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DESIGN OF SOLID DOSAGE FORMULATIONS

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36.1 INTRODUCTION

The oral route is the most common way of administering drugs. It not only represents a convenient (self-administered) and safe way of drug administration but is also more profitable to manufacture than the parenteral dosage forms that must be administered, in most cases, by trained personnel. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systematic effects are marketed as oral dosage forms. Among the oral dosage forms (Table 36.1), tablets of various different types are the most common because of their low cost of manufacture (including packaging and shipping), increased stability, and virtual temper resistance.

Following oral administration of tablets, the delivery of the drug to the systemic circulation requires initial transport through the gastrointestinal (GI) membrane. The drug absorption from the GI tract requires that the drug is brought into solution in the GI fluids and that it is capable of crossing the intestinal membrane into the systemic circulation; therefore, the rate of dissolution of the drug in the GI lumen can be a rate-limiting step in the absorption of drugs given orally. Particles of drugs, for example, insoluble crystalline forms or specific delivery systems such as liposomes, are generally found to be absorbed to a very small extent. The cascade of events from release of the drug from tablet, that is, disintegration of tablet into granules or aggregates followed by dissolution of the drug in the gut lumen, interactions and/or degradation within the lumen, and the absorption of the drug across the intestinal membrane into the systemic circulation, is schematically shown in Figure 36.1. The slowest of these events (dissolution and/or absorption) determines the rate of availability of the drug from the tablet formulation. Many factors in each step influence the rate and extent of availability of the drug. Physical, chemical, and biopharmaceutical properties of the drug, as well as the design and production of the tablet, play a very important role in its bioavailability after oral administration. These considerations make the seemingly simple tablet formulation approach complex to formulate in reality. These realizations have resulted in a change in philosophy of tablet formulation design in the last decade or more, wherein it is no longer considered an art but well-defined science.

The single greatest challenge to the tablet formulator is in the definition of the purpose of the formulation and the identification of the suitable materials to meet development objectives. A good formulation must not only be bioavailable but also be manufacturable, and chemically and physically stable from manufacturing through the end of shelf life. In addition, many quality standards and requirements must be met to ensure the efficacy and safety of the product.

All these formulation goals can be described as the target product profile (TPP). A TPP is a summary of characteristics that if achieved will provide optimal efficacy, patient compliance, and marketability. A TPP (Table 36.2) often includes attributes such as pharmacokinetic information (e.g., immediate release (IR) versus extended release (ER)), dosage form (e.g., tablet versus injectable), and shelf life information (e.g., 2 years at 25°C/60% relative humidity (RH)). There are also many other potential inputs for drug development that a formulator may or may not need, such as warnings, and precautions, adverse reactions, drug interactions, use in specific populations, drug abuse and dependence, clinical studies, and patient counseling information.

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TABLE 36.1 Types of Solid Oral Dosage Forms

Type of Oral Dosage Form	Characteristics
Immediate release tablets	Disintegrate in stomach after taken orally
Delayed release tablets	Enteric-coated tablets to keep tablets intact in stomach and disintegrate in intestine for absorption
Sustained/controlled release tablets	Release drug slowly over a period of time to decrease the frequency of administration
Chewable tablets	Tablets are broken by chewing before swallowing with water
Orally disintegrating tablets	Disintegrate in oral cavity without drinking water to form a suspension for ease of swallowing
Hard gelatin capsules	Two-piece capsule shells filled with granules, powders, pellets, sprinkles, semisolids, oils
Soft gelatin capsules	One-piece capsule filled with oily liquid
Sachets	Single-dose unit bag containing granules

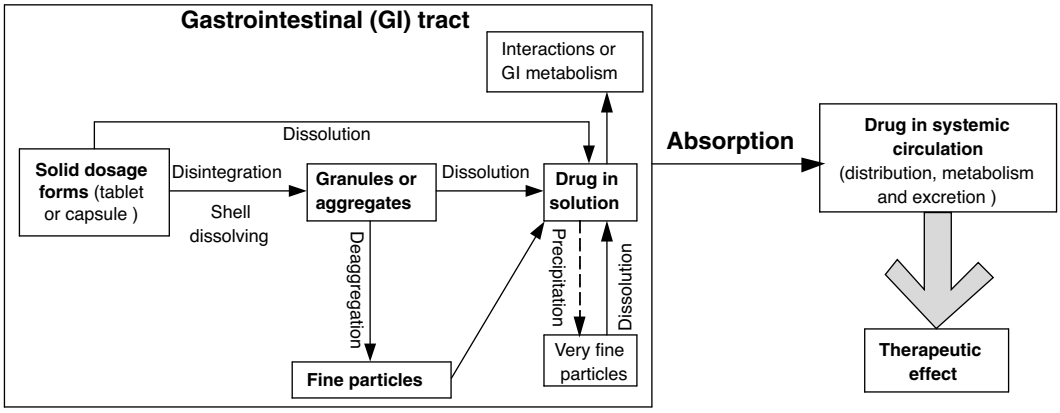


FIGURE 36.1 Fate of solid dosage form following oral administration.

It is important to establish the TPP so that the formulation effort can be effective and focused. When the formulation requirements are defined by the TPP, a strategy must be established to facilitate effective formulation development. To establish a formulation strategy, one must consider the physical, chemical, and biopharmaceutical characteristics of the drug; optimal technologies to achieve formulation goals; and the manufacturing capabilities to support the product.

This chapter examines tablet formulation design and development of an immediate release oral solid dosage form using a mix of pharmaceutical science, statistical, and engineering approaches. The chapter is aimed toward providing

TABLE 36.2 Typical Target Product Profile for an Immediate Release Tablet

Characteristic	How Used by a Formulator	Typical for IR Tablet
Indications and usage	Examine other products in the same class: examine improvements	Once a day (QD) Twice a day (BID) Three times a day (TID)
Dosage and administration	Good to know what is expected before one starts formulating	Oral tablet
Dosage forms and strengths	Multiple strengths may be needed depending on the population being targeted (adults versus children)	Dependent on drug, typically 10–500 mg
Overdosage	Useful if designing an extended release dosage, in which overdose (dose dumping) is a possibility	Dependent on drug
Description	This is up to the formulator and marketing: shape, size, and color of the tablet	A tablet with markings and color
Clinical pharmacology	Helps determine where the drug is absorbed and how fast the drug must get into solution	Dependent on drug
How supplied/stored/handled	Important as most people do not like refrigerated dosage forms	Two years room temperature shelf life

engineers an overview of the key physicochemical, mechanical, and biopharmaceutical properties of the drug and their influence on the selection of formulation process platform. Subsequently, critical tablet characteristics that affect the stability and bioavailability of the drug product are discussed. Finally, strategy for tablet process optimization and scale-up is defined to select proper equipment and to define operational design space. A systematic scientific approach to tablet formulation and process development along with practical examples is discussed to expedite the drug product development.

36.2 UNDERSTANDING DRUG SUBSTANCE

Integration of physicochemical, mechanical, and biopharmaceutical properties of a drug candidate is a prerequisite in developing a robust and bioavailable drug product that has optimal therapeutic efficacy. The measurement of physical, mechanical, and chemical properties not only helps guide the selection of dosage form but also provides an insight into their processability and storage to ensure optimal drug product quality. Figure 36.2 lists the critical physicochemical, mechanical, and biopharmaceutical properties that need to be understood to aid in design of tablet formulation.

36.2.1 Physicochemical Properties

Prior to the development of tablet dosage form, it is essential to determine certain fundamental physical and chemical properties of the drug molecule along with other derived properties. This information dictates many of the subsequent approaches in tablet formulation development and is known as preformulation. It should be kept in mind that many of these properties are dependent on the solid form, and complete characterization of each of the most relevant solid forms is needed to provide a complete physicochemical picture.

36.2.1.1 Solubility and Drug Dissolution Solubility of a drug candidate may be the critical factor in determining its usefulness, since aqueous solubility dictates the amount of compound that dissolves, and therefore, the amount available for absorption. A compound with low aqueous solubility could be subject to dissolution rate-limited absorption within the GI residence time.

Dissolution is the dynamic process by which a material is dissolved in a solvent that is characterized by a rate (amount dissolved per time unit), while *solubility* is the amount of material dissolved per unit volume of a certain solvent that is characterized by a concentration. Solubility is often used as a short form for "saturation solubility," which is the

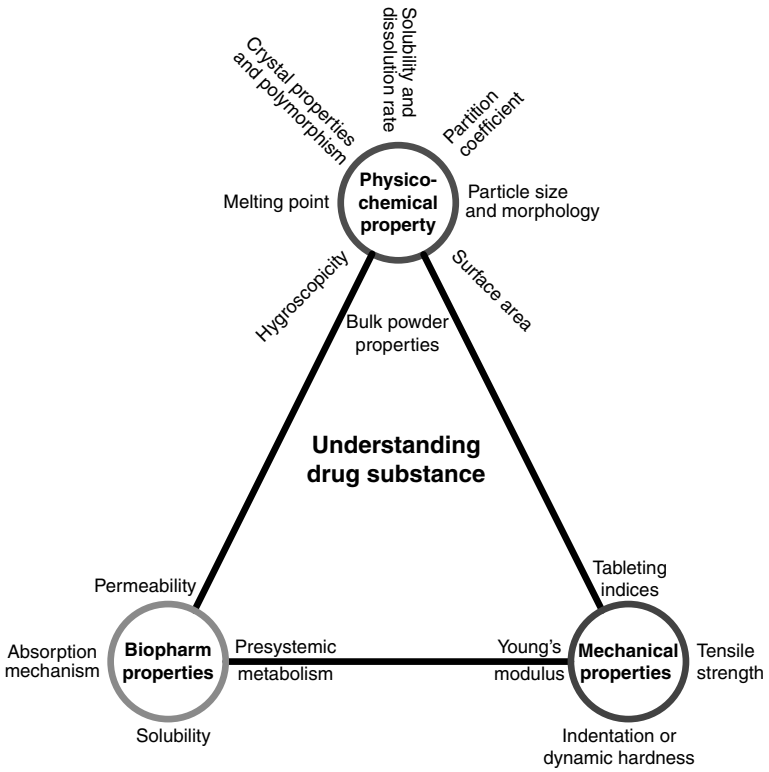


FIGURE 36.2 Understanding drug substance properties.

maximum amount of drug dissolved at equilibrium conditions. Finally, *intrinsic solubility* is the solubility of the neutral form of an ionizable drug.

Dissolution rate is directly proportional to the aqueous solubility, C_s, and the surface area, A, of drug exposed to the dissolution medium. It is a common, when developing an immediate release dosage form of poorly soluble drug, to increase drug dissolution rate by increasing the surface area of a drug through particle size reduction.

The dissolution rate of a solute from a solution is described by the Noyes–Whitney equation as follows [1]:

$$\frac{dC}{dt} = \left(\frac{D \times A}{h}\right) \times (C_s - C_t) \tag{36.1}$$

where D is the diffusion coefficient of the drug substance in a stagnant water layer around each drug particle with a thickness h, A is the drug particle surface area, C_s is the saturation solubility, and C_t is the drug concentration in the bulk solution at a given time.

The dissolution rate, rather than the saturation solubility, is most often the primary determinant in the absorption process of a sparingly low soluble drug. Determining the dissolution rate is critical. The main areas for dissolution rate studies are evaluations of different solid forms of a drug (e.g., salts, solvates, polymorphs, amorphous, stereoisomers) or different particle sizes of the drug. The dissolution rate can be determined either for a constant surface area of the drug in a rotating disk apparatus [2] or as a dispersed powder in a beaker with agitation (as detailed in pharmacopoeias such as U.S. Pharmacopoeia, etc.).

The impact of solubility and dissolution rate on formulation selection is discussed later in the chapter.

36.2.1.2 Partition Coefficient Partition coefficient is the relationship between chemical structure, lipophilicity, and its disposition *in vivo* and has been reviewed by a number of authors [3]. The lipophilicity of an organic compound is described in terms of a partition coefficient $\log P$, which is defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

$$\log P = \frac{[\mathrm{A}]_{\mathrm{organic}}}{[\mathrm{A}]_{\mathrm{aqueous}}} \tag{36.2}$$

For ionizable drugs, the ionized species does not partition into the organic phase, and the apparent partition coefficient, D, is calculated from the following equations:

$$\text{Acids} : \log D = \log P - \log[1 + 10^{(\mathrm{pH} - \mathrm{p}K_a)}] \tag{36.3}$$

$$\text{Bases} : \log D = \log P - \log[1 + 10^{(\mathrm{p}K_a - \mathrm{pH})}] \tag{36.4}$$

$\mathrm{p}K_a$ is the dissociation constant.

Since it is virtually impossible to determine $\log P$ in a realistic biological medium, the octanol/water system has been widely adopted as a model of the lipid phase [4]. There has been much debate about the suitability of this system [5], but it remains the most widely used in pharmaceutical studies.

Generally, compounds with $\log P$ values between 3 and 6 show good passive absorption, whereas those with $\log P$'s of less than 3 or greater than 6 often have poor passive transport characteristics. The role of $\log P$ in absorption processes occurring after oral administration has been discussed by Navia and Chaturvedi [6].

36.2.1.3 Crystal Properties and Polymorphism Most drug substances appear in more than one polymorphic form. Polymorphs differ in molecular packing (crystal structure), but share the same chemical composition [7]. Hydrates or solvates are often called "pseudopolymorphs" because in addition to containing the same given drug molecule, they also contain molecules of solvents that are incorporated into the crystal lattice. Amorphous forms are characterized by absence of long-range order.

Polymorphism has a profound implication on formulation development and biopharmaceutical properties because polymorphs may exhibit significantly different solubility, dissolution rate, compactibility, hygroscopicity, physical stability, and chemical stability [7]. Figure 36.3 provides a detailed list of physical properties that can differ among the polymorphs.

Higher solubility and faster dissolution rates of the metastable polymorph may lead to significantly better oral bioavailability. Chloramphenicol palmitate [9] (bacteriostatic antimicrobial) and ampicillin [10] (antibiotic) are examples of the anhydrous form that gave higher blood serum levels than the less soluble trihydrate form.

Although use of a faster dissolving polymorph may have clinical benefit, it is important to keep in mind that a polymorph with a higher solubility or faster dissolution rate is also metastable (i.e., a higher energy form) and tends to convert to a thermodynamically more stable form over time or in certain conditions. Conversion from a metastable form to a stable form could lower a drug's oral bioavailability and lead to inconsistent product quality. From a formulating perspective, it is desirable to use the thermodynamically stable form of the API; however, biopharmaceutical and processability considerations may dictate the deliberate selections of a metastable form for processing.

It is important to keep in mind that polymorphic form conversion from the most stable form may still occur, even when a stable crystal form is chosen for development. Polymorphic transformations can take place during pharmaceutical processing, such as particle size reduction, wet granulation, drying, and even during the compaction process and compression process [11, 12], as each of these processes

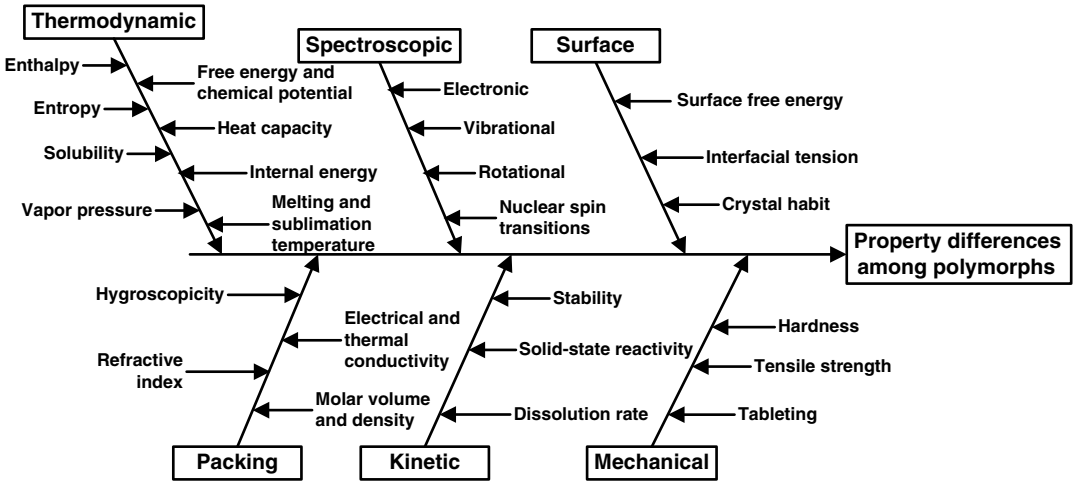


FIGURE 36.3 Fishbone schematic of physical properties differences among polymorphs (adapted from Ref. 8).

may add the energy required to move the drug to the unstable form.

36.2.1.4 Particle Size, Particle Morphology, and Surface Area Bulk flow, compactability, formulation homogeneity, and surface area control dissolution and chemical reactivity, which are directly affected by size, shape, and surface morphology of the drug/API (active pharmaceutical ingredient).

Spherical particles have the least contact surface area and exhibit good flow, whereas acicular particles tend to have poor flow [13]. Milling of long acicular (or needle) crystals can enhance flow properties; however, excessively small particles tend to be cohesive and aggravate flow problems.

In addition to the flow properties, crystal shape and size has been demonstrated to impact mixing and tabletability. L-Lysine monohydrate with plate-shaped crystals exhibited greater tabletability than the prism-shaped crystals [14]. Kaerger et al. [15] studied the effect of paracetamol particle size and shape on the compactibility of binary mixture with microcrystalline cellulose (MCC), showing that compressibility increased with particle size and irregular crystals whereas compactibility increased with decrease in particle size.

Particle size affects drug content uniformity (CU). For low dose direct compression formulations, where drug content uniformity is of particular concern, the particle size of the drug substance has to be small enough to meet the U.S. Pharmacopoeia requirement on content uniformity [16]. For example, Zhang and Johnson [17] showed that low dose blends containing a larger drug particle size (18.5 μm) failed to meet the USP requirement, whereas a blend containing smaller particle sizes (6.5 μm) passed.

Surface areas of drug particles are important because dissolution is a function of this parameter (as predicted by the Noyes–Whitney equation (36.1)). This is particularly true in those cases where the drug is poorly soluble. Such drugs are likely to exhibit dissolution rate-limited absorption. For such drugs, particle size reduction (e.g., micronization) is often utilized to increase the surface area that enhances the dissolution rate; for example, micronization enhanced the bioavailability of felodipine when administered as an extended release tablet [18].

Methods to determine particle size and shape include light diffraction, scanning electron microscopy (SEM), sieve analysis, and various electronic sensing zone particle counters. Methods available for surface area measurement include air permeability and various gas adsorption techniques.

36.2.1.5 Bulk Powder Properties Density and porosity are two important pharmaceutical properties that are derived from the information on particle size, particle shape, and surface area. A comparison of true particle density, apparent particle density, and bulk density can provide information on total porosity, interparticle porosity, and intraparticle porosity. Generally, porous granules dissolve faster than dense granules, since pores allow water to penetrate more readily.

$$\text{Interparticle (interspace) porosity} = 1 - \frac{\text{bulk density}}{\text{apparent particle density}} \tag{36.5}$$

$$\text{Intraparticle porosity} = 1 - \frac{\text{apparent particle density}}{\text{true particle density}} \tag{36.6}$$

$$\text{Total porosity} = 1 - \frac{\text{bulk density}}{\text{true particle density}} \tag{36.7}$$

The increase in bulk density of a powder is related to the cohesivity of a powder. Bulk density and tapped density are

used to calculate compressibility index and Hausner ratio, which are measures of the propensity of a powder to flow and to be compressed. *A rule of thumb*: a compressibility index of higher than 30% indicates poor powder flow. The Hausner ratio varies from about 1.2 for a free flowing powder to 1.6 for cohesive powders.

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad (36.8)$$

$$\text{Compressibility (carr index)} = \frac{100 \times (\text{tapped density} - \text{bulk density})}{\text{bulk density}} \quad (36.9)$$

36.2.1.6 Melting Point and Hygroscopicity Low melting materials tend to be more difficult to manufacture and handle in conventional solid dosage forms. *A rule of thumb*: melting points below 60°C are considered to be problematic. Temperatures in conventional manufacturing equipment, such as fluid bed dryers and tablet presses, can exceed 50°C. During the milling process, hot spots in the milling chamber may have much higher temperatures.

Moisture uptake is a concern for pharmaceutical powders and is known to affect a wide range of properties, such as powder flow, compactibility, and stability. On the other hand, moisture may improve powder flow and uniformity of the bulk density, as well as appropriate amount of moisture may act as a binder to aid compaction. Thus, knowledge of the type and level of moisture is critical for understanding its impact not only on deformation behavior but also on the attributes of the final product.

36.2.2 Biopharmaceutical Properties[a]

Complete oral absorption occurs when the drug has a maximum permeability coefficient and maximum solubility at the site of absorption, which results in rapid and uniform pharmacological response. Based on this premise, a key objective in designing a rational oral dosage form is having sound understanding of multiple factors, including physicochemical properties of the drug and dosage form components, and physiological aspects of GI tract.

Generating formulations with relevant oral bioavailability depends on a number of factors including solubility, permeability,[b] and metabolic stability.[c] Absorbability is related to the first two factors whose importance has been recognized in the guise of the biopharmaceutical classification system (BCS) [19, 20]. This approach bins drugs and drug candidates into four categories based on their solubility and permeability properties. The Food and Drug Administration (FDA) has issued guidelines to define low and high solubility and permeability [21].

The primary objective of the BCS[d] is to guide decisions with respect to *in vivo* and *in vitro* correlations and need for bioequivalence studies; it is also used to identify dosage form strategies that are designed at overcoming absorption barriers presented by solubility and/or permeability related challenges as depicted in Table 36.3.

The BCS nomenclature is centered on the premise that most orally administered drugs are absorbed via passive diffusion[e] process through the small intestine and excludes other important factors such as the drug absorption mechanism (carrier-mediated,[f] P-glycoprotein efflux,[g] etc.) and presystemic degradation or complexation that may enhance or limit oral bioavailability.

36.2.3 Mechanical Properties

Material mechanical properties play a role in manufacturing drug product. Particle properties influence the true areas of contact between particles and can affect unit operations, such as compression, milling, and granulation. Characterization of mechanical properties of drug substance is important in three areas: choosing a processing method, such as granulation or direct compression; selecting excipients with properties that mask the poor properties of the drug; and helping to document what went wrong, that is, when a tableting process is being scaled up or when a new bulk drug process is being tested. Since all these can influence the quality of the final product, it is to the formulator's advantage to quantify and understand the importance of the mechanical properties of the active and inactive ingredients and their combinations.

Pharmaceutical materials are elastic, plastic, viscoelastic, hard, tough, or brittle in the same sense that metals, plastics, or wood have similar properties. The same concepts that

[a] Biopharmaceutics is defined as the study of the relationships between physicochemical properties, dosage forms, and routes of administration of drugs and its effect on the rate and extent of absorption in the living body.
[b] Permeability determines the ability of drug to move across the lipophilic intestinal membrane in gastrointestinal tract (GIT). Permeability of a drug may be predicted using computational (*in silico*) models or measured using both physicochemical and biological methods (*in vitro*, *in situ*, or *in vivo*).
[c] Metabolic stability refers to ability of a drug to withstand metabolism or degradation in the gut wall and the liver.
[d] BCS (Biopharmaceutics Classification System) is a guidance for predicting the intestinal drug absorption using solubility and permeability as defined by the U.S. Food and Drug Administration.
[e] Passive diffusion is a transport process, wherein drug molecules pass across the lipoidal intestinal membrane from a region of higher concentration in the lumen (GIT) to a region of lower concentration in the blood (systemic circulation). Mathematically, it is described by Fick's first law of diffusion.
[f] Carrier-mediated transport may be subdivided into active transport and facilitated diffusion or transport. Active transport is a process whereby drug is bound to a carrier or membrane transporter and is transported against the concentration gradient across a cell membrane. Facilitated diffusion differs from active transport in that it cannot transport a substance against a concentration gradient of that substance.
[g] P-glycoprotein is one of the key countertransport efflux proteins that expel specific drugs back into the lumen of the GIT after they have been absorbed.

TABLE 36.3 Dosage Form Options Based on Biopharmaceutical Classification System[a]

Class I: high solubility, high permeability • No major challenges for immediate release dosage form • Controlled release dosage forms may be needed to limit rapid absorption	Class II: low solubility, high permeability • Formulation are designed to overcome solubility • Salt formation • Precipitation inhibitors • Metastable forms • Solid dispersions • Lipid technologies • Particle size reduction
Class III: high solubility, low permeability • Prodrugs • Permeation enhancers • Ion pairing • Bioadhesives	Class IV: low solubility, low permeability • Formulation would have to use a combination of the approaches identified in class II and III • Strategies for oral administration are not really viable. Often use alternative delivery methods such as intravenous administration

[a]A drug is considered to be highly soluble when the highest dose is soluble in 250 mL or less of aqueous media over the pH range 1–8. A drug is considered to be highly permeable when the extent of absorption in humans is expected to be greater than 90% of the administered dose.

materials/mechanical engineers use to explain/characterize tensile, compressive, or shear strength are relevant to pharmaceutical materials. A number of characterization tools as outlined in Table 36.4 are available for understanding the mechanical property of the material.

Based upon the analysis of the physicochemical, mechanical, and biopharmaceutical properties of the drug substance, selection of excipients and the formulation process is performed. The next section discusses excipients, their types, and the selection procedure based upon their effect on the drug substance properties.

36.3 EXCIPIENTS

Excipients facilitate formulation design to perform a wide range of functions to obtain desired properties for the finished drug product. Historically, pharmaceutical excipients have been regarded as inert additives, but this is no longer the case. Each additive must have a clear justification for inclusion in the formulation and must perform a defined function in the presence of the active and any other excipients included in the formulation. Excipients may function, for example, as an antimicrobial preservative, a solubility enhancer, a stability enhancer, or a taste masker, to name a few.

Excipients are selected based on their chemical/physical compatibility with drugs, regulatory acceptance, and processability. First, excipients shall be chemically compatible with drug substances. Second, at the time of globalization, excipients are to meet the requirements of not only the FDA or EMEA but also the regulatory agencies of other potential marketing countries. Third, excipients impact the properties of a powder mixture, such as flowability, density, compactibility, and adhesiveness. For example, different fillers are selected carefully to balance the plasticity, elasticity, and brittleness of the precompaction powder mixture, in order to make large-scale production feasible.

For tablets, excipients are needed both for the facilitation of the tableting process (e.g., glidants) and for the formulation (e.g., disintegrants). Except for diluents, which may be present in large quantity, the level of excipient use is usually limited to only a few percent and some lubricants are required at $<1\%$. Details of the types, uses, and mechanisms of action of various excipients for tablet production have been discussed at length in multiple of articles and books. The types and functions of excipients for tablet production are summarized in Table 36.5.

It is worth noting that some of these tableting excipients may exert effects in opposition to each other. For example, binders and lubricants, because of their respective bonding and waterproofing properties, may hinder the disintegration action of the disintegrants. In addition, some of these tableting excipients may possess more than one function that may be similar (e.g., talc as lubricant and glidant) or opposite (e.g., starch as binder and disintegrant) to each other.

Furthermore, the sequence of adding the excipients during tablet production depends on the function of the excipient. Whereas the diluents and the binders are to be mixed with the active ingredient early on for making granules, disintegrants may be added before granulation (i.e., inside the granules) and/or during the lubrication step (i.e., outside the granules) before tablet compression.

36.4 DRUG–EXCIPIENT COMPATIBILITY STUDIES

Excipient compatibility testing provides a preliminary evaluation of the physical and chemical interactions that can occur. Testing is carried under stressed temperature and humidity conditions between a drug and potential excipients. This helps excipient selection, particularly for tablet formulations in order to minimize unexpected formulation stability problems during product development.

Traditionally, a binary mixture of drug with the excipient being investigated is intimately mixed, and the ratio of drug to excipient is often 1:1; however, other mixtures may also be investigated. These blends are stored at various

TABLE 36.4 Characterization Tools for Understanding Mechanical Properties of Materials

	Quasistatic Testing	Dynamic Testing
API required	1–100 g	2–10 g
Advantages	"Independently" dissect out and investigate various mechanical properties	Understand the mechanics of materials at speeds representative of production tablet compaction
Limitations	Cannot determine properties at representative production scales	Difficult to factor out the individual mechanical property "component"
Characterization tests	Tensile strength • Describes the global strength of the material • Measured using traditional tablet hardness tester [22] or transverse compression in tensile tester [23] • Typical desired value greater than 1 MPa Indentation/dynamic hardness • Describes the "local" plasticity of the material • Measured using pendulum impact device or free falling indenter [24] Young's modulus • Describes stiffness and toughness of the material • Measured using both four- and three-point beam bending, flexure testing [25] Tableting indices • Dimensionless numbers that integrate above described tests Bonding index (BI) • Defines the tendency of the material to remain intact after compression • Desired value >0.01 Brittle fracture index (BFI) • Measure of brittleness of a material • BFI $= 1$ represents very brittle material and BFI < 0.3 is relatively nonbrittle material Strain index (SI) • Indirect measure of elastic strain	Force–displacement profiles • Indicator of tablet-forming ability of powder • Assessment of the elastic properties • Thermodynamic analysis of the process of compact formation Tablet volume–applied pressure profiles • Measured using hydraulic press, rotary press, compaction simulator, and compaction emulator Heckel equation • Tablet porosity–applied pressure function

temperatures and humidity and analyzed for potential degradation products.

More recently, the use of a model formulation approach to excipient screening has become much more widespread across the industry. Model formulations include commonly used excipients in each functional category such as fillers, binders, disintegrants, and lubricants and those with different chemical structures, namely, celluloses, starches, and sugars. Both wet and dry model formulations may be prepared for stability testing. It is recommended that a DOE be used to assist in the development and interpretation of results for these types of studies. Table 36.6 contains an example of the model formulation approach. It lists excipients and their approximate composition that would be found in a typical tablet formulation.

Powders are physically mixed and may be granulated or compacted to accelerate any possible interaction. Samples may be exposed in open pans or scaled in bottles/vials to mimic product packaging. The storage conditions used widely vary in terms of temperature and humidity, but a temperature of 40°C for storage of compatibility samples is considered appropriate. Some compounds may require higher temperatures to make reactions proceed at a rate that is measured over a convenient period. Methods of analysis also vary widely, ranging from thermal techniques (DSC) to chromatographic techniques (TLC, HPLC) to microcalorimetry.

An example of an excipient compatibility study utilizing partial factorial design (2^{7-3}) is illustrated in Table 36.7. In this study, a model compound (BCS class II) is blended with excipients (shown in Table 36.6) to make 16 formulations and stationed on open dish stability at 25°C/60% RH, 40°C dry, and 40°C/75% RH. The study duration is 3 months, which is analyzed for physical and chemical stability.

Figure 36.4 shows a regression model that is defined for assessing the effect of formulation and time on degradation

TABLE 36.5 Types and Functions of Tableting Excipients

Excipient	Function	Some Examples of Excipients
Diluents	Act as bulking/filling material	Sugars, lactose, mannitol, sorbitol, sucrose, calcium salts, microcrystalline celluloses (MCC),
Binders and adhesives	Holds powder together	Sugars, glucose, polymers, starch, gelatin,
Disintegrants	To facilitate the breakup of the tablet in the gastrointestinal tract	Croscarmellose sodium (CCS), sodium starch glycolate (SSG), crospovidone
Glidants	Improve the flow of granules, needed for compression	Silica, magnesium stearate (MgSt), talc
Lubricants	Reduce friction between granules and the compression equipment	Magnesium stearate, stearic acid, talc, sodium lauryl sulfate (SLS),
Antiadherents	To minimize the problems if sticking to the tablet punch head	Talc, cornstarch, SLS, MgSt
Colorants	For identification and marketing	Natural pigments and synthetic dyes
Flavors and sweeteners	To improve the taste of chewable tablets	Mannitol, aspartame

TABLE 36.6 Typical Excipients Selected for a Model Formulation Study

Excipient Type	% Composition	Level 1	Level 2
API	10	–	–
Filler 1	38–40	MCC	Mannitol
Filler 2	38–40	Dicalcium phosphate (ATAB)	Spray-dried lactose
Surfactant	0–4	None	Sodium lauryl sulfate (SLS)
Binder	4	Polyvinylpyrrolidone (PVP)	Hydroxy propyl cellulose (HPC)
Disintegrant	5	Sodium starch glycolate (SSG)	Croscarmellose sodium (CCS)
Lubricant	1	Magnesium stearate (MgSt)	Sodium stearyl fumarate (SSF)
Wet granulation	20% w/w water	No	Yes

TABLE 36.7 Formulation Composition for Excipient Compatibility Study

Number	Formulation Composition							
	10%	38–40%	38–40%	0–4%	4%	1%	5%	20% w/w water
1	API	MCC	ATab	None	PVP	MgSt	SSG	Dry (no)
2	API	MCC	ATab	None	HPC	MgSt	CCS	Wet
3	API	MCC	ATab	SLS	PVP	SSF	CCS	Wet
4	API	MCC	ATab	SLS	HPC	SSF	SSG	Dry (no)
5	API	MCC	Lactose	None	PVP	SSF	CCS	Dry (no)
6	API	MCC	Lactose	None	HPC	SSF	SSG	Wet
7	API	MCC	Lactose	SLS	PVP	MgSt	SSG	Wet
8	API	MCC	Lactose	SLS	HPC	MgSt	CCS	Dry (no)
9	API	Mannitol	ATab	None	PVP	SSF	SSG	Wet
10	API	Mannitol	ATab	None	HPC	SSF	CCS	Dry (no)
11	API	Mannitol	ATab	SLS	PVP	MgSt	CCS	Dry (no)
12	API	Mannitol	ATab	SLS	HPC	MgSt	SSG	Wet
13	API	Mannitol	Lactose	None	PVP	MgSt	CCS	Wet
14	API	Mannitol	Lactose	None	HPC	MgSt	SSG	Dry (no)
15	API	Mannitol	Lactose	SLS	PVP	SSF	SSG	Dry (no)
16	API	Mannitol	Lactose	SLS	HPC	SSF	CCS	Wet

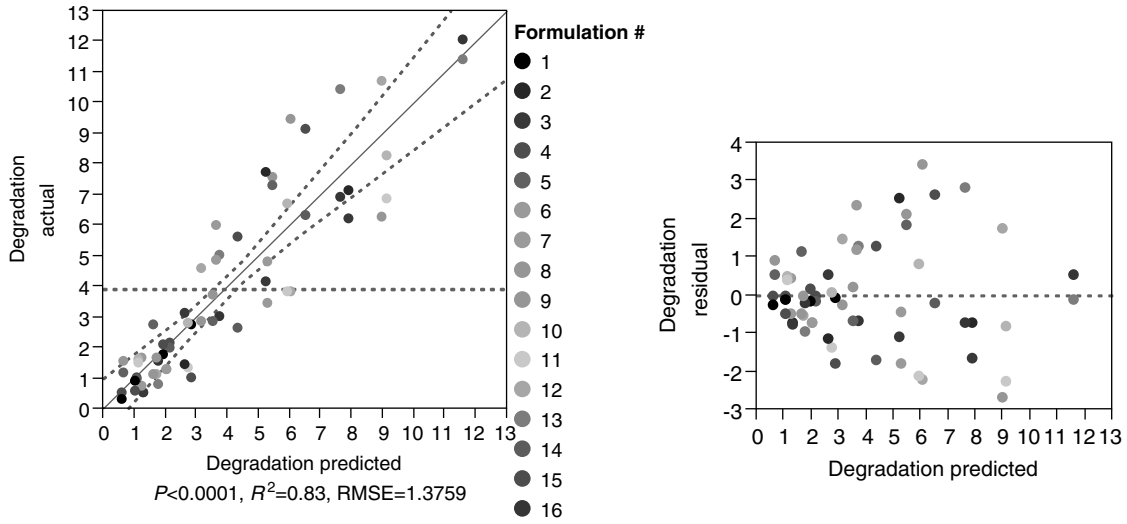


FIGURE 36.4 Degradation actual versus predicted plot and degradation residuals versus degradation predicted plot. The residuals are evenly distributed, indicating that there is no bias in the model. The symbol represents the formulation described in Table 36.7.

growth at storage condition of 40°C/75% RH. A regression analysis is completed for data at 40°C/75% RH to determine which excipient affects the growth of degradation products. From the analysis (Table 36.8), it is found that time, filler 1, disintegrant, and granulation have effect on degradation, as well there are some interactions between time and filler 1, time and disintegrant, and time and granulation (borderline as p value ≈ 0.05).

The parameters analyzed that did not show significance were filler 2, surfactant, binder, and lubricant and were subsequently removed from the model during stepwise regression.

The prediction profiler and the interaction profiles (Figure 36.5) provide information on the specific excipient within a significant class (from Table 36.7) and the sensitivity of each of the variables on the degradation growth. As seen from the prediction profiler, within filler, mannitol causes more degradation compared to MCC. Similarly, SSG is better than CCS among disintegrant and dry blend is better than wet granulation as the latter causes more degradation.

These results suggest that both mannitol and CCS could be detrimental to the stability of the API and are not being assessed for formulation development. Also, wet granulation is to be avoided to increase the shelf life.

36.5 PROCESSING OF FORMULATIONS

The properties of a drug substance dictate the design of formulation composition and the choice of formulation processing platform technology. The most commonly used processing platforms for solid oral dosage form include direct compression and granulation (wet and dry).

Direct compression is the term used to define the process where powder blends of the drug substance and excipients are compressed on a tablet machine. There is no mechanical treatment of the powder apart from a mixing process.

Granulation is a generic term for particle enlargement, whereby powders are formed into permanent aggregates. The purpose of granulating tablet formulations is to improve

TABLE 36.8 Regression Results from the Excipient Compatibility Experiments

Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	−0.029267	0.338094	−0.09	0.9313
Time (months)	2.4060773	0.179126	13.43	<.0001*
Filler 1[mannitol]	0.9593669	0.171987	5.58	<.0001*
Disintegrant [CCS]	0.6043247	0.171987	3.51	0.0009*
Granulation [Dry]	−0.717924	0.171987	−4.17	0.0001*
(Time (months) − 1.625) × filler 1 [Mannitol]	0.640884	0.179126	3.58	0.0007*
(Time (months) − 1.625) × Disintegrant [CCS]	0.5068487	0.179126	2.83	0.0065*
(Time (months) − 1.625) × Granulation [Dry]	−0.358106	0.179126	−2.00	0.0505

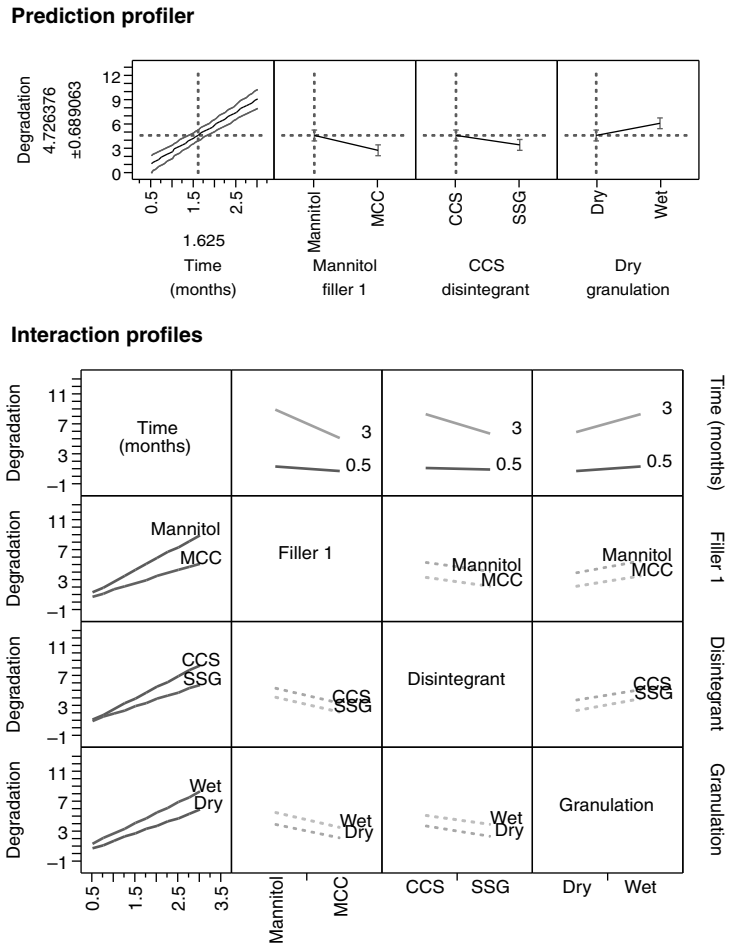


FIGURE 36.5 Prediction profiler and interaction profiles for drug–excipient compatibility studies.

the flow and compaction properties. A number of methods are used to achieve agglomeration or aggregation; these are normally classified as either wet granulation, where a liquid is used to aid the agglomeration process, or dry granulation, where no liquid is used.

36.5.1 Dry Granulation

In the dry methods of granulation, the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a "slug") is produced in a heavy-duty tableting press (a process known as "slugging") or the powder is squeezed between two rollers to produce a sheet of material ("roller compaction"). In both cases, these intermediate products are broken using a suitable milling technique to produce granular material that is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method may be used for drugs that do not compress well after wet granulation, or those that are sensitive to moisture.

36.5.2 Wet Granulation

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent that must be volatile so that it is removed by drying. Typical liquids include water, ethanol, and isopropanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved *adhesive* (also referred to as a *binder* or *binding agent*) that is used to ensure particle adhesion once the granule is dry.

The three main methods of producing pharmaceutical granulates are low shear granulation, high shear granulation, and fluid bed granulation. Low shear mixers encompass machines such as Z-blade mixers and planetary mixers that, as their name suggests, impart relatively low shear stresses onto the granulate.

High shear granulators are closed vessels that normally have two agitators: an impeller that normally covers the diameter of the mixing vessel and a small chopper positioned perpendicular to the impeller. The powders are dry mixed

TABLE 36.9 Processing Platforms: Advantages and Disadvantages

Processing Platform	Advantages	Disadvantages
Direct compression	Simple, cheap process Suitable for heat and moisture labile drugs Prime particle dissolution	Generally limited to low dose compounds Potential to segregation Expensive excipients
Dry granulation (slugging)	Imparts flowability to formulation Suitable for heat and moisture labile drugs	Dusty process Not suitable for all compounds Slow process
Dry granulation (roller compaction)	Imparts flowability Suitable for heat and moisture labile drugs Limits segregation tendency	Slow process Loss of compactibility for tableting No hydrophilization of surfaces
Wet granulation (aqueous)	Robust process Improves flowability Can reduce elasticity problems Can improve wettability Reduces segregation potential	Expensive Specialized equipment Stability concerns for moisture sensitive, thermolabile, and metastable drugs with aqueous granulation
Wet granulation (nonaqueous)	Suitable for moisture-sensitive drugs Vacuum drying techniques can reduce/remove need for heat	Expensive equipment Explosion proof Solvent recovery

using the impeller, and then the granulating fluid is added. Wet massing takes place using the impeller and the chopper, and granulation is usually completed in a span of minutes.

Fluid bed granulation involves spraying the dry powder with a granulating fluid inside a fluid bed dryer. The powder is fluidized in heated air and then sprayed with the granulating fluid. When all the granulating liquid has been added, the fluidization of the powder continues until the granules are dry.

Seager et al. [26] produced a detailed analysis of the influence of manufacturing method on the tableting performance of paracetamol granulated with hydrolyzed gelatin. The main difference in the granules produced by different methods is their final density: high shear mixers producing denser granules than low shear granulators that in turn produced denser granules than fluid bed granulations. Disintegration times were greater for tablets produced from the denser granulates. A detailed description of granulation process development and scale-up is found in the literature [27].

The advantages and disadvantages of each process are detailed in Table 36.9.

Each processing platform has unique characteristics and complexity in terms of unit operations. Table 36.10 lists the unit operations required for manufacturing immediate release tablet using the processing platform discussed earlier.

Since more than one platform technology may be used to manufacture a drug product, selection of the most appropriate processing platform is affected by many factors as shown in Figure 36.6.

36.6 TABLET FORMULATION DESIGN

Having decided on a formulation design strategy, the process of preparing and screening initial formulation possibilities begins. It is important to appreciate that the goal is to develop a "robust" formulation, and this objective facilitates identification of the factors that influence the selection of a design

TABLE 36.10 Unit Operations Required for Various Processing Platforms

Unit Operation	Direct Compression	Dry Granulation	Wet Granulation
Raw materials (weighing and sieving)	✓	✓	✓
Blending	✓	✓	✓
Compaction		✓	
Wet granulation			✓
Wet screening			✓
Drying			✓
Milling		✓	✓
Tablet compression	✓	✓	✓

process as depicted in Figure 36.6. The first major design criterion is the nature of the API and in particular the possible dosage level (described in preformulation report and TPP). The knowledge of biopharmaceutical class to which the API belongs helps in deciding the formulation rationale. In particular, the implications of low permeability and low solubility must be carefully considered prior to the selection of the processing platform. For example, a poorly soluble drug often tends to be poorly wettable, too. If the objective is to obtain a fast dissolving and dispersing dosage form, inclusion of a wetting agent such as sodium lauryl sulfate or polysorbate 80 may be appropriate or even necessary.

Processing methods may also significantly impact dosage form performance. For example, it may not be appropriate to wet granulate amorphous drug because water may lower the glass transition temperature and facilitate recrystallization during or after processing. In other situations, wet granulation can be used to avoid potential segregation and content uniformity problems where there is a significant difference in particle size or bulk density between the drug and excipients.

Another major consideration must be the anticipated dosage level. It is worth emphasizing that in the case of a high dose active form, a major proportion of the processing difficulties are traced to the physicochemical and mechanical properties of the API. Unfortunately, the key properties of the API may change during scale-up of the synthetic API process, or from lot to lot when outsourced. It follows that continuous monitoring of critical quality attributes (CQAs) of API that affect the process is an essential policy. Figure 36.7 depicts a decision-guiding flowchart for selection of the processing platform.

36.7 TABLET CHARACTERISTICS

There are two important classes of tablet characteristics. The first set examines the tablet immediately after manufacturing and the second class examines what happens to the tablet over time.

Immediately after manufacturing and during the formulation process of a tablet, the release of the tablet is of utmost importance. If the tablet does not disintegrate or dissolve in the body, then the efficacious effect desired is likely not going to occor. There are many factors that can affect this, from excipient choice to manufacturing.

After manufacturing a tablet must maintain consistency over time. Similarly to drug release, excipients and processing can affect the shelf life of a tablet.

36.7.1 Release Profile: Factors That Affect *In Vivo* Performance

Release profile of a tablet can affect *in vivo* drug performance, and as this is the case, it is important to measure this characteristic during development. The FDA guidance, Dissolution of Immediate Release Solid Oral Dosage Forms, states the dissolution requirements for an immediate release drug. Dissolution testing is useful in development to determine how processing and formulations can potentially affect *in vivo* performance. What is a dissolution test?

> Dissolution is a test that provides some assurance of tablet performance by an indication of the mass transfer the drug into solution.

There are many stages in the development of a dissolution method. The final quality control (QC) form of the method is

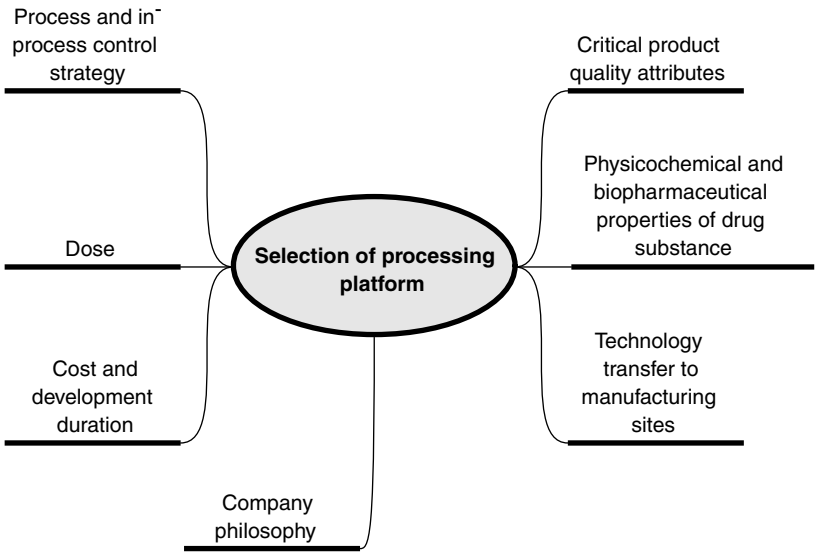


FIGURE 36.6 Factors affecting selection of processing platform.

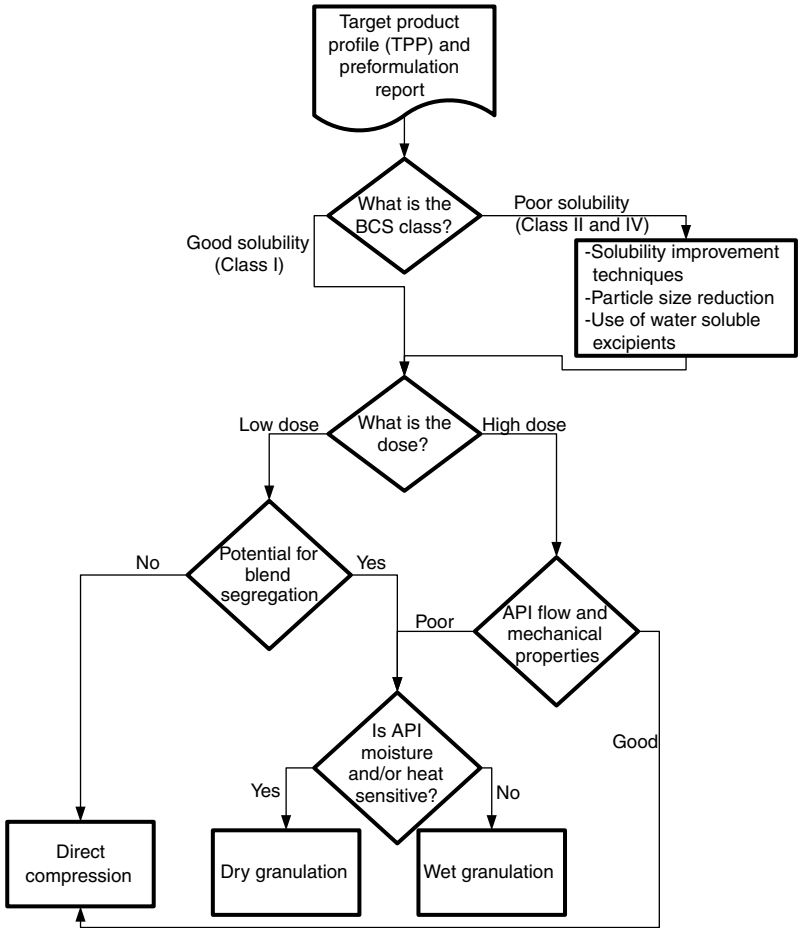


FIGURE 36.7 Flowchart for selection of adequate processing platform.

used in day-to-day production to ensure consistency of the tablets produced. In early development, dissolution testing is useful in screening formulations, but this dissolution test may not be or even resemble the final QC test used when the drug has been approved. The development of a dissolution method at each stage of development is the responsibility of the analytical development (AD) group in a company. Figure 36.8 shows a "typical" immediate release dissolution profile.

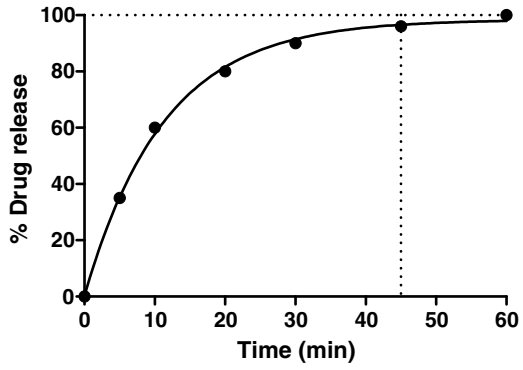


FIGURE 36.8 Typical drug release profile; very fast initial release with a leveling off.

Even though it is generally the responsibility of AD group to develop the dissolution method, it is critical for the drug developer to understand the final QC requirements from a regulation perspective so as to aid in developing a final drug product. A final QC dissolution method is carried out according to the guidance defined as:

> Dissolution testing should be carried out under mild test conditions, basket method at 50/100 rpm or paddle method at 50/75 rpm, at 15-minute intervals, to generate a dissolution profile. For rapidly dissolving products, generation of an adequate profile sampling at 5- or 10-minute intervals may be necessary. For highly soluble and rapidly dissolving drug products (BCS classes 1 and 3), a single-point dissolution test specification of NLT 85% (Q = 80%) in 60 minutes or less is sufficient as a routine quality control test for batch-to-batch uniformity. For slowly dissolving or poorly water soluble drugs (BCS class 2), a two-point dissolution specification, one at 15 minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 minutes) to ensure 85% dissolution, is recommended to characterize the quality of the product. The product is expected to comply with dissolution specifications throughout its shelf life. If the dissolution characteristics of the drug product change with

time, whether or not the specifications should be altered will depend on demonstrating bioequivalence of the changed product to the original biobatch or pivotal batch. To ensure continuous batch-to-batch equivalence of the product after scale-up and post approval changes in the marketplace, dissolution profiles should remain comparable to those of the approved biobatch or pivotal clinical trial batch(es) [28].

This is important knowledge to ensure compliance when developing and changing formulations. The QC method described above is not always the best method to use during development to assess potential impact on bioavailability; alternate media or methods may provide additional insight.

36.7.2 Problems and Troubleshooting Dissolution Testing

Beyond compliance, dissolution is used to determine performance of the tablet. Assuming a well-developed dissolution method, there are many things that can affect the dissolution of the tablet:

- Processing conditions: compressing the tablet too hard and/or overblending the lubricant
- Excipients: choice and amount
- API physical properties
- Storage: over time the tablet dissolution may slow down due to excipient interactions with the drug and excipient reaction with each other

A discriminating dissolution method is useful in developing a tablet formula and manufacturing process; however, a proper method may take time for the AD group to develop, just as it takes a while to develop a reliable process.

36.7.2.1 Problems with Dissolution: Nonengineered Mixing Vessels and Troubleshooting Assuming a good dissolution method may not be the best assumption. Dissolution is a QC test required for regulatory compliance; however, there are many problems with the dissolution test.

Dissolution apparatus 1 (Figure 36.9) is a paddle mixer in a cylindrical vessel; from an engineering standpoint, this does not provide good mixing. If an engineer is designing this, he/she would have put a baffle or two in there to promote top to bottom mixing. As is imagined, there may be problems with bottom settling and coning with tablets that disintegrate into large particles having a high density. In this case, the dissolution results have significant variation as how the drug settles and the percentage of the drug setting has an effect on the results.

Apparatus 2 is a basket mixer in a cylindrical vessel; again from an engineering standpoint, this does not provide good mixing. There is little mixing power associated with the method; if the powder flows out of the basket, the powder settles, floats, or suspends depending on the buoyancy of powders. If the powder stays in the basket, the method has a high probability to be reliable [29].

FIGURE 36.9 Typical dissolution apparatuses.

When examining dissolution results method, there are five considerations to determine if results are method biased.

1. What is the media used in the dissolution bath? What is the solubility of the drug in the media? This determines the mass transfer driving force for the drug to go into solution.
2. Does my drug change forms in the dissolution media? If it does, the form it changes into may not have the same solubility. Form conversion is a stochastic event and affects the consistency of the results.
3. Are the particles suspended and flowing? This also affects the mass transfer of the drug into the media.
4. Is the tablet submerged in the media? Often a floating tablet provides many problems and inconsistent results.
5. What is the dissolution medium comprised of? The media may react with the API or excipients used in the tablet.

When analyzing a change in dissolution profiles ensure that the changes made are due to the process and formula versus problems with the method. It is always a good idea to observe the dissolution testing so as to see what is actually occurring.

36.8 USING DISSOLUTION TO DETERMINE CQAs

Assuming an acceptable dissolution method has been developed, dissolution is a useful tool to determine CQAs for the

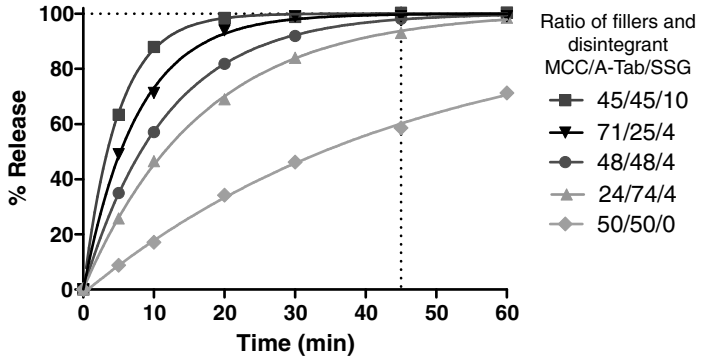


FIGURE 36.10 Dissolution comparison between different excipient ratios and a constant drug load of 20%.

tablet. Dissolution can help determine the maximum tablet hardness, the optimal drug substance particle size and/or density, and the proper ratio or the amount of excipients.

36.8.1 Using Dissolution to Determine the Ratio of Excipients

A tablet formulation can affect the dissolution profile. A tablet often contains a mixture of water-soluble and insoluble fillers/binders and disintegrants that all have the potential to affect the dissolution profile. Determining the optimal loading of excipients is a difficult task even after the compatible excipients have been chosen.

Let's examine excipient optimization of a BCS class II tablet based on dissolution performance. For example, compressing a tablet consisting of 20% API with a particle size of 29 μm at a hardness of ∼10 kP. The remaining 80% of the tablet consisting different ratios of filler, binder, and disintegrant. Two commonly used fillers MCC and calcium dibasic phosphate (A-Tab), and a commonly used disintegrant SSG, are used based on excipient compatability example. These are in five different compression ratios, and dissolution results are shown in Figure 36.10.

As is seen in the Figure 36.10, different excipient ratios can affect tablet performance. From this example, it looks like 71/25/4 MCC/A-Tab/SSG has most optimal performance without putting an excess amount of disintegrant in the tablet (Table 36.11).

36.8.2 Using Dissolution to Determine the Optimal API Particle Size and Tablet Hardness

The next properties that can affect dissolution are API particle size and tablet hardness. API particle size has the potential to affect dissolution based on different surface area or particle morphology and the tablet hardness can affect how fast the tablet disintegrates into primary particles

TABLE 36.11 Percent Release Data from Figure 36.10

	Release Data of Tablets with Different MCC/A-Tab/SSG Ratios				
Time (min)	48/48/4	45/45/10	25/71/4	71/25/4	50/50/0
0	0	0	0	0	0
5	35.0	63.4	25.8	49.1	8.8
10	57.1	87.9	46.5	71.3	17.1
20	81.8	98.5	69.0	94.0	34.2
30	91.9	98.8	84.0	99.1	46.2
45	98.1	100.3	93.0	99.1	58.6
60	99.6	100.4	98.6	99.1	71.3

Note: Due to method variability, it is common to see tablet performance slightly above or below 100%.

enabling the API to dissolve. As a rule of thumb about particle size:

> There is never an instance where bigger particles will improve the immediate release performance but there are many instances where it will not change the performance.

In optimizing the release of the drug, first a target CQA must be defined, which is determined from IVIVC[h] or good scientific reasoning. A hypothetical CQA could be NLT (not less than) 70% release at 30 min to ensure proper absorbance in the body; 30 min is chosen as it is the approximate gastric emptying time of an empty stomach [30].

Continuing with the example, for determining the optimal hardness and API particle size range, dissolution is chosen at the CQA at $t = 30$ min. Starting with the "optimal" formulation from the example (71/25/4 MCC/A-Tab/SSG), the material is compressed at five hardnesses, ranging from ∼10 to 30 kP, and four different API average particle sizes (d_{50}), ranging from 29 to 73 μm. Table 36.12 indicates the

[h] IVIVC: *In vitro–in vivo* correlation, by which benchtop data accurately correlate to human bioavailability.

TABLE 36.12 Effect of API Particle Size μ and Tablet Hardness (kP) at the 30 min Dissolution Time Point

%Dissolved	d_{50}	Hardness	%Dissolved	d_{50}	Hardness (kP)
99.1	29	9.7	87.18	50	10.3
85.17	29	15.6	75.91	50	14.4
77.45	29	20.8	65.03	50	20.4
64.3	29	25.6	52.42	50	24.7
54.15	29	30.2	40	50	30.2
89.04	42	10.7	72.65	73	9.6
84.35	42	14.7	60.13	73	15.3
69.17	42	20.9	50.84	73	20.9
61.31	42	24.1	43.62	73	25.4
46.61	42	29.4	26.97	73	29.6

results attained, and from observation there is an effect of both hardness and API particle size.

On examining Figure 36.11, it is found that the data have a linear relationship between % release and hardness; moreover, there is a relationship between release and particle size. It is noted that 8 of 20 experiments met the CQA requirement of NLT 70% release at 30 min. From this point, a design equation is developed to mathematically describe the design space.

Regression is completed providing an expression for the relationship of acceptable hardness and API particle size combinations. The expression is used to describe the design space (Tables 36.13 and 36.14).

Based on this information, the relationship between hardness, particle size, and % release at 30 min is

$$\%R_{@30\text{ min}} = 139.2 - 0.59 \times d_{50} - 2.25 \times \text{hardness} \quad (36.10)$$

This is not an ideal form of the equation as >100% release is predicted at some values; however, it is used to determine the maximum range of hardness and particle size to attain release >80%. The model is further developed to attain the curvature but more data above 30 kP and smaller particle sizes are required. Determining tablet and API properties there is sufficient information for control.

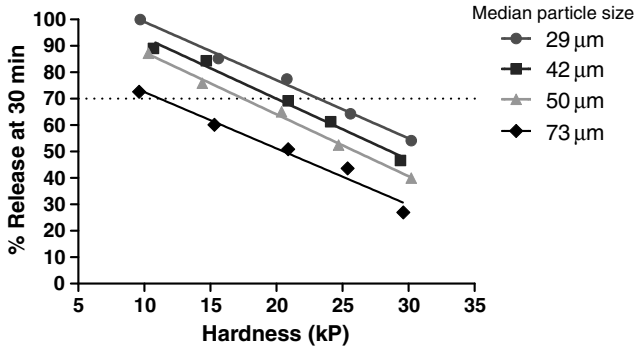


FIGURE 36.11 Comparison of hardness and API particle size to dissolution release at the 30 min time point.

TABLE 36.13 Results from the Linear Regression

Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	139.2	1.99	69.9	<0.0001*
d_{50}	−0.592	0.0289	−20.5	<0.0001*
Hardness	−2.247	0.0659	−34.0	<0.0001*

The asterisk indicates that the variable is significant.

TABLE 36.14 Summary of Fit of the Regression

R^2	0.989
R^2 adj	0.988
Root mean square error	2.070
Mean of response	65.31
Observations	20

To determine the acceptable combinations of hardness and particle size to maintain the CQA of NLT 70% release at 30 min, equation 36.10 is rearranged.

$$69.3 \geq 0.59 \times d_{50} + 2.25 \times \text{hardness} \quad (36.11)$$

As long as this equation is satisfied, the CQA is maintained. The design space is described in Figure 36.12.

The last check is examining the residuals to ensure there is no systematic error. Shown in Figure 36.13 are the randomly distributed data, indicating the regression does not have a systematic error. Another way is to confirm that the model residuals are normally distributed by using a goodness of fit.

36.8.3 Physical Tablet Characteristics

The physical attributes of the tablet are important for processing and ensuring that a consistent quality drug product is delivered to the customer. Physical attributes include tablet hardness, thickness, friability, disintegration, and weight.

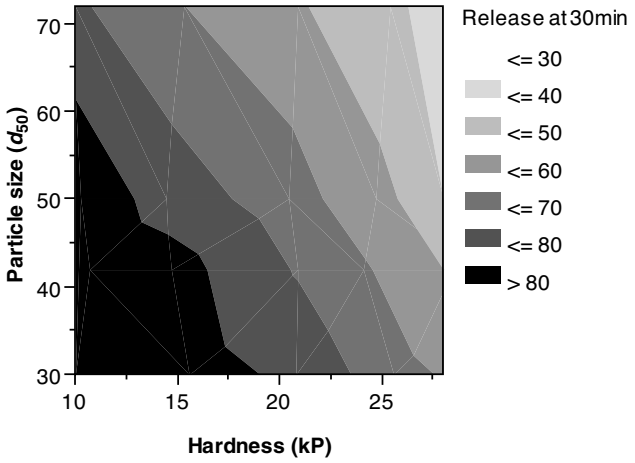


FIGURE 36.12 Contour plot showing dissolution as a function of particle size and hardness.

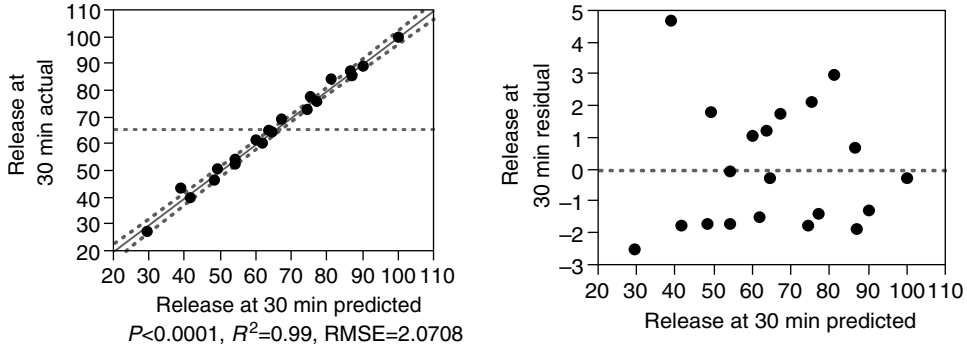


FIGURE 36.13 Residual plot from the regression. The data are randomly distributed and nonsystematic.

When determining tablet characteristics, consider how the material is to be handled after compression (Table 36.15).

36.9 DRUG PRODUCT STABILITY

Stability is critical in all drug product/formulation design; without stability, there is no commercial product. Stability is examined in two different manners: meeting the minimum regulatory requirement needed to launch a drug, and/or examining the root causes of degradation. From a scientific/engineering perspective, it is important to determine what affects the stability of the drug to design a drug product process around these factors.

36.9.1 Regulatory Requirements for Drug Product Stability

Regulatory requirements for stability need to be done in the intended primary commercial package. There is ICH guidance that governs the expectations of pivotal stability studies—see "Stability Testing of New Drug Substances and Products Q1A(R2)." The minimum required for submission is shown in Table 36.16; real-time data are needed for shelf life dating over 2 years.

This is an excellent guide for the regulatory requirements once a package(s) has been chosen for clinical trial, registration, and commercial distribution. Registration batch minimum is three lots of at least 100,000 tablets and at least 1/10 of the expected commercial batch size that is packaged into the intended commercial package. But there is much work required before selecting the primary package.

36.9.2 What Affects Stability and How to Predict Shelf life?

In a QbD world, the minimum is generally not sufficient to launch a product—the more a scientist determines what affects stability, the better engineered is the product.

Packaging is usually not known in early development and it can range from blister packaging to bottles to pouches. Each packaging type can vary significantly in the materials used. Different materials can protect from light, moisture,

TABLE 36.15 Tablet Attributes and Their Effect on Final Dosage Form

Attribute	Effect	Measurement
Hardness	*Too soft*: the tablet can break in storage shipping, coating, packaging	Hardness tester
	Too hard: the tablet cannot dissolve and may not have the required clinical effect	Typical units: kP, N
Friability	*Too friable*: tablet cannot be able to withstand further testing	*Friabilator*: 100 revolutions; % weight loss; if capping/lamination occurs
	Not friable: nothing wrong	
Thickness	*Too thick*: may not fit into packaging equipment/package. May not be able to swallow (poor marketing compliance)	Caliper
	Too thin: may clog packaging equipment	
Weight	*Too heavy*: the drug may be overpotent	Scale
	Too light: there may not be enough drug (poor clinical efficacy)	
	Too much variability: may fail content uniformity. Too much yield loss during manufacturing	
Disintegration	*Too slow*: may not be efficacious	Disintegration, dissolution bath
	Too fast: may have issues in humid environments and coating	
Elegance	*Nonelegant*: shows inconsistent production and may turn off customers	Acceptable quality limit (AQL)

TABLE 36.16 Minimum Guideline from the ICH Q1A(R2) for Room Temperature Product

Study	Storage condition	Minimum time period covered by data at submission
Long term[a]	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate[b]	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

[a] It is up to the applicant to decide whether long-term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
[b] If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

oxygen, and other environmental factors. Early research on the effect of heat, moisture, oxygen, and light enables primary and secondary packaging selection. Though these studies are comprehensive, studies still need to be completed with the primary package to ensure that no reaction occurred between the packaging material and the drug product. The primary packaging may have leachables, extractables, or antistatic properties that may react with the drug product.

A structured approach helps determine the conditions under which a drug converts into a degradation product. This occurs given there is enough time in certain temperature, relative humidity, or light conditions. Packaging is often used to prevent such occurrence; the proper choice and storage conditions are critical depending on the stability of the product.

Determining package type is as easy as answering a few questions: what is the drug product sensitive to—temperature, moisture, light? Is the drug sensitive to impurities/components in the packaging, impurities/components in the excipients, or starting impurities in the drug substance?

This section provides a framework to determine what affects stability and how. The simplest experiments are placing the product at open dish conditions, and an example of this is provided in the excipient compatibility section, though a more integrated set of experiments is used to create a predictive model on how the tablet can degrade. From the initial readout of stability, a more extensive experimentation is completed to model the stability of the drug.

36.9.3 Open Dish Experiments

These are the easiest experiments to get a quick read on how the drug product can degrade and what changes in formulation affect degradation. Using conditions of 40°C dry and 40/75% RH provides immediate (i.e., 1–4 weeks) information of how the drug reacts with both temperature and humidity and the degradants or form change to expect upon stability.

Open dish experiments are used to test specification of excipients. Possible effects on stability can occur from changing excipient vendors or lot-to-lot variation within a vendor. For example, MCC, a commonly used binder, has often a residue on ignition (ROI[i]) specification of not more than (NMT) 0.050%, so it is possible to receive material with ROI of 0.040%, 0.005%, and 0.020%. A tablet is compressed with these different lots of MCC and placed on open dish stability and depending on the drug, the results could affect the stability. Figures 36.14 and 36.15 show the results from this example.

Both Figures 36.14 and 36.15 show a relationship between ROI and impurity growth. A regression analysis is completed and shown in Table 36.17. The regression shows that both time and ROI affect stability, but relative humidity (RH) does not affect stability.

Another manner to examine the data is plotting the slopes from Figures 36.14 and 36.15 (degradation rate) against ROI of the MCC. Figure 36.16 shows how the ROI affects the growth rate of impurities; this could be important and may provide justification in setting excipient specifications.

Open dish studies are useful in determining what can degrade the drug, but these are harsh conditions and do not simulate what would happen upon shelf life. However, they do give an indication of what to look for on stability.

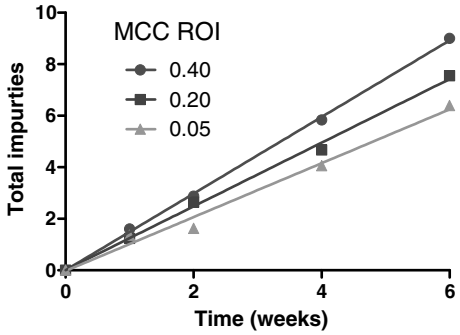
36.9.4 Modeling and Predicting Shelf Life.

Using information gained from open dish studies, a more elegant study is then conducted to determine the drug shelf life. Experiment on the effect of temperature and tablet moisture on impurity growth is used to develop a model to predict shelf life. This type of study is called the TRH study that models the effects temperature (*T*) and RH have on tablet shelf life.

Setting up this study requires tablets, RH equilibration chambers, foil pouches, and a heat sealer for the pouches. Tablets are equilibrated at different RH conditions, and then packaged in foil pouches to ensure the moisture content of the tablet remains constant throughout the time material is on stability. As well, every time point and condition should be individually packaged to maintain the tablet moisture, as opening and closing packages could adulterate the tablets. The idea is to equilibrate separate tablets to a minimum of three different groups of RH (i.e., 15%, 25%, and 45%); equilibration may take up to 2–7 days. The last three steps are as follows:

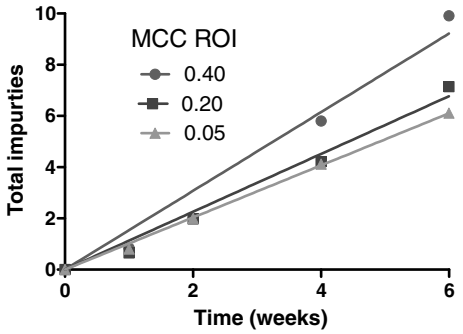
1. Measure the tablet moisture content (Karl Fisher (KF) is one of the more effective measurements) and

[i] The ROI test measures the amount of residual substance not volatilized from a sample when ignited in the presence of sulfuric acid. The test determines the content of inorganic impurities. USP <281>.



ROI (%)	0.40	0.20	0.05
Slope	1.49	1.24	1.04
Intercept	0	0	0
r^2	0.9992	0.9965	0.9870

FIGURE 36.14 A hypothetical effect of MCC ROI and the growth of tablet impurities/degradants at 40°C/75% RH open dish conditions.



ROI (%)	0.40	0.20	0.05
Slope	1.54	1.13	1.02
Intercept	0	0	0
r^2	0.9815	0.9912	0.9958

FIGURE 36.15 A hypothetical effect of MCC ROI and the growth of tablet impurities/degradants at 40°C dry open dish conditions.

separate the tablets into three moisture categories (i.e., 1%, 2%, and 5.5%)

2. Determine the amount of time pulls required (i.e., 1, 3, 6, 9, 12, 18, 24 months)
3. Determine the storage temperatures (T) to place the tablets at; a minimum of three is recommended (i.e., 25, 30, and 40°C), and these are typical ICH temperatures.

The study described requires 63 foil pouches to cover each time point and condition. This is an extensive study but does not account for different lots of API or excipients. Much is learned from this study about packaging protection requirements. To expand the study, excipient ROI is examined as a factor, which increases the study samples by three times.

In the experimental results shown in Figure 36.17, the data set is extensive, but it is important to analyze interim data and guide the packaging decisions. At the end of the study, a complete predictive model for temperature, moisture, time, and excipient ROI is attained to guide decisions made around storage temperature, shelf life, and excipient specifications.

A regression analysis is completed to provide a prediction equation to determine what and how much each of the

TABLE 36.17 Regression Results for the Material Stored at 40°C Dry and 40°C/75% RH

Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	−0.902499	0.136978	−6.59	<0.0001*
Time (weeks)	1.2841237	0.029206	43.97	<0.0001*
ROI (%)	3.29304	0.438798	7.50	<0.0001*
RH conditions[75]	0.1093065	0.062911	1.74	0.0946
(Time (weeks) − 2.6) × (ROI − 0.21667)	1.5833776	0.203707	7.77	<0.0001*

Asterisk indicates that the term is statistically significant (Prob < 0.05).

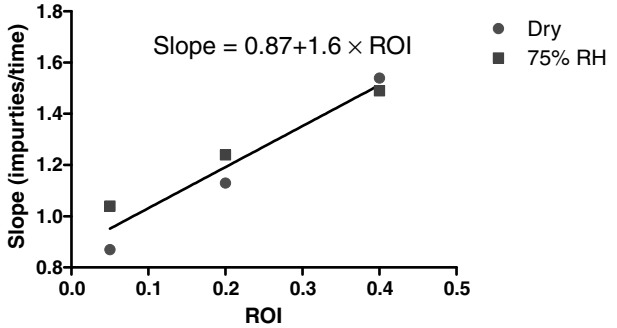


FIGURE 36.16 Comparison between impurity growth rate and ROI of excipient.

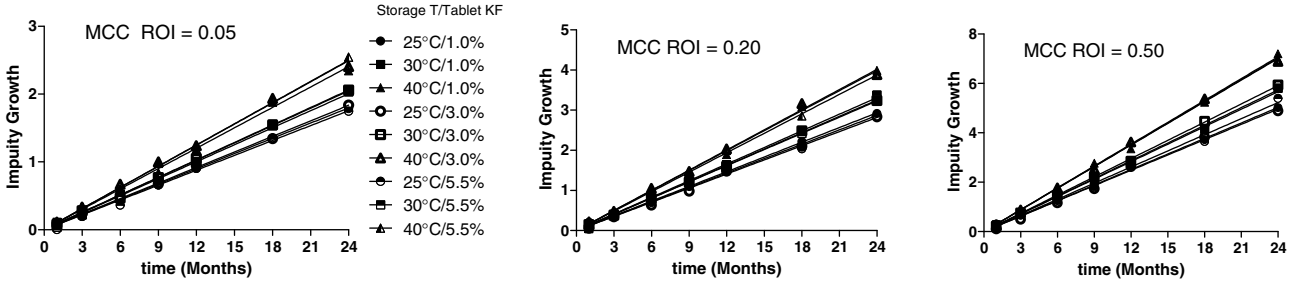


FIGURE 36.17 Result from the temperature moisture study completed by examining the effect of MCC ROI at three different levels 0.05%, 0.20%, 0.50%. The figure seems to indicate that temperature, time, and ROI have the largest effect on impurities.

variables affects impurity growth. The analysis indicates that time, temperature, and ROI have effect on degradation; in addition, there are some interactions between time and temperature, time and ROI, and temperature and ROI (Table 36.18). As expected, tablet moisture content did not affect stability as is seen from Figure 36.17.

Figure 36.18 shows that the regression is not biased and the residuals are evenly distributed.

$$\begin{aligned}\text{Impurities} = {} & 0.633 - 0.041 \cdot T - 0.020 \cdot t + 1.17 \cdot \text{ROI} \\ & + 0.00035 \cdot (t \cdot T) + 0.360 \cdot (t \cdot \text{ROI}) \\ & + 0.080 \cdot (T \cdot \text{ROI}) \end{aligned} \quad (36.12)$$

The above equation is the expression for expected impurities at any given time, storage temperature, and MCC ROI. This is used to test different scenarios such as what would the ROI need to be to attain room temperature (25°C) storage condition with acceptable amount of impurities or what would the shelf life be in warmer climates 30°C. It must be noted that impurity levels are set by a combination of toxicity and process capability.

Contour plots (Figure 36.19) are useful as the sensitivity of each variable is more easily visualized.

TABLE 36.18 Regression Results from the TRH Experiments

Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	−2.11	0.043	−49.12	<0.0001*
Time, T (months)	0.160	0.00102	156.82	<0.0001*
Temperature, t (°C)	0.037	0.00125	29.60	<0.0001*
MCC ROI	3.71	0.042	89.00	<0.0001*
(Time (months) − 10.43) × (temperature (°C) − 31.67)	0.0035	0.00016	21.60	<0.0001*
(Time (months) − 10.43) × (MCC ROI − 0.25)	0.360	0.0055	65.99	<0.0001*
(Temp (°C) − 31.67) × (MCC ROI − 0.25)	0.080	0.0067	11.91	<0.0001*

All parameters shown are significant. The parameters analyzed that did not show significance were tablet moisture and all tablet moisture interactions.

Stability is important and knowing what can predict stability is valuable in determining packaging and excipient grade selection.

36.10 PROCESS OPERATIONS AND SCALABILITY OF DOSAGE FORM

There are many considerations in scaling up unit operations that manufacture solid dosage forms. Scaling up through preclinical → early clinical (phase I and phase II) → late clinical (phase IIb and phase III) → registration → engineering/validation batches has many challenges (Table 36.19). Scale-up usually takes the course of laboratory experiments, pilot scale tests, and finally commercial-scale operation and continuous improvement [31,32].

Beyond development, scale-up or scale-down also occurs after approval, in which case changes are governed by Post-Approval Changes (SUPAC[j]) guidelines as specified by the Center for Drug Evaluation and Research (CDER). Finally, tech transfer (TT) is needed if multiple plants or CMOs are required.

Limited and costly API or drug substance (DS) and resources may hinder the experimental understanding that could be gained; therefore, know-how prior to manufacturing is extremely valuable. Understanding and using engineering first principles, dimensional analysis, and design of experiments (DOE) improves the likelihood that the process(es) and drug product (DP) will succeed.

Pharmaceutical process scale-up shall consider formulation, process development, and marketing needs. A risk-based approach is to examine how the TPP of the drug is affected by CQAs of the final dosage form and the design space of the process. Quality by design (QbD) principles are used to ensure a safe and efficacious product. Design space, controls, and specifications are continuously improved through continuous learning.

[j] http://www.fda.gov/Drugs/default.htm.

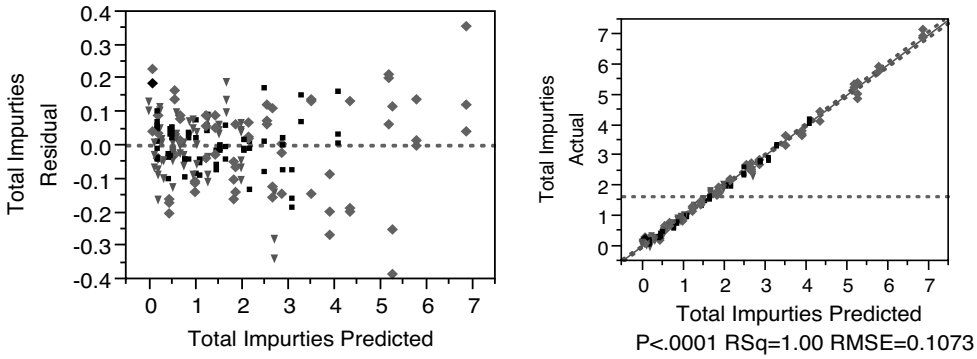


FIGURE 36.18 The residuals plot of predicted versus actual. The residuals are evenly distributed, indicating there is no bias in the model. ▼ is 0.05 ROI, □ is 0.20 ROI, and ♢ is 0.50 ROI.

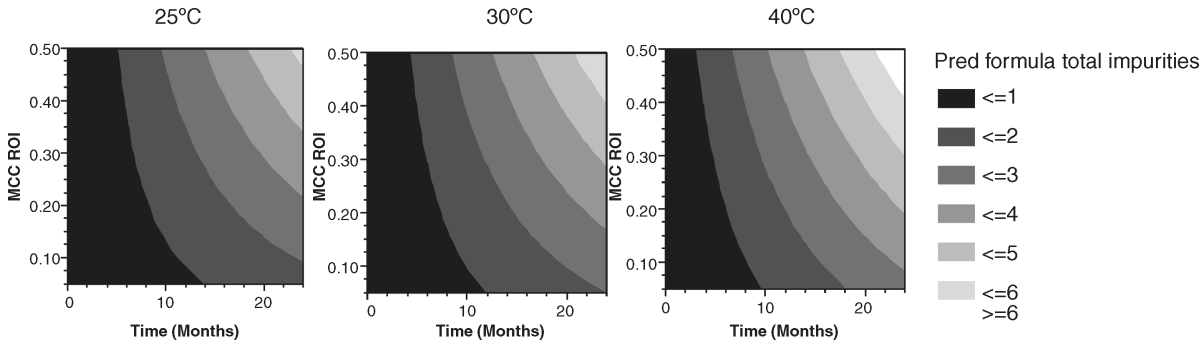


FIGURE 36.19 Contour plots examining total impurities versus time and MCC ROI.

Definitions referring to pharmaceutical manufacturing are given as follows (adapted from PQRI) [33]:

Critical Quality Attribute: A quantifiable property of an intermediate or final product that is considered critical for establishing the intended purity, efficacy, and safety of the product. That is, the property must be within a predetermined range to ensure final product quality.

Target Product Profile: A summary of characteristics that if achieved provides optimal efficacy, patient compliance, and marketability. A TPP often includes attributes such as pharmacokinetic information (e.g., immediate release versus extended release), dosage form (e.g., tablet versus injectable), and shelf life information (e.g., 2 years at 25°C/60% RH).

Design Space: The design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases, design space can also be applicable to formulation attributes.

Critical Process Parameter (CPP): A CPP is a process input that, when varied beyond a limited range, has a direct and significant influence on a CQA.

Critical Material Attribute (CMA): A CMA is an attribute that has direct impact on the processability or CQA of the drug product. CMAs could include impurities from the excipient or raw materials.

Normal Operating Range (NOR): A defined range, within the proven acceptable range (PAR), specified in the manufacturing instructions as the target and range at which a process parameter is to be controlled, while

TABLE 36.19 Typical Scale-Up

Stage	Typical Material Required	Reason
Preclinical	0.05–1 kg	Early toxicology testing
Phase I and II	0.2–50 kg	Healthy volunteers and early proof of concept
Phase IIb and III	10–1000 kg	Proof of concept and verification trials
Registration	>100 kg and >100,000 unit dosages and minimum 1/10th commercial batch size	From FDA guidance
Engineering/validation	Based on registration and expected product demand	Final process testing and process confirmation runs

producing unit operation material or final product meeting release criteria and CQAs.

Proven Acceptable Range: A characterized range at which a process parameter may be operated within, while producing unit operation material or final product meeting release criteria and CQAs.

Another useful tool during scale-up is process failure modes effects analysis (pFMEA) that is used to understand the failure modes of the CQAs to help mitigate risks in unit operations [34, 35]. This is done by understanding the severity, occurrence, and detection of any or all potential failure modes. pFMEA is different from root cause analysis (RCA) as a RCA is performed after deviations have already occurred. Risk prioritization numbers (RPNs; scores from 1 to 100) are calculated using pFMEA (RPN = severity $[1-10] \times$ occurrence $[1-10] \times$ detection $[1-10]$) and point the engineer toward corrections that are implemented to reduce risk to the drug product. Usually, an engineer starts to look to ameliorate problems with high RPN numbers.

Besides CQAs, critical business attributes (CBAs) are also considered. Business decisions that involve scale-up can relate to choice of CMO, batch size, operators needed, equipment purchases, use of PAT tools, and so on.

It is imperative to learn the CPPs of the unit operation at hand. This is done through an evolution of understanding the engineering principles and the processing knobs at the engineer's disposal. These CPPs affect any or all the CQAs of the DP [34].

Unit Operation	CQAs	CPPs	Potential Failure Mode
Roller compaction	Ribbon density, degradants, downstream dissolution	Roll speed feed screw speeds, roll force/pressure, roll separation/gap, room temperature/humidity	Ribbon density variation, high degradation
Slugging	Hardness, dissolution	Slugging force	Too little or too much
Wet granulation	Particle size, powder density, degradants, downstream dissolution	Granulation fluid mixing time, granulation fluid mixing speed, granulating fluid amount, granulating fluid addition rate, granulating fluid temperature, spray nozzle air volume, dry mixing time, wet mixing time, impeller speed, chopper speed, power consumption	Too little or too much
Fluid bed granulation	Particle size, powder density, powder wetness, degradants, downstream dissolution	Granulation fluid mixing time, granulation fluid mixing speed, granulating fluid amount, granulating fluid addition rate, granulating fluid temperature, spray nozzle air volume, bed mixing time, supply air flow rate, temperature, dew point, product bed temperature, exhaust air temperature, dew point, filter shaking intervals	Loss of yield, powder degradation
Milling	Particle size, degradants	Impeller speed, feed rate, room temperature, humidity	Undesired particle size, degradation
Lyophilization	Degradants, physical form, product wetness	Pretreatment, freezing, drying, temperature, cycle times, chamber pressure	Degradation, loss of stability, yield loss
Blending	Blend uniformity, content uniformity (CU)	Blend time (pre- and postlube), rotation rate, agitator speed, room temperature, humidity	Underblending may lead to bad CU, overblending may lead to poor compressibility
Encapsulation	Powder density, downstream dissolution, weight	Speed, dosing	Improper weight, broken capsules, too much dense powder in capsule
Tableting	Hardness, thickness, weight, dissolution, degradants, content uniformity	Tablet weight, press (turret) speed, main compression force, precompression force, feeder speed, upper punch entry, room temperature, humidity	Capping if dwell time is too low, low weights or high weight variability if powder flow is bad
Tablet coating	Appearance, dissolution	Coating suspension mixing time, coating suspension mixing speed, coating suspension solids load, atomization pressure, preheat time, jog time number, type of guns, gun to bed distance	Twinning if tablet shape is not round, spray drying of coating suspension if temperature is too high, nonuniform coating if pan speed is too slow, tablet defects if pan speed is too fast
Tablet printing	Appearance, degradants	Ink dosage amount, force, location	Ink degrades product

There are many unit operations that are used for drug product manufacture; the easiest and most economical is direct compression (DC). In oral solid dosage manufacturing, direct compression process technology is the most effective and efficient way to make powder materials suitable for tableting or encapsulation without a step to increase the particle size [36]. In the example, the TPP is a DC tablet that focuses on the unit operations of (1) blending, (2) compression, and (3) coating.

36.10.1 Blending Scale-Up

Blending is a critical operation that determines how well the product is to perform in the next phases. Achieving and maintaining homogeneous mixing of powders is critical, especially in formulations involving small amounts of high-potency components. Lack of blend uniformity at the blending stage may result in the lack of CU in the finished product dosage forms.

Tumbling blenders are typically used. The most common types of blenders are in-bin and V-shell blenders. In-bin blenders are typically used for high drug load blends and are good for storage of said blend. V-shell blenders are used in intermediate drug load blends (Figure 36.20). The main difference in these blenders is the geometry.

There are three mechanisms of particle mixing: convection, dispersion, and shearing [37]. In tumbling blenders, convective and dispersive mixing are dominant, unless intensifier bars or chopper blades are added to cause shear mixing. For example, within a V-shell blender, convective blending occurs within each shell side during tumbling, and dispersive mixing happens between shells.

Blending in a DC case consists of a prelubricant and a postlubricant blend ahead of compression. Lubricants such as sodium starch fumarate (SSF) and magnesium stearate are normally used.

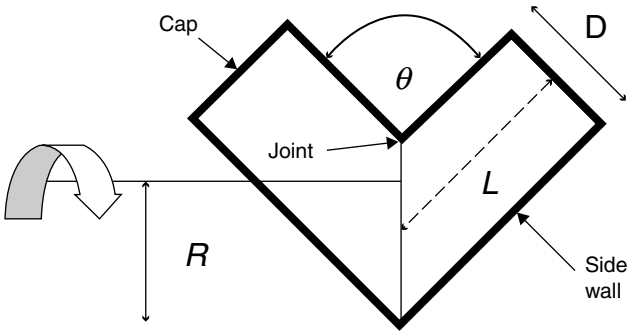


FIGURE 36.20 V-shell blender schematic.

Important parameters are as follows:

CMA/CPP	CPP/CQA/CBA It Can Affect
Particle shape and size	Blend uniformity, content uniformity, compressibility
Powder density	Blend uniformity, content uniformity, compressibility
Fill level	Blend uniformity, content uniformity
Loading procedure	Blend uniformity, content uniformity
Number of rotations (pre- and postlube addition)	Blend uniformity, content uniformity
Rotation speed	Blend uniformity, content uniformity
Blender size	Throughput
Room humidity	Degradants, compressibility

There are many ways to determine if a blend is well blended. Three simple ways are the following:

1. Use online process analytical technology (PAT) of near-infrared (NIR) technology
2. Perform thief sampling over blending time and test
3. Simply compress the blend material and access CU

The NIR region spans the wavelength range 780–2526 nm, in which absorption bands mainly correspond to overtones and combinations of fundamental vibrations. NIR spectroscopy is a fast and nondestructive technique that provides multiconstituent analysis of virtually any matrix. As NIR absorption bands are typically broad and overlapping, chemometric data processing is used to relate spectral information to sample properties.

The left graph in Figure 36.21 shows the second derivative of spectral data gathered from the API and the other components/excipients in the blend. The right graph shows when the API spectra reach a $<1\%$ RSD distribution within the blend, which is the blend end point. Commonly, 1 min after $<1\%$ RSD for the API is accomplished, called as the blend end point, but the engineer can see the asymptote of the line over time, sample number. Other determinations of blend end point are used as well, and method development is to be used for particular blends. This tool is useful as the engineer receives online data without sampling bias.

If PAT tools cannot be used, a more traditional sample method is used. Samples are commonly pulled from many locations (Figure 36.22) within the V-shell blender in order to understand if there is any location bias versus blend uniformity.

Usually, blenders are scaled from V-shell (laboratory, pilot scale, commercial scales); however, depending on the product and manufacturing needs, the blending operation may be transferred to an in-bin blender (pilot, commercial scales). Changing geometric characteristics of tumbling blenders may lead to different mixing behaviors;

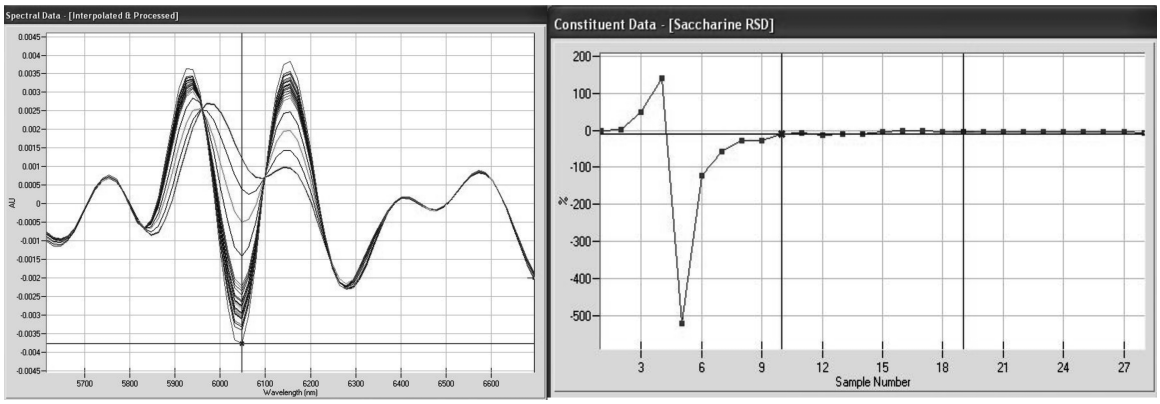


FIGURE 36.21 NIR spectral and constituent data for a blend containing saccharine as a model API[k].

therefore, a straightforward transition cannot be accomplished unless engineering principles are used. Some scale-up approaches are matching Froude (Fr) number, matching tangential/wall speed, or scaling particle surface velocities (Figure 36.23) [38–40].

36.10.2 Compression Scale-Up

Compression is important to make robust tablets. Tablets that are too soft cannot withstand the downstream coating or packaging processes without chipping or breaking and losing tablet weight/active component. Tablets that are too hard cannot dissolve effectively and therefore also cannot be efficacious when considering the TPP.

Compression is typically used to make solid oral dosage forms of core tablets. Many types of equipment are manufactured; some include single station, rotary presses. Typical manufactures are Korsch, Elizabeth Hata, SMI, GEA Courtoy, and Manesty. Tablet presses are capable of using tooling of various sizes such as A, B, and D.

Parameters that may be critical in tablet production are as follows:

CPP	CQA It Affects
Incoming blend	Tablet weight (flowability), compressibility in general
Feeder speed	Tablet weight
Fill depth	Tablet weight
Press speed (dwell time)	Appearance (defects via capping or lamination)
Precompression	Tablet hardness
Main compression	Tablet hardness
Upper punch entry	Tablet hardness
Room humidity	Compressibility in general, degradants, tablet water content
Press temperature over time	Tablet hardness, degradants, possible change in physical form

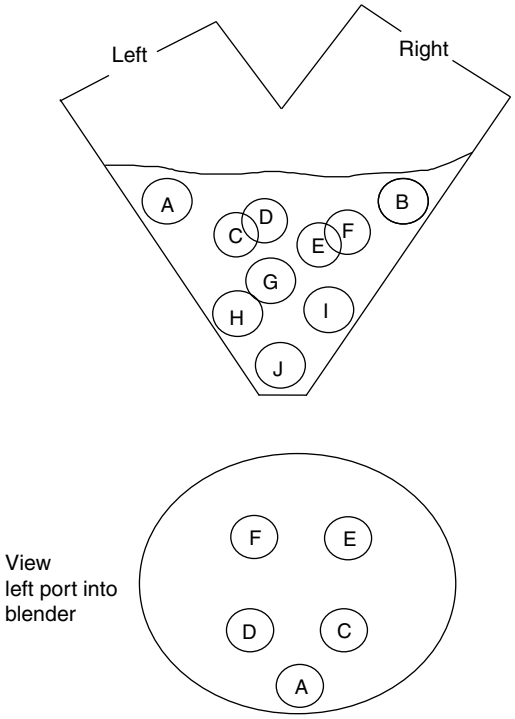


FIGURE 36.22 Example of sampling points within a V-Shell blender.

To access compressibility of the drug product DOEs are performed to evaluate precompression force, main compression force, and press speed (Figure 36.24). Tests such as tablet weight, thickness, hardness, friability, and dissolution are performed to understand the processing affects on the CQAs. These data are used to determine processing targets, NORs, and PARs.

Tablet dies and tooling may be the same from laboratory to pilot to commercial scale; the change is in tooling dwell time.

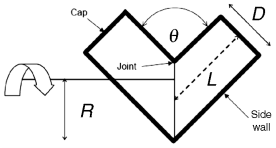
$$\text{DwellTime} = \frac{60,000 \times \text{Punch HeadFlatDiameter}}{\pi \times \text{PitchCircle Diameter} \times \text{PressSpeed}} \tag{36.13}$$

[k]NIR technology from CDI Pharma

1. **Matching of froude number (Fr),** $Fr = [\Omega^2 R]/g$
2. **Matching of tangential speed (wall speed) of blender,** $2\pi\Omega R$
3. **Scaling of particle surface velocities,**

$$V = kR\Omega^{2/3}\left(g/d\right)^{1/6} \quad \text{for } \Omega \le 30 \text{ rpm}$$

$$V = KR\Omega^{1/2}\left(g/d\right)^{1/4} \quad \text{for } \Omega > 30 \text{ rpm}$$



Ω - rotation rate
d - vessel diameter
k, K – dimensionless constants

FIGURE 36.23 Common scale-up techniques for the process of blending.

Different dwell times can cause problems such as tablet capping or lamination. Tools such as compaction simulators could be used early on to save both time and money. Scaling up based upon mechanical similarity and quality attributes of the product is important, but sometime also is scaling down. Analytical techniques such as shear cells to understand powder flow and compaction simulators to understand compressibility behavior have been developed with the mindset of scaling down.

36.10.3 Coating Scale-Up

Tablet coating is the unit operation consisting of spray coating functional or nonfunctional/aesthetic coating onto the surface of the already compressed tablets. There are various sizes of tablet coaters, ranging up to ≥60 in. coating pans. Coating pans are either perforated or nonperforated. PAT tools may be implemented, for example, NIR for water content.

Important parameters are as follows:

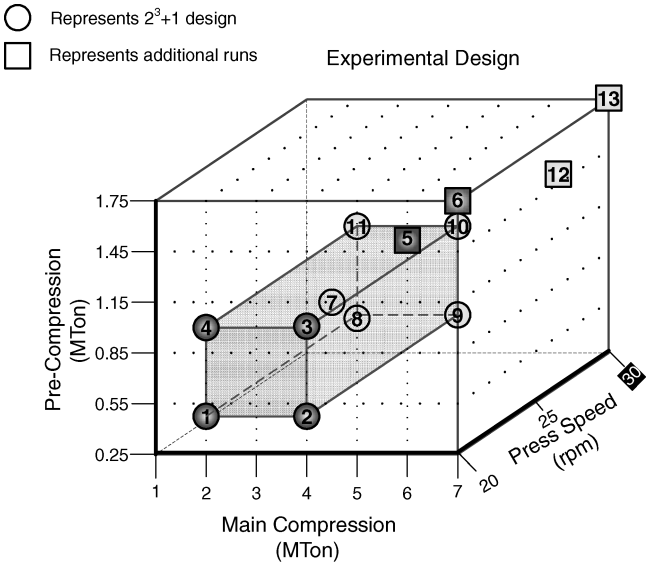


FIGURE 36.24 Fractional factorial experimental design for tableting.

CPP	CQA It Affects	Potential Problems
Pan load	Appearance, tablet water content	Improper pan loading for the scale being used
Spray gun to bed distance	Appearance	Improper spray to tablet bed
Number of spray guns	Appearance	
Exhaust temperature	Degradants, tablet water content	Spray drying of coating suspension
Atomization air flow rate	Appearance, tablet water content	Improper spray
Pattern air flow rate	Appearance, tablet water content	Improper spray
Spray rate	Appearance, tablet water content	Improper spray
Spray formulation	Appearance, dissolution	May impede tablet dissolution
Weight gain	Appearance, dissolution	Too high may impede tablet dissolution, too low may not cover tablets/ appearance
Pan speed	Appearance	Too high of pan speed
Jogging	Appearance	Too much or too little jogging of the tablet bed
Incoming tablets	Appearance, dissolution	Too soft tablets, too much disintegrant, especially on the surface of the tablets

TABLE 36.20 Spray Coating Design and Number of Defects Observed in an 800 Tablet Sample

Experiment	Spray Rate (g/min)	Exhaust Temperature (°C)	Pan Speed (RPM)	Suspension Concentration (wt%)	Defects
1	350	50	5	18	4
2	350	50	10	22	1
3	350	60	5	22	7
4	350	60	10	18	0
5	450	50	5	22	12
6	450	50	10	18	2
7	450	60	5	18	9
8	450	60	10	22	2
9	300	55	7.5	20	1
10	300	55	7.5	20	0

Postcoated tablets are examined by AQL for the number and type of defects (minor, major, or critical) (ANSI/ASQ Z1.4-2008). Common reasons for defects stemming from film coating include the following:

- Improper EEF, thermodynamic conditions
- Incoming raw material including tablets
- Operating conditions (nonthermodynamic)

Thomas Engineering Inc. provides a thermodynamic analysis of aqueous coating (TAAC) model for coating scale-up that uses thermodynamic heat and mass transfer equations to characterize the environmental conditions inside a coating pan during a steady-state film coating process [41, 42].

The environmental equivalency factor (EEF) is the most important piece of data output by the TAAC program. It is a dimensionless number proportional to the ratio of the dry area of the tablet bed to the wetted area and, as such, is indicative of the drying rate of the film being applied. The dimensionless EEF lumps together all thermodynamic terms for ease of modeling or scaling up.

If there is a concern with water content increase, changing parameter values to increase the EEF helps; however, too high an EEF may cause unwanted spray drying of the coating suspension, leading to undesired tablet defects. A balance is usually found empirically. *A good rule of thumb*: use an EEF of 2–5, with 3.3 being a typical production value.

A spray coating half factorial design around the parameters of spray rate, exhaust temperature, pan speed, and suspension concentration is executed to better define the coating processing design space with respect to tablet defects.

Table 36.20 shows the experiment and the number of defects seen in a sample size of 800. Stepwise linear regression of the data yields the model shown in Figure 36.25 and Tables 36.21 and 36.22.

Spray rate, pan speed, and suspension concentration were all seen to be significant parameters on the response of tablet defects. Exhaust temperature is removed from the model as it is insignificant in the range studied. Two interaction terms were also found to be significant: spray rate × pan speed and

TABLE 36.21 Summary of Fit for Defects Model

R^2	0.990806
R^2 adj	0.979314
Root mean square error	0.598029
Mean of response	3.8
Observations (or sum wgts)	10

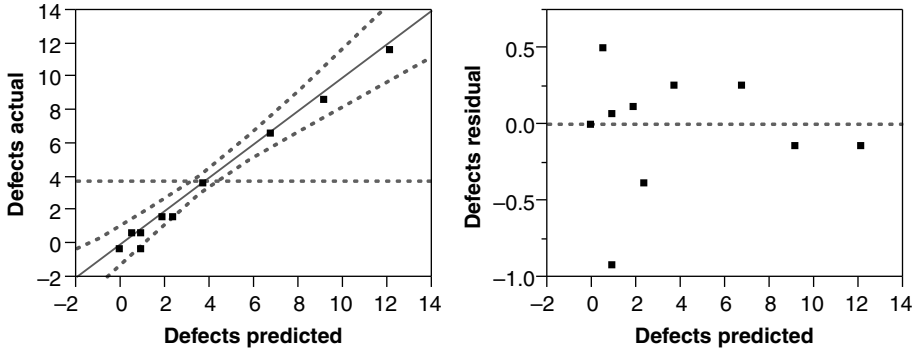


FIGURE 36.25 Defects actual versus predicted and defects residuals versus predicted.

TABLE 36.22 Parameter Estimates for Defects Model

Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	−9.702778	2.531304	−3.83	0.0186*
Spray rate (g/min)	0.0363889	0.003152	11.55	0.0003*
Pan speed (RPM)	−1.21	0.091089	−13.28	0.0002*
Suspension concentration (wt%)	0.4375	0.105718	4.14	0.0144*
(Spray rate (g/min) − 380) × (pan speed (RPM) − 7.5)	−0.007	0.001691	−4.14	0.0144*
(Pan speed (RPM) − 7.5) × (suspension concentration (wt%) − 20)	−0.125	0.042287	−2.96	0.0417*

The asterisk indicates that the variable is significant.

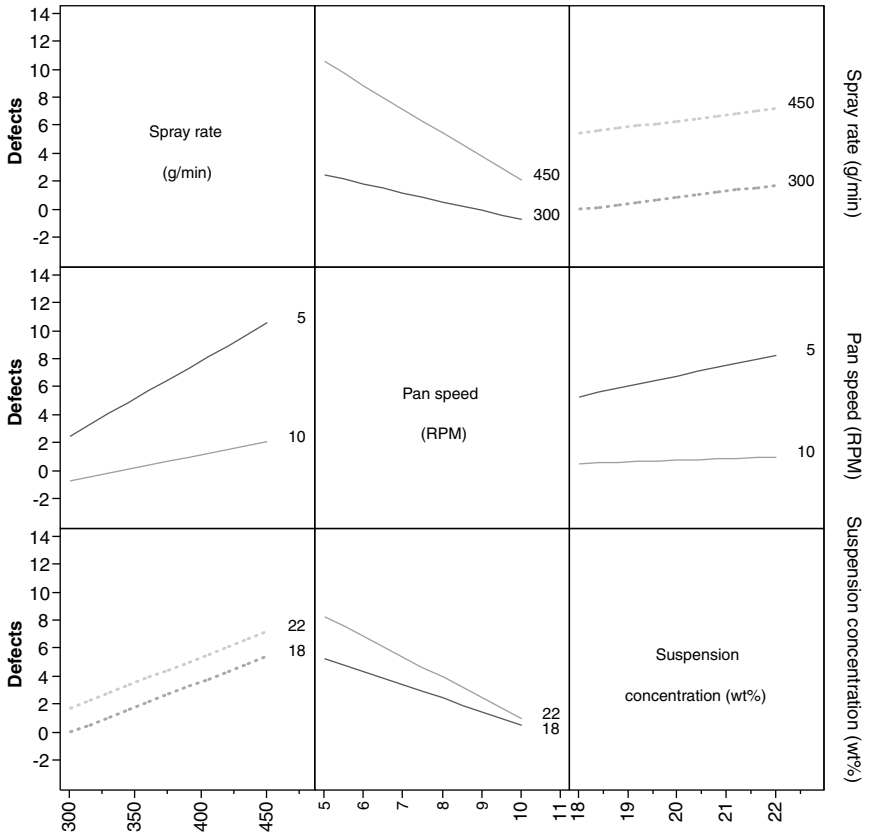


FIGURE 36.26 Interaction profiler for the tablet defects model.

pan speed × suspension concentration. The interaction profiles are shown in Figure 36.26. The engineer optimizes the process by using the parameters of the strongest leverage. For example, higher pan speeds were shown to have fewer defects.

36.11 CONCLUSION

This chapter demonstrated an approach to drug product development. There are many different approaches; a good engineer examines the best approach for the situation. Defined in the chapter was a systematic manner in which to develop an immediate release tablet. First, account for the physical characteristics of the drug substance: particles characteristics, solubility, BCS classification, and stability. Next, the release and stability characteristics of the tablet become important. Finally, determine the processability and scaleability of the tablet.

Overall, a wise selection of excipients and processes relies on a sound understanding of the physical, chemical, and mechanical properties of the drug and excipients. A formulation may be successfully scaled up and consistently meet performance and manufacturing requirements

only when one fully understands the complex relationship between the drug, excipients, processing, and desired dosage form performance criteria.

When formulating any pharmaceutical dosage form, it is important to remember that there is equilibrium between the bioavailability of the product, its chemical and physical stability, and the technical feasibility of producing it. Any changes made to a formulation in an attempt to optimize one of these properties are likely to have an effect on the other two parameters that must be considered. This is especially true of immediate release solid dosage forms.

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