Understanding Drug Properties in Formulation and Process Design of Solid Oral Products

Deliang Zhou and Yihong Qiu

"Product and Process Design" discusses scientific and technical principles associated with pharmaceutical product development useful to practitioners in validation and compliance. We intend this column to be a useful resource for daily work applications. The primary objective for this feature: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Yihong Qiu at qiu.yihong@abbott.com or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS
The following key points are discussed:

• A solid dosage form is a complex mixture of multiple solid components. A systematic application of scientific principles to formulation and process design results in an increased level of product and process understanding. This approach enables higher levels of assuring assurance of product quality and performance, more robust manufacturing processes, improved efficiency, and other benefits. This approach is consistent with the basic principle of quality by design (QbD).
• The goal of product design is to consistently deliver the intended dose of a drug in a bioavailable, safe, and efficacious manner.
• Most drug substances do not possess desirable or consistent physical, chemical, biopharmaceutical, and mechanical properties to allow for a straightforward application of simple formulation and process. Proper design of enabling formulation and manufacturing processes is usually necessary.
• Rational formulation and process design starts with understanding drug properties such as solubility, dissolution rate, permeability, stability, and mechanical properties, and how they may influence product quality, performance, and manufacturing.
• Properties and required dose of a drug substance generally affect formulation and process design, including selection of dosage form, mode of drug release, bioavailability, stability, manufacturing process and manufacturability.
• In selecting formulation composition and processing technology, it is important not only to aim at achieving predefined product quality attributes, but also to strive for understanding and anticipating how the selected composition and process may influence product quality and performance. Further, variability in the chosen materials and processes must be effectively controlled and monitored such that formulation or process can consistently yield desired quality attributes throughout the product lifecycle.

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• A unified approach to formulation and process development should be adopted in order to achieve desired product quality attributes, improve formulation and process understanding, anticipate the impacts of formulation and process on product quality and performance, and consistently produce products with predefined quality.

• The primary objectives in the preformulation studies are to elucidate various drug properties, identify potential barriers, and evaluate strategies to overcome such barriers.

• Drug properties, required dose, and mode of drug delivery usually dictate the choice of the type of dosage form to be developed. Options comprise immediate release (IR) and modified release. Modified release includes delayed release (DR) and extended release (ER).

• The in vivo performance of a drug product in terms of bioavailability is an important product quality that provides a link to the clinical performance of the product. The active pharmaceutical ingredient (API) is categorized using the biopharmaceutics classification system (BCS).

• Different solid forms, such as polymorphs, hydrates, amorphous, and salts are known to exhibit different properties that often affect solubility, stability, and processing behavior. Selection of an appropriate solid form with desired properties is also an integral part of formulation and process design.

• Chemical and physical stability is a critical product quality attribute that is directly linked to potency, purity, efficacy, and safety of a drug product throughout its shelf life. Common drug degradation pathways include thermolytic (e.g., hydrolysis), oxidative, and photolytic. Physical stability refers to changes in the physical characteristics of the formulation ingredients of a drug product such as phase transformation of the drug or excipients. The degradation susceptibility of a drug molecule can often be predicted to a large extent from the knowledge of the drug, its molecular structure, past experience, and theoretical calculations.

• Designing effective, efficient, and robust manufacturing processes plays an important role in achieving and assuring product quality and performance in accordance with QbD.

• It is important for validation and compliance personnel to have a general understanding of the principles of rational formulation and process development, the potential impacts of changes in drug properties, formulation, process, and their interplays in order to gain better product understanding, to ensure quality product, and to facilitate changes and continuous improvement post product launch.

• Two case studies demonstrating the importance of understanding API properties are discussed. One study addressed API physical changes in wet granulation. The other optimized the product pH to achieve maximum product stability.

• By systematically applying multidisciplinary knowledge and understanding drug properties, formulation and processing technologies, and their interactions, a product and a robust manufacturing process can be developed. An increased level of understanding will assure product quality and performance, define product and process control, develop risk management strategy, improve efficiency and streamline post approval changes, and offer opportunities for continual improvement post product launch.

INTRODUCTION

A solid dosage form (i.e., tablets, capsules, powders, and similar products) is a complex mixture of multiple solid components consisting of many solid phases. Because of the challenges in applying the principles of basic and applied sciences in understanding such systems, various approaches have been utilized in solid product design. Some scientists may tend to rely more heavily on empirical or even “shotgun” approaches that often result in low efficiency or poorly understood product and process. Others use a more rational approach by systematically applying scientific principles to formulation and process design for an increased level of product and process understanding. Adopting the latter approach can result in many benefits for the patients, industry, and the regulatory bodies such as higher levels of assurance of product quality and performance, more robust manufacturing process and control, improved efficiency, increased cost savings, and enhanced opportunities for first cycle regulatory approval. It can also help develop risk management strategy, streamline post approval changes, and offer opportunities for continual improvement post product launch. In fact, this approach is consistent with the basic principle of quality by design (QbD).
Rational formulation and process design should start with understanding drug properties that play a critical role in determining whether or not a specific target product profile (TPP) can be achieved. Among the most important properties that should be considered during formulation and process design are solubility, dose, dissolution rate, permeability, stability, deformation, flow, and compaction properties. These properties have been discussed in previous columns (1-5). This column discusses considerations and application of these properties in formulation and process design.

SELECTION OF FORMULATION COMPONENTS AND PROCESSING TECHNOLOGY

The goal of product design is to consistently deliver the intended dose of a drug in a bioavailable, safe, and efficacious manner. One of the key components in rational formulation and process design is to acquire and utilize knowledge of drug properties to facilitate the application of various basic and applied sciences, such as pharmaceutical sciences, various branches of chemistry, biological sciences, engineering principles, and statistics in the product development process. Properties of a drug molecule often dictate how readily the drug is absorbed from the gastrointestinal (GI) tract (bioavailability), how long the product can be stored (stability), and whether the drug product can be manufactured consistently on a commercial scale (manufacturability) especially when drug loading is relatively high or very low. Potential challenges and barriers to the development of a drug product with desired quality and performance can be identified and evaluated through the assessment of drug properties. Hence, understanding drug properties in relation to formulation and process characteristics and biopharmaceutics is essential to the successful design of a high quality product with predefined delivery and pharmacokinetic performance.

Most drug substances do not possess desirable or consistent physical, chemical, biopharmaceutical, and mechanical properties to allow for a straightforward application of simple formulation and process development including direct compression or direct blending for capsule filling. For example, many high-dose drugs lack acceptable flow and compaction properties. Many low-dose drugs (e.g., milligram or micrograms) may not have desired particle density, shape, and size distribution for producing consistently uniform powder blends especially at larger scales. Some drugs may be chemically labile. Some drugs are poorly water soluble and unfavorable to oral absorption. Proper design of formulation and manufacturing processes that address problematic drug properties is usually necessary. To illustrate how a formulation is assembled and an associated manufacturing process is selected, conventional immediate release (IR) tablet dosage forms are considered.

Design of an IR Dosage Form

Composition of an IR tablet formulation typically consists of the active drug (from <1% to > 50%), fillers or diluents, binder, disintegrant, lubricant or glidant, and other inactive ingredients as needed (e.g., stabilizer, dissolution enhancer, processing aid, etc.). Various excipients and grades of the same excipients are available to serve similar or same functions in a tablet formulation. However, each excipient has its unique physical, chemical, and mechanical characteristics that require consideration. Common process options for manufacturing the tablets include direct compression, wet granulation, dry granulation, and melt granulation. Each of these includes several unit operations such as milling, sizing, blending, compaction, coating, and so on. Furthermore, processing operations of each type of the processes also vary with equipment used. For example, wet granulation processing conditions are different for a fluid bed and a high-shear granulator. Unit operations and process parameters of a melt granulation process differ depending on whether higher shear, spray-congealing, or melt-extrusion method is used. The general aspects of solid dosage forms, excipients, related formulation and processing technologies can be found in commonly used textbooks and reference books (6). In many cases, tablets with similar quality attributes can be prepared using different combinations of formulation and manufacturing processes. However, consistency, scalability, efficiency, and robustness of different formulations and processes often depend on whether the design of a product and associated manufacturing process is based on an empirical or a science-based rational approach.

In selecting formulation composition and processing technology, it is important not only to aim at achieving predefined product quality attributes, but also to strive for understanding and anticipating how the selected composition and process may influence product quality and performance. Further, variability in the chosen materials and processes must be effectively controlled and monitored such that formula-
tion or process can consistently yield desired quality attributes throughout the product lifecycle. To achieve these objectives, formulation and process should not be selected in isolation. Instead, a unified view of formulation and process development should be adopted and knowledge of drug properties and their interrelations with formulation and manufacturing process should be utilized. For example, designing formulation composition requires consideration of the properties, functionality, and processing characteristics of its ingredients with respect to product quality and performance and possible material-process interactions. Selection of the process train needs to consider how each unit operation may affect material characteristics and product quality and performance. An integrated formulation and process design based on understanding of drug properties is essential to the development of robust product and manufacturing processes. It also helps ensure optimal efficiency and productivity, and minimize potential material-related processing issues or process-related performance and quality problems.

**CONSIDERATIONS OF DRUG PROPERTIES IN FORMULATION AND PROCESS DESIGN**

Design of a drug product should start with the end in mind (i.e., formulation and process design should be centered on a predefined quality target product profile [QTPP]) (7). International Conference on Harmonisation (ICH) Q8 defines QTPP as the prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, safety, and efficacy of the drug product. QTPP forms the basis of design for the development of a new product. QTPP generally includes route of administration, dosage strength, dosage form, container closure system, product quality attributes (e.g., purity, stability, and drug release), and predefined delivery and pharmacokinetic performance. Additional factors that also require consideration include production, commercial needs, intellectual property, etc.

Dosage form development involves design and development of formulation and its manufacturing process. With a predefined QTPP, the first step in formulation and process design is to gain knowledge of the drug substance including its physicochemical, biopharmaceutics and mechanical properties, and compatibility with excipients through preformulation investigation or literature search. The next step is to design the formulation and evaluate process feasibility and options. Because there are often more than one ways to produce a solid dosage form with predefined quality attributes, selection of appropriate formulation components and manufacture process should be based on scientific knowledge and technological, economical, and practical considerations. More specifically, choice of formulation ingredients requires systematic understanding of their functionality, properties, and processing behaviors in relation to the drug substance and in the context of a specific process train. Selection of a manufacturing process requires consideration of existing processing technologies, characteristics of drug substance and excipients, development cost and time, process complexity, robustness, scale-up challenges, manufacturability and control, commercial production cost, capacity and efficiency, along with equipment availability, facility, and environmental impact.

It has been well established that drug properties, such as solubility, permeability, purity, stability, solid form, morphology, particle size and distribution, surface properties, and mechanical properties, can potentially impact quality and processing behaviors of drug products. The primary objectives in the preformulation studies are to elucidate various drug properties, identify potential barriers, and evaluate strategies to overcome such barriers. For example, low or erratic oral bioavailability that is often observed with poorly soluble drugs may be overcome by designing a solid dispersion containing amorphous drug. For a moisture-sensitive drug, tablets can be prepared using dry granulation or a direct compression manufacturing process, or a more stable solid form of the drug substance. To facilitate formulation and process design and ensure consistent product quality, a drug substance with reproducible characteristics should be used. In the following sections, the influence of drug properties on formulation and process design is discussed in the context of certain key components of product QTPP and manufacturability.

**Dosage Forms and Mode of Drug Release**

Drug properties, required dose, and mode of drug delivery usually dictate the choice of the type of dosage form and determine the overall approach to formulation and process design. Main formulation components and technologies for drug delivery and product manufacturing process may be selected once a specific mode of drug release and type of dosage form are defined.

**Immediate release.** Immediate release (IR) dosage forms are designed to render drug molecules
Delayed release (DR) dosage form is designed to provide drug-release characteristics that are chosen to accomplish therapeutic or convenience objectives not offered by an IR dosage form. These include both delayed and extended release drug products (8).

**Modified release.** A modified-release (MR) dosage form is designed to provide drug-release characteristics that are chosen to accomplish therapeutic or convenience objectives not offered by an IR dosage form. These include both delayed and extended release drug products (8).

**Delayed release.** Delayed release (DR) dosage forms are designed to release a drug at a time other than immediately following oral administration. The need for a DR delivery usually varies with the physicochemical or biopharmaceutical properties of drug molecules. For instance, certain drug molecules that are acid-labile require a delay of drug release in the acidic stomach until it reaches the small intestine. Some drugs intended for treating local condition in the lower GI tract (e.g., colon) are also designed as a DR dosage form. In most cases, delayed release dosage forms are manufactured by coating single unit or multi-particulates using an enteric polymer. Enteric polymers are insoluble at gastric pH and dissolve at intestinal pH. Depending on drug properties and design objective (e.g., the extent of release delay), different polymers or different amount of a polymer may be used. For example, Eudragit L 55 consisting of random copolymer of ethyl methacrylate (EMA) and methacrylic acid (MA) at ~ 1:1 ratio is soluble at pH > 5.5. Eudragit L 100, a copolymer of methyl methacrylate (MMA) and methacrylic acid (MA) at ~1:1 ratio, is soluble at pH > 6. Eudragit S (100) made of the same monomers but with more insoluble component (MMA : MA = 2:1) is soluble at pH > 7. These polymers may be used alone or in combination to achieve a predetermined release delay. With regard to coating dosage forms, a pan coater is often chosen for single-unit tablets containing drug with low-high required dose, while Wurster coating in a fluidized bed is generally used for multi-particulates for drugs that require low-medium dose.

**Extended release.** Extended-release (ER) dosage forms are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as an IR dosage form. Several types of ER delivery technologies have been commonly utilized over the years, such as a reservoir system, osmotic pump, and the hydrophilic matrix tablet. Each technology has its unique features, advantages and disadvantages. Drug properties and required dose usually play an important role in selecting appropriate ER technologies and formulation composition. For example, assessing technical feasibility and designing an extended-release dosage form should be based on an understanding of permeability and solubility of the drug substance. If a drug molecule is poorly absorbed in the lower GI tract, it is generally not a suitable candidate for developing an ER dosage form. For a drug with low solubility, a hydrophilic matrix or bilayer osmotic pump system should be used to achieve zero-order release. Reservoir delivery systems are not suitable because they require high concentration gradient (solubility) across the rate-controlling membrane as its driving force for drug release.

**Oral Bioavailability**

The *in vivo* performance of a drug product in terms of bioavailability (BA) is an important product quality that provides a link to the clinical performance of the product with respect to safety and efficacy. Oral bioavailability depends on properties of drug, formulation, and process design that usually determine the extent and rate at which the drug dissolves in the gastrointestinal tract. Among drug properties that are most critical to oral absorption are solubility and intestinal permeability as defined by the biopharmaceutics classification system (BCS) discussed previously (3, 4).

When designing formulation and process for an IR dosage form of BCS class I drugs with favorable solubility and permeability, oral bioavailability is often not a major concern as long as rapid dissolution can be ensured and inactive ingredients selected do not significantly affect absorption of the active ingredients. Thus, the primary focus is generally on ensuring acceptable stability and designing a robust manufacturing process based on the understanding of the physical and mechanical properties of the drug and excipients. Similar design considerations also apply to BCS III compounds, as rapid dissolution can often be achieved via conventional formulation design and intestinal permeability is normally the rate-controlling step in oral drug absorption. However, attention should be given to the excipients to ensure that they do not affect drug permeability or drug intestinal residence time.
Achieving high or consistent exposure of BCS II and IV drugs in the systemic circulation is often more challenging due to low solubility. Hence, integrated formulation and process design becomes more important for these types of drugs. Selection of enabling formulation technologies should be based on consideration of drug properties in order to enhance dissolution or bioavailability and ensure stability while designing a matching process that facilitates or is synergistic with formulation technology, does not result in negative impact on solubility or stability, and is scalable and robust. For example, the use of a small quantity of wetting agents (e.g., surfactants) is one of the formulation approaches to improve dissolution rate of an insoluble compound through increasing effective surface area. The effectiveness of such approach depends on the manufacturing process. When the small amount of wetting agent incorporated in the formulation is dissolved in the granulation fluid in a wet granulation process, its efficiency can be greatly enhanced via coating on the surface of drug particles following drying operation when compared to dry mixing the surfactant(s) with drug and excipients or using a direct compression or dry granulation process.

**API polymorphism and other solid forms.** Different solid forms, such as polymorphs, hydrates, amorphous, and salts are known to exhibit different properties that often affect solubility, stability, and processing behavior. Thus, selection of an appropriate solid form with desired properties is also an integral part of formulation and process design. In fact, improving solubility and dissolution via selection of an optimal solid form has become an essential part of drug product development, especially for BCS II or IV drugs. For example, among various solid forms, amorphous drug is known to have the highest apparent solubility or dissolution rate as a result of its high free energy compared to the crystalline counterparts. With increased understanding of amorphous materials in pharmaceutical development over the past decade, amorphous solid dispersion (ASD) has become one of the most important technologies for improving bioavailability of poorly water soluble compounds. However, the amorphous phase is thermodynamically unstable and will eventually revert to a crystalline phase if uncontrolled, negating its intended benefit. As a result, physical stability of amorphous solid dispersions often represents a significant challenge in formulation and process design. In recent years, significant progress has been made in understanding the physical stability of amorphous drugs and amorphous solid dispersions. It has been found that molecular motion provides a necessary condition for physical or chemical instability and mobility is a key determining factor. Studies have also suggested that configurational entropy of the amorphous phase plays an important role. ASD contains amorphous drug substance dispersed in a polymeric matrix. In designing amorphous dispersions, proper selection of formulation components provides an opportunity to control and inhibit the crystallization tendency of the drug. For example, physical stability can be enhanced by using a dispersion containing both polymer and surfactants (e.g., Tween and Span) to improve solubilization of the drug substance, thereby reducing thermodynamic driving force for crystallization as compared to the use of pure amorphous drugs. Furthermore, selection of an appropriate polymer that may inhibit crystallization of the amorphous phase during storage and during in vivo dissolution is also an important consideration in achieving acceptable shelf life and bioavailability. In many cases, polymers that are typically used as an ASD carrier (e.g., Kollidone, PVP, HPMC, HPMCAS) also increase the glass transition temperature (Tg), resulting in decreased molecular mobility. All these factors should be considered during formulation and process design in order to optimize its physical stability.

**Chemical and Physical Stability**

Stability is a critical product quality attribute that is directly linked to potency, purity, efficacy, and safety of a drug product throughout its shelf-life. For most drug substances, the stability of the drug product depends not only on properties of drug, but also on formulation and process design.

**Chemical stability—hydrolysis, oxidation, and photolysis.** When a drug molecule is chemically unstable, the first step in product design should be to understand the intrinsic stability of the drug molecule and its degradation mechanisms. Common drug degradation pathways include thermolytic (e.g., hydrolysis), oxidative, and photolytic. Among them, the photolytic degradation can be usually mitigated by reducing or eliminating light exposure using coating or appropriate container closure system. The most prevalent drug degradation pathway is hydrolysis, followed by oxidation. Hydrolysis is a well understood pathway that can be found in many standard organic chemistry textbooks. Oxidative degradation is more complex and has been less understood until more recently. In general, three mechanisms exist for oxidation: Nucleophilic/electrophilic, electron
transfer, and autoxidation. Nucleophilic/electrophilic process occurs between drug and peroxide. Electron transfer often proceeds via the catalysis of transition metals, such as Fe$^{2+}$ and Cu$^{2+}$. Autoxidation is mediated by free-radicals. Oxidative degradation is usually exacerbated by minor impurities such as peroxides and metals that often exist in various excipients.

Drug degradation in crystalline solids is often initiated by defects (i.e., the non-crystalline [amorphous] regions) and various other crystal imperfections such as surface imperfections. Most of these reactions are mediated by moisture because a pure topochemical reaction is rare for drug degradation. Water can be involved directly in a reaction such as hydrolysis. The presence of moisture may form a thin layer of solution on the crystal surface or can plasticize the amorphous regions (11), resulting in increased molecular mobility and reactivity. The presence of moisture may also facilitate the creation of a microenvironment that enhances drug degradation.

Drug degradation is more complex in a formulated product, a multi-component heterogeneous system. Some commonly-used excipients are known to interact directly with certain drug molecules. A well-known example is the Maillard reaction between a primary or secondary amine and a reducing sugar (e.g., lactose/glucose). However, many interactions between drug molecules and excipients are non-specific and not well understood. This type of non-specific drug-excipient interactions may sometimes lead to significant stability problems in formulation while the drug substance alone is stable. In such cases, level of degradation is often linked to drug loading rather than the absolute amount of drug. More significant degradation is usually associated with lower drug loading in the formulation due to higher excipient-to-drug ratio. Drug degradation may also be enhanced due to the change of microenvironment pH created by the excipients present in the formulation. In addition, excipients can be a source of various impurities such as peroxide and metal ions that have been linked to increased drug oxidation. It is known that peroxides exist in a number of excipients such as povidone, crospovidone, polyethylene glycol, polysorbates, and other modified excipients containing polyoxyethylene moieties. Therefore, rational selection of formulation components based on understanding of properties of drug and excipient as well as and their interaction is essential.

Physical stability. Physical stability refers to changes in the physical characteristics of the formulation ingredients of a drug product such as phase transformation of the drug or excipients. Typical phase transformations include polymorphic conversion, hydration or dehydration, crystallization or amorphization, salt-to-parent form conversion, glass transition, and other mechanisms. Because the physical, chemical, and mechanical properties may differ significantly among various solid forms, these phase transformations can potentially alter the quality attributes and processing behaviors of a drug product. For example, partial or complete phase transformation may occur during processing operations (12) resulting in increased levels of defect or formation of amorphous phase that can be detrimental to chemical stability. Therefore, rational design of a manufacturing process should be based on understanding of properties of drug substance and its interplay with each unit operation.

Predicting drug stability. The degradation susceptibility of a drug molecule can often be predicted to a large extent from the knowledge of the drug, its molecular structure, past experience, and theoretical calculations. Thus, formulation and process should be designed to resolve or control chemical or physical instability problems through understanding of the drug substance. For example, to minimize hydrolysis, control of moisture and microenvironment pH in the formulation, incorporation of desiccants in the container closure system, or selection of a dry manufacturing process may be considered during the product design. To mitigate oxidative degradation, an antioxidant and oxygen scavenger may be incorporated into a formulation or container closure system. To avoid or control process-induced phase transition, proper selection of the unit operation or ingredient(s) that inhibit phase changes may be considered. In certain case, appropriate solid form may be selected to reduce or minimize degradation such that no additional stability remedies via the formulation, processing, and packaging are necessary.

Manufacturability

Designing effective, efficient, and robust manufacturing processes plays an important role in achieving and assuring product quality and performance according to QbD. It forms the foundation for consistent production of quality products, process control, overall plant performance, efficiency improvements and cost reductions while maintaining regulatory compliance. To prevent or mitigate the risk of producing an inconsistent or low quality product, process design
should be based on considerations of both engineering aspects of a chosen process train and properties of the drug substance and excipients. More specifically, it requires an increased level of scientific understanding of how formulation and process factors as well as interactions between raw materials and processing operations affect product quality and performance, process capability, and process control.

Capsule and tablets are the most common solid dosage forms. The most important material properties to consider in the process design are powder flow and powder compaction, both of which are a function of physical and mechanical properties of the drug and excipients. Many drug substances are not suitable candidates for simpler manufacturing process, such as direct blending or compression due to a lack of adequate flowability or favorable compaction properties. Thus, enabling or improving manufacturability via an appropriate formulation and process design is usually necessary, especially for products with high drug or low drug loading. Granulation processing technology is most commonly used to improve the flow, compaction properties, or content uniformity and to prevent powder segregation during powder handling. Excipients with complementary powder consolidation mechanisms or favorable flow properties are also used in designing a drug product. For example, starch and microcrystalline cellulose primarily undergo plastic deformation, while lactose and dicalcium phosphate are less sensitive to strain rate during compaction. A combination of these excipients is often used to aid the design of a product with a robust manufacturing process. In designing a bilayer tablet, choice of ingredients of the two layers requires consideration of bonding properties, deformation mechanisms, and strain-rate sensitivity of both the drug substance and the excipients. Use of materials with significantly different strain-stress behaviors between layers can result in time-dependent delamination of the bilayer tablet.

Other properties of the drug substance that require consideration during process design include solubility, stability, solid form, deformation property, morphology, particle size, density, melting point and their interactions with excipients. Different solid phases usually have different processing characteristics. Thus, solid form selection of the drug substance may be used to modify drug properties for overcoming processing problems or for improving manufacturability. For instance, crystal forms of acetaminophen are known to exhibit different compressibility. Form II has been reported to have improved tableting properties and can be used in direct compression due to the presence of slip planes (13). Drugs or solid forms with low melting points are often undesirable due to their propensity to cause problems during unit operations such as milling, drying, and compaction. One of the approaches to solve this problem is by forming a salt with stronger crystal packing if feasible. However, for melt extrusion process, a lower melting solid form is sometimes preferred over a high crystalline, high melting salt form. Solid phase transformation induced by manufacturing process is known to potentially affect quality attributes and processing behaviors of a drug product. For example, solid-state transition (recrystallization) of amorphous or metastable form of an active or excipient formed during processing (e.g., granulation, compaction) may take place slowly over time, especially during storage under increased temperature or humidity. This type of transition may lead to increasing hardness of a tablet and decreasing dissolution rate over time for an IR tablet.

IMPLICATIONS OF PRODUCT AND PROCESS UNDERSTANDING IN VALIDATION AND COMPLIANCE

The information discussed in this article is fundamental to the rational design of formulation and manufacturing process for solid oral dosage forms. Validation and compliance personnel should have a general understanding of the properties of the drug and their role in the drug product and process design. Specifically, they should be very aware of the drugs that may interact with excipients and manufacturing processes as well as processes that may potentially impact drug properties with respect to solubility, dissolution, and stability. They should be especially vigilant of formulation and manufacturing changes that may impact product quality and manufacturability. Validation protocols developed in response to such changes should require appropriate sampling and testing in support of the changes. Knowledge of the principle of formulation and process design must also be considered in determining appropriate validation testing.

Special attention should be paid to drugs of which the properties are most susceptible to changes in manufacturing process and excipients (i.e., source, grade, properties, etc.). Validation and compliance personnel should be watchful of changes in unit operations with potential to impact the solid form of drugs and excipients as well as other physicochemical
and mechanical properties known to affect solubility, stability, and processing behaviors. Consultation with development scientists is encouraged to thoroughly evaluate any proposed changes in formulation and manufacturing processes.

CASE STUDIES

ABT-232
ABT-232 (see Figure 1) is a compound selected for development as a potent uroselective $\alpha_1$A agonist (14). Preformulation studies showed that it is highly water-soluble, and chemically stable in the crystalline solid state as anhydrate or monohydrate. An amorphous form was also isolated, but it is highly hygroscopic and rapidly reverted to the crystalline form under ambient conditions in less than 10 minutes. No incompatibility was identified with a range of standard excipients except for lactose (Maillard reaction).

Solid dosage forms were developed to support clinical trials. Given the chemical stability and high solubility of ABT-232, a conventional IR tablet dosage form was prepared using commonly used functional excipients discussed previously. An ER matrix tablet formulation was also designed to evaluate effect of changing release rate on bioavailability. In the design of both formulations, drug loading was low due to the low dose (0.5 – 2 mg). To ensure content uniformity of low dose formulations, a wet granulation process was selected. However, upon storage under accelerated conditions, significant loss in potency (e.g., up to 15% under 40°C/75% RH for 6 months) and an increase in related substances were observed for the IR tablet. This finding appeared to be inconsistent with the results of the excipient compatibility study. Further investigations indicated that the drug was rendered mostly amorphous after granulation and drying operations. Because of the high water solubility and low dose, ABT-232 in the formulation was first dissolved during the wet granulation process and subsequently converted to amorphous drug upon drying. Unlike the pure drug substance, the resulting amorphous API in the formulation did not re-crystallize during the drying, likely due to the inhibitory effects on re-crystallization by polymeric excipients present in the formulation. The process-induced phase transformation was indirectly confirmed in an investigation using a model granulation containing higher drug loading (30%) which showed that, even after six weeks of storage at 40°C/75% RH, ~60% of the total drug substance in the granulation still remained amorphous. To overcome this chemical stability problem caused by solid phase transformation, direct compression tablets were designed. Acceptable content uniformity was achieved through selecting excipients with desirable flow properties and physical properties to prevent segregation. It should be noted that chemical instability was not observed with the ER matrix tablets based on hydroxypropyl methylcellulose (HPMC) though the same manufacturing process and similar drug loading were used. This is likely related to the type and quantity of polymers used in the ER formulation. This example highlights the importance of understanding properties of materials, their interactions with each other, and with manufacturing process in formulation and process design.

Moexipril Hydrochloride
Moexipril (Figure 2) is a dipeptide angiotensin-converting enzyme (ACE) inhibitor. The compound has two ionizable groups: the carboxylic acid group with $pK_{a1} = 3.0$ (25°C), and the amino group with $pK_{a2} = 5.4$ (25°C). Preformulation studies indicated that moexipril is highly water soluble but stability may be of concern (15). The compound undergoes intramolecular aminolysis leading a diketopiperazine.
(DKP) formation at pH < 4, hydrolysis at pH > 5, and epimerization in addition to hydrolysis at pH > 7. The pH-rate profile is shown in Figure 3. The effect of ionization on the overall reactivity is evident and the most stable region is pH 4-5.

A compatibility study of moexipril hydrochloride and various excipients was conducted to support product development and to address the potential stability issue (16). The study confirmed the challenging nature of the stability problem, particularly when the drug is exposed to moisture. Based on the pKa’s of moexipril, the saturated solution of the drug substance, a hydrochloride salt, is expected to have a pH of approximately 2, which falls within the unstable region of the pH-rate profile. Thus, the sensitivity of the drug to moisture can be attributed to the low pH of the solution on the surface of the solid drug substance. In general, for this type of drug, manufacturing process involving water should be avoided and moisture level of the dosage form should be controlled. However, it was also found in a further study that product stability could, in fact, be enhanced by wet granulating moexipril hydrochloride with basic excipients. The improved stability is likely a result of increased microenvironment pH in the formulation by incorporation of basic excipients (e.g., sodium bicarbonate, sodium carbonate, calcium carbonate).

It should be pointed out that based on pKa, the free base of moexipril is expected to result in a pH of approximately 4.2 on the solid surface, which falls within the stable region of the pH-rate profile. Therefore, the free base, instead of salt, should be selected for product development from the standpoint of chemical stability. If solubility enhancement of the free base is required, approaches other than salt formation may be used (e.g., amorphous solid dispersion). If solubility of the drug needs to be improved through salt formation, a counter ion should be chosen based on consideration of both solubility and stability. This example illustrates the importance of comprehensive evaluation of drug properties in the rational design of formulation and manufacturing process.

**SUMMARY**

One of the most critical aspects in rational design of solid product and manufacturing process is understanding the properties of the drug substance. Drug properties play a crucial role in determining how components and processing steps should be selected and whether a specific target product profile can be achieved. Among the most important properties that require consideration are physicochemical, biopharmaceutical, and mechanical properties.

By systematically applying multidisciplinary knowledge and understanding drug properties and formulation and processing technologies and their interactions, a product and a robust manufacturing process can be developed. An increased level of understanding will assure product quality and performance, define product and process control, develop risk management strategy, improve efficiency and streamline post approval changes, and offer opportunities for continual improvement post product launch.

**REFERENCES**


ARTICLE ACRONYM LISTING
ACE Angiotensin-converting Enzyme
API Active Pharmaceutical Ingredient
ASD Amorphous Solid Dispersion
BCS Biopharmaceutics Classification System
DKP Diketopiperazine
DR Delayed Release
EMA Ethyl Methacrylate
ER Extended Release
GI Gastrointestinal
IR Immediate Release
MA Methacrylic Acid
MMA Methyl Methacrylate
MR Modified Release
QbD Quality by Design
QTPP Quality Target Product Profile
TPP Target Product Profile