapidly hydrolyzes to form the acid. Such sugar esters of pencilloic acids were indeed identified for ampicillin and benzylpenicillin (89,90). However, other studies did not report the existence of such intermediate esters. In these cases, kinetically indistinguishable mechanisms involving the polyhydroxy excipient and the hydroxide ion are also plausible, such as the sugar hydroxyl group facilitating the attack of the hydroxide ion on the ester or the amide (88).

Nucleophilic catalysis is also proposed for the rate accelerating effect of hydroxypropyl methycellulsoe (HPMC) on the degradation of an oxadiazole derivative in spray dried dispersions (93). The rate of degradation in the HPMC solid dispersion was higher than in the API or PVP-VA solid dispersion despite the higher moisture uptake by PVP-VA solid dispersion compared to HPMC. The nucleophilic attack by the hydroxyl groups of HPMC on the methine carbon of the oxadiazole to form a stable tetrahedral intermediate was proposed as the mechanism for HPMC catalysis. PVP-VA, which lacks the presence of a nucleophile, resulted in a more stable solid dispersion.

In addition to nucleophilic catalysis, reducing sugars have been reported to facilitate amide hydrolysis by another mechanism. Hydrolysis of $Trp^{28}Ser^{29}$ peptide bond on the B-chain of the protein hormone human relaxin was observed in lyophilized solid formulations containing glucose (79). Since other lyophilized formulations with mannitol or trehalose did not exhibit the same reaction, it can be inferred that the catalysis mechanism is not due to the hydroxyl groups which are present on all three excipients. Glucose, however, is the only reducing sugar among the three with a carbonyl group. A mechanism involving initial hemiacetal formation between the serine hydroxyl and glucose carbonyl group was proposed. The hemiactal subsequently forms a cyclic intermediate. Hydrolysis of the imine bond in this cyclic intermediate yields the peptide bond hydrolysis products. This mechanism can potentially also result in the the hydrolysis of the amides of other 2-amino alcohols by reducing sugars (Fig. 3).

pH Effect of Excipients. Degradation rate of many drug molecules in solution is a function of solution pH. For those compounds, degradation rate in the solid dosage form is also affected by the microenvironmental pH (94). The microenvironmental pH of a formulation is determined by the active ingredient and the excipients in the formulation. Excipients with inonizable functional groups act as pH modifiers and may impact formulation pH (68). These excipients include disintegrants (croscarmellose sodium and sodium starch glycolate), fillers (calcium carbonate and dicalcium phosphate), and lubricants (magnesium stearate and stearic acid). The decrease in microenvironmental pH of solid formulations by enteric coating polymers was also reported (95,96). In certain cases, pH modifiers are intentionally added in the formulation to modulate the pH and optimize dissolution rate. Organic acids such as citric, tartaric, and succinic acid have been used in immediate and controlled release dosage forms of weakly basic drugs to enhance their dissolution rate (97–100).

Acceleration of degradation rate by pH modifying excipients has been reported (101). In these cases, excipients result in enhancement of a degradation pathway inherent to the drug molecule by alteration of the microenvironmental pH to a region on the pH stability profile where degradation rate is faster. The counter ion of the salt form also impacts microenvironmental pH. For basic drugs, counter ions derived from conjugate acids with higher pKa tend to have higher microenvironmental pH. Thus, the acetate salt (pKa of acetic acid, ~4.76) of an amidine derivative was found to have higher microenvironmental pH than the mesylate salt (pKa of methanesulfonic acid, −1.2), which increased the rate of drug degradation (102).

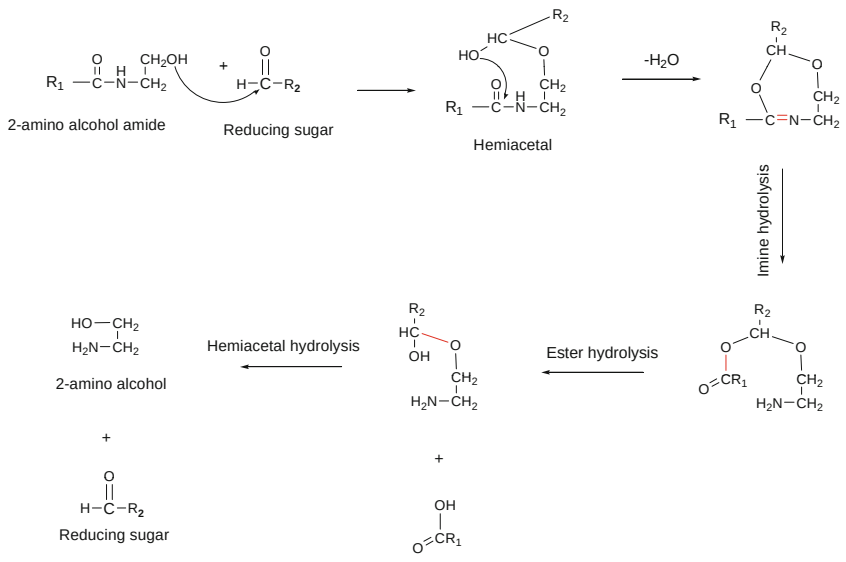

Fig. 3 Mechanism of reducing sugar catalysis of amino alcohol amide hydrolysis. The mechanism involves initial hemiacetal formation between the hydroxyl and reducing sugar carbonyl group.

Physical Interactions That Lead to Chemical Instability

It is a common experience that drug molecules with inherent instability exhibit more degradation in the solid dosage forms compared to the API. The degradation products are usually the same as the API, but the rate of their formation is significantly higher than in the API. As discussed above, this could be attributed in some cases to chemical catalysis of the degradation by the excipients or due to their effect on the microenvironmental pH. However, excipients can also accelerate drug degradation by a non-chemical mechanism.

Drug degradation in the solid state usually takes place in disordered regions, in crystal defects, or on the surface of the crystals ("Crystal Imperfections as Reaction Sites"). The higher molecular mobility in those disordered regions results in faster degradation rate than the crystal lattice. In addition, the disordered regions have higher water content due to absorbed water, which further enhances degradation rate in those less ordered regions for reactions in which water acts as a reactant (*e.g.* hydrolysis). Mechanical energy experienced by solid formulations during processing can result in the disruption of API crystallinity and the formation of amorphous dispersion of a small fraction of the drug substance in amorphous excipients (103–106). The exposure of API to shear forces during processing can be enhanced in the presence of abrasive excipients, such as colloidal silicon dioxide (as discussed in "Form Changes"). Although the fraction of the drug in amorphous state may be small, sometimes even below detectable limits of common analytical instrumentation, this leads to a measurable impact on the stability of the dosage form since the acceptable specification limit of a degradant in a drug product is typically very low.

Drug Interactions with Excipient Impurities

Mechanistic studies on drug degradation in solid dosage forms increasingly highlight the importance of drug interactions with impurities in excipients, rather than the excipients themselves. Predominant among these reactions are drug reactions with peroxides, aldehydes and acids, and metals in the dosage form, which are often present in excipients as impurities.

Peroxides

Peroxides are very reactive and they tend to form N-oxides and other oxidative impurities. Peroxides in solid dosage forms can exist as either alkyl peroxides (ROOR') or hydroperoxides (ROOH). Both these species are highly labile, reacting directly or breaking down to hydroxyl (HO•) and/or alkoxyl (RO•) radicals, which are themselves highly oxidizing species (107).

A general free-radical mechanism of peroxide generation involves homolytic cleavage of the C-H bond next to a heteroatom, followed by the addition of oxygen which leads to peroxy radical formation (ROO•) (98). The peroxy radical can then participate in an autocatalytic cycle by abstraction of hydrogen atom from another reactant to form a hydroperoxide, while generating another carbon free radical (108). The O-O bond in peroxides is particularly weak and can cleave to form alkoxy (RO•) and hydroxy (•OH) free radicals (98). Peroxides and free radicals can also lead to the formation of other reactive oxygen species, such as superoxide anion (O^{2-}•), hydrogen peroxide (H_2O_2), and organic hydroperoxides (R′OOH) (98).

Hydroperoxide (HPO) is a common trace level impurity observed in excipients such as polyethylene glycol (PEG), povidone, hydroxypropyl cellulose, and polysorbate (109). For example, the formation of N-oxide derivative of raloxifene hydrochloride was traced to residual peroxides in povidone and crospovidone (110). While crospovidone and povidone could be the source of residual peroxide, excipients such as croscarmellose sodium can act a scavenger for peroxide. Thus, tablet formulation of a compound containing piperazine ring showed reduced amount of N-oxide degradant when croscarmellose sodium was used as a disintegrant in addition to crospovidone (111). Peroxide mediated drug degradation reactions can be investigated during drug-excipient compatibility study where, in addition to residual levels of reactive species, other factors such as drug loading, effects of temperature and humidity, and microenvironmental pH can be studied (112,113).

Control Strategy for Peroxides

Peroxides are highly reactive species and trace levels of peroxides are found in commonly used excipients such as PEG, povidone, and crospovidone. In studies where peroxides in excipients were implicated in the oxidative degradation of drugs in their formulations, control of initial peroxide concentration was recommended for drug product stabilization (98,114–116). In line with these recommendations, the European Pharmacopoeia does not allow more than 400 ppm of peroxides in crospovidone. Although the crospovidone monograph in USP/NF still has no official limit, some excipient vendors provide "peroxide free" crospovidone, which is produced to meet the PhEur or tighter limit. The compendial limits on peroxide level may or may not be sufficient to assure satisfactory product stability. This is because peroxide levels often increase in excipients during storage (117), which was observed for povidone (118) and PEG (119).

The most prudent approach is to conduct a stability study using excipient lots representing a range of concentrations

or spiking one lot of excipient with different amount of peroxide. For example, raloxifene hydrochloride tablets were spiked with different quantities of hydrogen peroxide equivalent to 200 to 800 ppm peroxides over the amount already present in povidone and crospovidone. Based on the formation of the degradant product, a rational limit of peroxide was proposed for these two excipients (110).

Treatment with silicates reduced peroxide levels in excipients (118). Treatment with silicates was shown to not affect the functionality of the povidone. This approach can further be combined with incorporating antioxidants in a formulation. With respect to antioxidants, water soluble antioxidants were more effective than water insoluble ones (Fig. 4) (118). Other approaches for reducing peroxides from excipients include the use of enzymes (120), metals (120), or other additives (121); chemical modification of the cross-linker (108); supercritical fluid extraction (122); and vacuum drying (123).

The control strategy for peroxides starts with developing a sensitive analytical method not only to monitor their initial levels in the excipients, but also in the dosage forms. Using a sensitive method, excipients or excipient lots with low HPOs can be selected. The analytical method can be further leveraged to select a manufacturing process that minimize HPO levels to improve product stability (109).

Aldehydes and Acids

Formic acid and/or formaldehyde can be present in the excipients as trace impurities. Drugs with amine group or hydroxyl group can react with formic acid or formate impurity to form amides or esters, respectively (Fig. 5) (124). Formaldehyde is known to react with amine drugs to form N-formyl adducts (hemi-aminals) that can further react to form dimer(s). Adefovir is known to react with formaldehyde to produce the reactive imine which can further undergo nucleophilic addition with another amine molecule to form a dimer (125). Nassar *et al.*, showed that BMS-204352 formed an adduct (hemiaminal) with formaldehyde impurity in the solubilizers, polysorbate 80 and PEG 300 (126). The impurity of lactose, 5-hydroxylmethyl-2-furfuraldehyde, has been reported to react with the carbonyl (ketone) of haloperidol to form a condensation product (127). In addition, aldehyde impurities in excipients are commonly known to affect the disintegration of capsule formulations by chemical crosslinking of gelatin (57). Capsules on storage show slower dissolution if any aldehyde contaminated excipients are used in a formulation.

Formaldehyde can also be generated as a degradant of a drug substance. For example, degradation of hydrochlorothiazide can generate formaldehyde (128). Formaldehyde can cross-link not only gelatin capsule shell, but also excipients. Hydrochlorothiazide (HCTZ) bead formulations with or without sodium starch glycolate (Primojel®) as disintegrant showed different dissolution stability upon exposure to humid environment. One with Primojel showed slower dissolution compared to one without it (129). The amount of formaldehyde detected in Primojel containing HCTZ formulation was less compared to one without it because formladehyde probably cross-linked Primojel and reduced its effectiveness as a disintegrant (129).

Moisture was shown to play an important role in dissolution instability of hydrochlorothiazide (HCTZ) capsules. HCTZ capsule formulation containing Fast-Flo® lactose, hydrous lactose, and anhydrous lactose showed 45, 25, and 10% slower dissolution, respectively, after 6 month storage at 50°C. The slower dissolution was attributed to

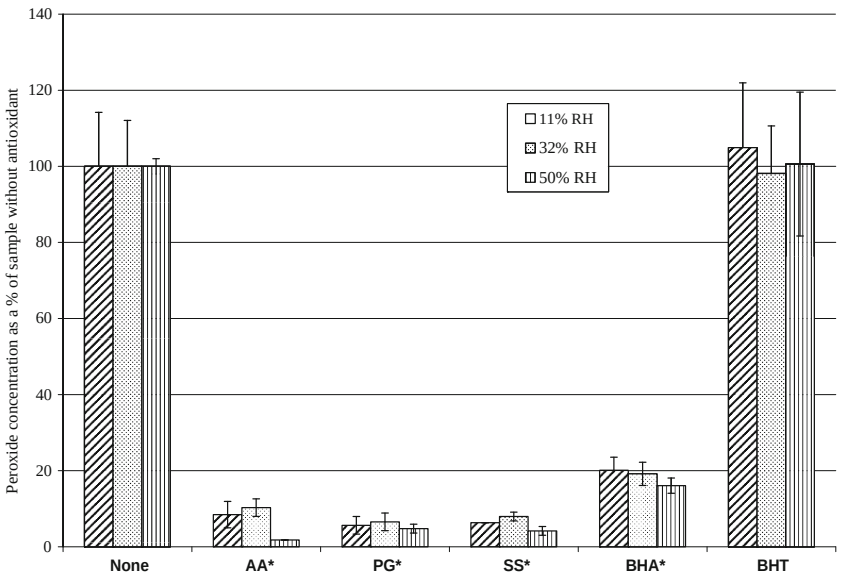

Fig. 4 Relative effectiveness of antioxidants in reducing peroxide concentration in povidone and its dependence on humidity at 40°C (118). Water soluble antioxidants were more effective than water insoluble ones. Abbreviations: BHA, butylated hydroxy anisole; BHT, butylated hydroxy toluene; AA, ascorbic acid; PG, propyl gallate; and SS, sodium sulfite. The results marked with an astrisk (*) were statistically significantly ($p < 0.05$) different from the sample without an antioxidant using a two-tailed *t*-test for comparing two sample means with the assumption of unequal variances. Reproduced with permission from Narang et al. (118)

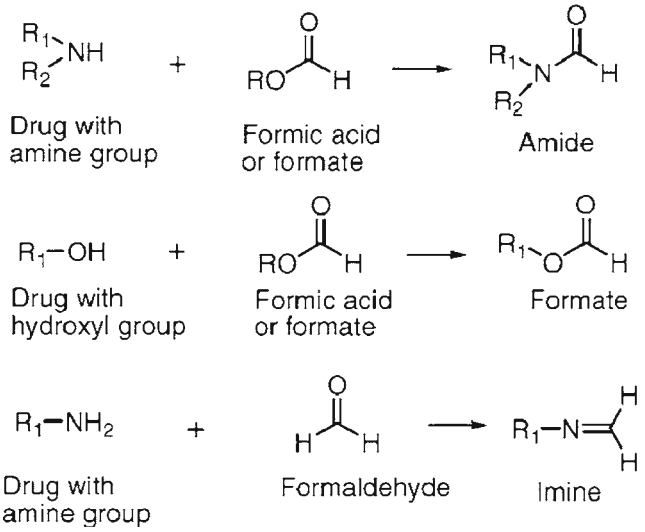

Fig. 5 Reactions of drugs with amine or hydroxyl functional groups with formaldehyde and formic acid, or formates, resulting in the formation of corresponding adducts. Drugs with amine group or hydroxyl group upon reaction with formic acid or formate impurity to form amides or esters, respectively.

degradation of HCTZ from moisture released from excipients and capsule shell. Anhydrous lactose contains least amount of moisture and capsules containing anhydrous lactose showed best dissolution stability. As mentioned above, formaldehyde was one of the degradants which reacted with a disintegrant such as sodium starch glycolate (Explotab®), croscarmellose sodium (Ac-Di-Sol®), or corn starch. However, when crospovidone was used as disintegrant, the dissolution stability of the capsules improved since crospovidone does not react with formaldehyde and has good moisture scavenging ability (130).

Antioxidants are commonly utilized for stabilization of susceptible drug products. Although such functional excipients, such as antioxidants, are generally assumed to be chemically pure, sometimes trace impurities in such excipients can lead to drug product instability. An example of such a scenario was encountered when commercial tablets of a drug product that contained BHA (as per the package insert) as an antioxidant were encapsulated in hard gelatin capsules for a blinding purpose for clinical studies (131). These capsules were put on long-term stability at room temperature to ascertain that the blinding process itself did not change chemical or dissolution instability for the blinded product. During the stability evaluation, dissolution slowdown was observed for some of the batches. Investigations into this phenomenon indicated no loss of potency and fast dissolution of encapsulated tablets, *i.e.*, when tablets from slow dissolving capsule lots were transferred into fresh capsule shells, faster dissolution was observed. Also, when new tablets were encapsulated in aged capsule shells, slower dissolution was observed. These implicated the capsule shell disintergation/dissolution as the cause of slowdown in dissolution. When the tablets from slow dissolving capsule shells were analyzed using HPLC, a peak for BHT along with the BHA peak was observed. This peak was much smaller in aged, slow-dissolving capsule lots. BHT can degrade into 2, 6-di-tert-butyl-4-hydroxy-benzaldehyde. It was hypothesized that this aldehyde degradant of BHT cross-linked gelatin capsule shells, causing the slowdown in dissolution of capsules. Importantly, BHT was not added to the drug product and was most likely present as a trace impurity, in BHA.

PEG is a commonly used plasticizer in coating materials. At elevated temperature and humidity it can generate formaldehyde. The oxidative degradation of PEG can result in the generation of formaldehyde and formic acid (132). Both formaldehyde and formic acid reacted with varenicline, a smoking cessation drug, to produce two separate degradants (132). Formaldehyde adduct was also observed for irbesartan tablets coated with HPMC-based formulation at an elevated temperature storage (133). PEG in the coating formulation was identified as a source of formaldehyde.

There are instances where reducing sugar as an impurity in commonly used excipients can create an instability for the product. Such instance was reported for lyophilized product of cyclic heptapeptide (134), where reducing sugar impurities in mannitol acted as an oxidizing agent and caused instability for the product. In the case of starch, the terminal glucose was reported to have reacted with hydralazine in the formulation (135). For oral ready to use liquid formulation, sucrose is most commonly used sweetener. During the development of entecavir ready to use liquid formulation, it was noted that a prototype formulation containing sucrose as a sweetener was degrading more at pH 4 than pH 6 or 7. Similar trend was also observed for two other guanine-based antivirals, acyclovir and lobucavir. LC/MS analysis of solution showed isomeric adducts of the drugs and reducing sugars. Sucrose, a disaccharide and non-reducing sugar was the sources of monosaccharides. It was proposed that main cause of degradation was nucleophilic addition of the primary amine group of the drugs to the carbonyl group of fructose and glucose. The increased degradation at pH 4 was due to more sucrose degradation generating more glucose and fructose at pH 4 compared to pH 6 or 7 (136).

Formic acid was observed in coating dispersions containing PEG (137). Formyl content of the drug product increases upon exposure to high temperature and humidity conditions. This is attributed to the degradation of polyethylene glycol (138–142). Formation of formyl species in the combination of PEG and PVA was higher than PEG alone, indicating an effect of PVA increasing the rate of formation of formic acid in PEG (143). The formic acid present in or

generated from PEG can exist as several species in the dosage form. Among the species that may be present are free formic acid, formyl ester of polyethylene glycol, formyl ester of the hydroxyl groups in the polyvinyl alcohol, and possibly other unknown species. The type and relative proportion of formyl species are unknown since the development of analytical methods for the separate quantitation of the different formyl and acetyl species is challenging (124). The formyl species detection methods usually require derivatization of the formyl species to an ester followed by high performance liquid chromatography (HPLC) or gas chromatography (GC) separation and detection. These methods are non-specific with respect to type and relative proportion of formyl species present in the starting materials.

Formic acid-induced drug instability in the formulations has been reported. Waterman *et al.* observed N-formylation and N-methylation of the secondary amine experimental compound varenicline, which were ascribed to the presence of formaldehyde and formic acid in the formulation (132). The formic acid was generated in the formulation by oxidative degradation of the PEG. The authors proposed the use of oxygen scavengers and the use of antioxidants in the coating to prevent PEG degradation and improve drug stability.

Fukuyama *et al.* observed the optical isomerization of an experimental compound (FK480) at an asymmetric carbon linking the pyrrolobenzodiazepine ring to another heterocyclic ring through an amide bond (144). The compound was formulated in a soft gelatin capsule formulation in a mixture of PEG 400 and glycerol. The authors noted that the degradation reaction was accelerated by the formic acid in the formulation and was retarded by the addition of amino acids to the solution.

Nishikawa and Fujii noted nonspecific degradation of a tertiary amine antifungal compound, miconazole, in a liquid formulation of hydrogenated castor oil and lactic acid (145). The degradation was attributed to the generation of hydroperoxides, formaldehyde, and formic acid from the hydrogenated castor oil on stability. The degradation could be prevented by nitrogen blanketing and the addition of hydroxyl radical scavengers such as potassium iodide and thiourea.

Control Strategy for Aldehydes and Acids

Since formaldehyde is very reactive, its presence in the excipients should be tested routinely (57). For capsule dosage forms, the dissolution should be conducted without enzymes as well as with enzymes. Normally, pepsin is used at pH 1.2 and pancreatin at pH 7.2, representing gastric and intestinal environment, respectively. Based on the dissolution data and other biopharmaceutical properties of a molecule an *in vivo* study may be needed. For example, using gamma scintigraphy, it was shown that rupture of severely cross-linked amoxicillin was delayed in the GI tract, but overall exposure was not affected (58). Another approach is to use HPMC-based capsule shells, which show similar performance to gelatin capsule shells in terms of handling on capsule machines and also their *in vitro* performance such as disintegration and dissolution (146,147). Some *in vivo* studies concluded that switching from gelatin-based capsule shells to HPMC-based capsule shell should not have any adverse impact on the bioavailability of the active ingredient (148,149).

A common approach is to avoid excipients which may degrade into more reactive species such as reducing sugars. For example, replacement of sucrose, a non-reducing sugar with a potential to generate reducing sugar, with maltitol, an alternate sweetener without any liability to generate reducing sugars improved the stability of guanine-based antivirals (136). The free aldehyde or ketone group in maltitol precursors is reduced to a hydroxyl group after the hydrogenation process making maltitol less susceptible to nucleophilic addition (136). For coating, PEG-free coating material can be used or even reduced amount of PEG can minimize the stability problem (132). Alternatively, PEG impact can be minimized by inclusion of antioxidants such as BHA.

Packaging modifications that can improve drug product stability include the use of bottles which minimize permeation of oxygen from the atmosphere or canisters which can absorb oxygen. Reducing moisture in the packages can also play a critical role. This can be achieved by appropriate selection of packaging components including types of bottles, head space, and number of desiccants inside the bottles. Instead of making these decisions on trial and error basis, they should be made using sound scientific rationale (47). This involves considering the initial moisture content of the excipients in the dosage form, moisture exchange based on a vapor moisture transfer rate (MVTR), and equilibrium between drug product and desiccants based on their moisture isotherm to provide relative humidity within the packaging (47).

Metals

Safety of drug products is a major concern of regulatory authorities worldwide. This concern is reflected in number of guidance documents dealing with impurities, trace metals, and residual solvents (150–152) For safety reasons, residual amounts of metal catalysts or metal reagent is tightly controlled in drug substance and excipients based on regulatory guidances (153,154). Therefore, there are very few reported cases in the literature where drug product degradation was caused by a metallic impurity.

Antioxidants are commonly added in formulations to prevent formation of oxidative degradants. Interestingly, the metallic impurity in antioxidants was linked to acceleration of formation of the degradants (155). Similarly, the

source of iron in iron-mediated photodegradation of a model drug was the buffer salt used in the formulation (156).

Control Strategy for Metal Ions

Depending on the degradation pathway of the molecule, stricter limits on metal ion content in excipients may be needed. The tolerable limits can be identified by spiking the drug substance or an excipient with metal ions and conducting an accelerated stability study (155). For a drug molecule susceptible to metal ion catalyzed degradation, instead of using metallic stearate as a lubricant, stearic acid should be used as a lubricant. Higher concentration of stearic acid may be needed to obtain optimum lubrication (157).

PROSPECTIVE STABILITY ASSESSMENT

Prediction of drug product stability is an urgent need in pharmaceutical development not only to select the best path forward in the selection of formulation composition, manufacturing process, and packaging components for clinical development and commercialization, but also for regulatory filings to justify proposed shelf life with limited data available at recommended and accelerated storage conditions.

Excipient Compatibility Studies and its Limitations

Significant drug-excipient incompatibilities are routinely sought to be prospectively identified in a series of screening studies that are broadly categorized as compatibility studies. These studies are designed to identify significant changes or drug degradation based on standard protocols and/or existing knowledge on potential degradation pathways or incompatibilities (2). Accordingly, compatibility studies on new molecular entities invariably start with evaluation of existing information and paper chemistry of the drug candidate to identify 'soft spots' and potential degradation pathways/instabilities in the molecule. Presence of reactive or unstable functional groups, pKa value, outcome of forced degradation studies, and known reactivities of similar compounds provide useful information for the selection of excipients. In addition, computational programs such as CAMEO®, SPARTAN®, EPWIN®, and Pharm D^3® and internal databases can help predict potential degradation pathways.

Design of compatibility studies might involve the use of mixtures of drug with one or more excipients (2). Compatibility studies are often carried out at high dilution of drug in the excipient to increase the proportion of reacting species, if contributed by the excipient, and increase the its diffusive transport to dispersed drug particles ("Diffusion Controlled Reactions"). Since physical mechanisms of instability in solid mixtures include the proximity and surface area of contact between drug and excipients, compatibility studies are sometimes carried out using compacted mixture of a drug and an excipient. These mixtures may be equilibrated at different stress conditions as physical mixtures *per se* or after compaction. Often water and other potentiators such as light and hydrogen peroxide are included to evaluate their role in accelerating drug-excipient interactions.

Physical observation of study samples forms the initial basis of excipient compatibility assessment. For example, physical instability evident in change in color, odor, flow properties (*e.g.*, aggregation of the powder mixture), or physical state (*e.g.*, deliquescence) are indicative of drug-excipient incompatibility. Chemical changes in the sample are analyzed by a chromatography-based assessment of potency and formation of degradants. In addition to physical and chemical changes the samples are frequently also analyzed by thermal methods such as spectroscopic and calorimetric techniques for rapid assessment of potential incompatibilities. In short, compatibility studies involve several choices for each stage of testing depending on the drug candidate, available literature, and the goals of the study (2).

Major limitations of compatibility studies include limited ability to predict all reaction pathways, assessment sometimes limited for substantial changes such as high levels of drug degradation or color change, and an open-ended design that lends itself to possible expansion into very long studies. Pragmatic considerations of time and resources often limit the extent and depth of compatibility testing that may be carried out. For example, Wyttenback *et al.* studied excipient compatibility of acetylsalicylic acid or fluoxetine HCl in binary mixtures with 7 excipients using bi-level factors of temperature (40° and 50°C), humidity (10% and 75% RH), and time (1 and 4 weeks), leading to a total of 56 experimental runs for each drug (158). The total impurity content of each run was measured by HPLC to determine the effect of each excipient on drug stability. In addition, they grouped together all excipients as a factor and interpreted the data by Analysis of Variance using F-ratio, to test whether the means of normally distributed populations are equal, and the calculation of p-value. The data presented interesting insights into the relative stability of the two drug substances as a function of these factors and their interactions. However, these only represent a fraction of all possibilities that may potentially arise in a commercial formulation.

Thus, in many instances, compatibility studies are aimed at retrospectively solving stability issues with a known formulation and manufacturing process. In such cases, studies are carried out with the exclusion of only one component in each sub-lot to identify the source of incompatibility (2). Such mini-formulation studies can be very informative and can be carried out to much greater depths, and are often

very useful. However, practical considerations of study volume still may require some statistical methods, such as the Plackett-Burman design, to reduce the number of experiments. This design minimizes the number of experimental runs and is capable of finding the excipients that cause major incompatibilities. It can examine *n* excipients in *n+1* experimental runs (159). This design was utilized by Durig and Fassihi to investigate the compatibility of pyridoxal HCl with 11 excipients at two temperature (25° and 55°C) and humidity (11% and 75% RH) conditions using only 16 experimental runs (160). In this study, they included 8 experiments over the minimum required to study the effect of 'pseudo-variables' to account for random experimental variation. This approach, however, does not take into account the variation in the concentration of excipients depending upon the number of components present in the mixture.

Thus, while compatibility studies do represent a vital screening tool to identify and avoid gross incompatibilities when selecting a formulation, their inherent limitations and low tolerance (acceptable concentration) for impurities in drug products frequently require more in-depth studies after formulation and process selection.

Accelerated Stability Testing and its Limitations

Accelerated stability testing is utilized for enhanced mechanistic understanding of physicochemical stability as well as for expiration dating of drug products. Typically, drug degradation rate studies are carried out at various fixed temperature and humidity levels with sampling and testing at different time points. For chemical degradation of the drug, only the initial rate of formation of the degradant is utilized since the permissible extent of formation of degradant in the drug product is low and the reaction kinetics could be very different between the initial and late phases. The initial degradation rates are frequently fit to a linear regression model with confidence intervals to account for variability in the data (161).

Sometimes, an isoconversional analysis is utilized, wherein time to a particular degradant level at different fixed temperature and humidity conditions is quantified. In either case, a humidity corrected Arrhenius equation (162) is used to estimate the combined effect of temperature and humidity on the rate of formation of a particular degradant. Thus, Eq. 8 describes the degradation rate, *k*, in terms of Arrhenius collision frequency constant, *A*, the activation energy, *Ea*, gas constant, *R*, temperature in Kelvin, *T*, and the humidity sensitivity constant, *B* as follows.

$$k = Ae^{-\frac{E_a}{RT} + B(RH)} \quad (11)$$

Mechanistic understanding of the degradation pathway forms the cornerstone of drug product stabilization and stability prediction. Limitations of accelerated stability testing become evident in limited predictability in cases where degradation mechanisms are not well understood. For example, free radical induced oxidative drug degradation often shows initial lag phase before the degradation becomes apparent. Similarly, crystallization of an amorphous drug in a solid dispersion follows a lag phase. Sinclair *et al.* reported the solid-state crystallization kinetics of an amorphous solid dispersed drug substance, ibipinabant, in a tablet (163). The authors observed a two-step rate process for the crystallization kinetics, which included an induction (nucleation) period and a cyrstal growth phase. The data was fit to the JMA model of random nucleation and crystal growth in amorphous systems, which indicated that crystallization consisted of either a sporadic nucleation process with an induction period followed by a rod-like crystal growth or an instantaneous nucleation process with disk-like crystal growth (163). In such cases, accelerated stability testing or limited real-time stability data may not be an accurate predictor of long term storage stability.

Modeling Tools Based on Mechanistic Studies

Construction of mathematical models that adequately predict drug product stability is feasible where degradation mechanism is elucidated and the factors influencing degradation are well controlled. For example, Kontny *et al.* utilized a sorption–desorption moisture transfer (SDMT) model to assess the level of moisture in a packaged drug product (164). The authors accounted for the moisture permeation properties of the package, the initial masses and moisture contents of the formulation and the desiccant, and the total moisture sorption capacity as well as the isotherm of the formulation and the desiccant to predict whether a desiccant would offer significant moisture protection for a sensitive product. This information can be utilized for predicting the humidity level inside the package throughout the storage condition using the SDMT (164) or other models (165). This strategy can be utilized for package selection to identify if a package can maintain the moisture content in the tablet below a threshold RH that is known to affect drug stability (47,166). This approach was extended by combining RH prediction within the package with kinetic equation for drug degradation rate dependence on temperature and humidity to predict the formation of a hydrolytic degradation product in tablets (167,168). This model allowed fairly accurate prediction of the extent of formation of the hydrolytic degradant at early time points during storage.

CONCLUSIONS

Emerging mechanistic understanding of the basis of drug-excipient interactions leading to chemical instability in solid

dosage forms has allowed distinction between drug-excipient interactions and drug interactions with excipient impurities. In addition, cases where interactions between excipients may impact drug product instability have become apparent. These mechanistic aspects have highlighted certain underlying themes, including the role of water affecting mobility of reactive components, and microenvironmental pH affecting disproportionation of salts, and proportion of more reactive free base or free acid form of the drug. The emerging understanding of common mechanistic themes have further implications on practical aspects of excipient compatibility studies, accelerated stability testing, and mathematical prediction of drug product instability over its shelf life storage. While general basis and emerging understanding in these areas are highlighted in this review, these areas continue to evolve with greater regulatory and industry emphasis on quality by design—which requires mechanistic understanding of causative phenomena affecting drug product stability. As highlighted in this paper, several mechanistic aspects of drug-excipient interactions are not yet fully understood, which can form the basis of further research in this area. Examples of such 'gaps' in mechanistic understanding include the basis of 'physical' drug excipient interactions that lead to generally higher drug degradation rates in solid dosage forms than APIs alone, degradation of excipients that lead to the formation of reactive impurities during storage, and the mechanism of dissolution slowdown sometimes attributed to changes in binder and disintegrant properties on stability instead of interaction of reactive impurities in the formulation with the excipients.

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