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ACHIEVING A HOT MELT EXTRUSION DESIGN SPACE FOR THE PRODUCTION OF SOLID SOLUTIONS

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42.1 INTRODUCTION

Industrial applications of hot melt extrusion date back to the early 1900s. This process has since grown in use, and today is one of the most widely applied unit operations in the polymer industry. Recent increases in both patents and publications indicate it is rapidly becoming a key processing route for pharmaceutical dosage units as well [1].

Pharmaceutical extrusion has been used to process pastes (e.g., wet granulation) and polymer melts in which an active pharmaceutical ingredient (API) is present in an amorphous and/or crystalline state. The extrusion process has enabled a wide range of product applications including [1] solid solutions for the oral delivery of insoluble poorly soluble APIs, [2] implants, [3] intra oral delivery, [4] ophthalmic delivery, [5] controlled release (via matrix or multiparticulates), [6] conventional (i.e., API is in crystalline state) tablets by continuous wet granulation, and [7] nanocrystalline formulations.

Although many uses exist for hot melt extrusion, its application to produce solid solutions meeting pharmaceutical quality requirements remains limited. This chapter outlines design for six sigma (DFSS) led development activities used to define the design space for an extrusion process generating a solid solution. The use of DFSS methodology is a natural fit given its long standing application to new technologies, and added benefit of having significant overlap with the FDA's quality by design (QbD) initiative. The benefits of QbD development include added regulatory flexibility enabling continuous process improvement post filing, more prioritized development and an overall more effective management of risk. This text outlines how QbD methodology was reduced to a development roadmap using the DFSS tool set.

This chapter begins with an overview of solid solutions to provide a motivation for implementing hot melt extrusion in the pharmaceutical industry followed by a more detailed review of the extrusion process itself. The risk assessment activities that set the stage for more focused development efforts are then reviewed and the final section summarizes the use of process analytical technology (PAT) to facilitate definition of a multifactor design space. The chapter ends with a forward-looking vision of how this design space ultimately might be translated into a control strategy.

42.2 INTRODUCTION TO SOLID SOLUTIONS

Solid solutions have been developed largely to modulate undesirable drug properties—particularly, the poor aqueous solubility and/or wetting behavior of development candidates. Product pipelines in major pharmaceutical companies are increasingly composed of insoluble drug candidates driving the need for alternative oral delivery strategies including nanocrystalline, lipid, and solid solution based formulation technologies [2]. By some estimates the fraction

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of development candidates considered very soluble has dropped below 10% [3]. A primary driver for deploying solid solution approaches in pharmaceutical development is to increase the exposure of orally administered poorly soluble active compounds and several reviews on this subject have been written [4–7].

Solid solutions are solutions of API in a glassy polymer often prepared by melt, solvent, and/or mechanical means by processes such as extrusion, spray drying, or mechanical activation, respectively. Increased oral absorption from solid solution formulations is achieved by supersaturation and/or *in situ* formation of nanoparticles [8, 9]. Increasing the apparent solubility of active compounds drives both potentially faster dissolution and permeability rates [10], making it possible to achieve dose proportional increases in exposure at higher doses and reduced potential for formulation related food effect. In addition to these benefits, solid solution formulations enable combination products in a solid format and have been used to bridge from liquid filled capsule type self-emulsifying and/or self-microemulsifying formulation approaches (Figure 42.1). Solid solutions have also found use in the preclinical setting, often in the form of suspensions [11]. The exposure increase compared to common alternative formulations can be dramatic (Figure 42.2). The benefit in exposure does come with a commensurate physical instability risk posed by these stabilized amorphous systems, although several compounds have been successfully launched.

Any process that reliably produces homogeneous glasses with consistent properties can be used to make solid solutions (Figure 42.3), however, there are relatively few papers that have discussed the relationship of process selection on product performance [12–16]. Those authors that have broached this subject have typically compared the performance of identical or unique formulations prepared at a single set of operating conditions using multiple preparation processes. It is not possible to make generalizations about superiority of a particular process for solid solution manufacture from the current body of published work. This is largely because an understanding of the operating space explored and associated characterization data used to determine if a homogeneous glass was produced in each case was not presented.

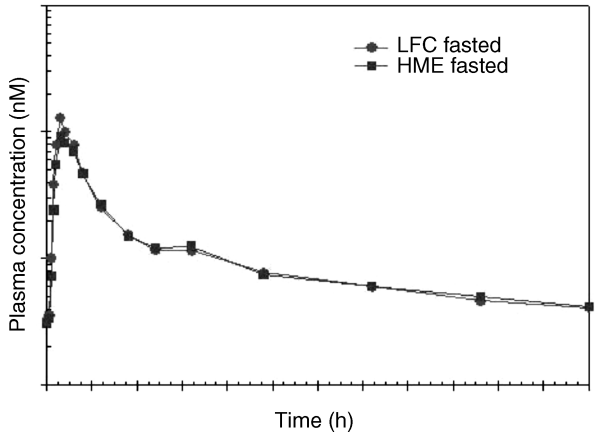


FIGURE 42.1 Plasma concentration following oral administration in fasted healthy adults of liquid filled capsule (circles) and a solid solution intermediate based tablet (squares) (Compound A; $n = 24$; 200 mg).

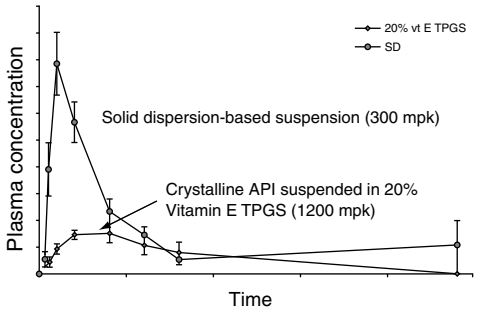
Each preparation process possesses advantages and disadvantages. Solvent-based processes are generally easier to scale down to mg-scale while extrusion approaches generally provide greater production rates per equipment volume. Access to multiple approaches is likely required to broadly enable a diverse portfolio of compounds with solid solution technology. The identification of drug candidate polymorphs may cause development challenges for spray drying process development in the identification of suitable solvent systems or extrusion processes in the case of thermal degradation or temperature-induced polymorphic transitions.

A particularly desirable aspect of extrusion in today's pharmaceutical development environment is the ability to continuously process in a direct-to-drug-product manner (Figure 42.4). Extrusion naturally lends itself to continuous processing from raw materials pneumatically conveyed into individual feed hoppers supplied by bulk containers to molded drug product fed into bulk product containers or even blister packages. This process has a small specific volume, making it amenable to real-time quality control and keeping the equipment footprint on a manufacturing floor exceptionally small. The product in an extrusion process naturally flows through a relatively narrow cross-section making continuous and direct process analytic interrogation straightforward (e.g., reducing issues of sampling).

42.2.1 Systematic Development Strategy

Prior to starting the design space definition process, efforts began by attempting to translate existing knowledge (i.e., experimental information, first principles understanding, models and best practices gleaned from peer reviewed literature) into a comprehensive view of the extrusion process. Process input parameters were summarized to ensure none of the process parameters were overlooked. This was facilitated with process mapping exercises following fishbone, or Ishikawa diagram methodology.

Subsequent risk assessment activities focused the parameters from the process map to a subset of potential critical process parameters (CPP's). These potential CPP's were identified as having a higher probability of impacting potential critical quality attributes (CQA's) as defined from an understanding of solid solution product requirements relevant to the patient. The risk-based evaluation of all parameters against the potential CQA's employed a quality function deployment (QFD) grid consistent with the house



Cpd	SD (susp. dose, mpk)	Reference formulation	Exposure increase
A	300	1200 mpk 20% vitamin E TPGS	2–8X
B	100	100 mpk Imwitor 742:PS 80	67X
C	100	300 mpk methocel suspension	2–6X
D	200	750 mpk 10% PS80	4–16X

FIGURE 42.2 Preclinical impact of solid solution suspensions. *Left*: Plasma concentration profile following oral administration in male Sprague-Dawley rats (Compound B; $n = 4$). *Right*: Cross-project preclinical formulation comparison of solid solution based suspensions and a variety of reference formulations (mpk = milligrams per kilogram).

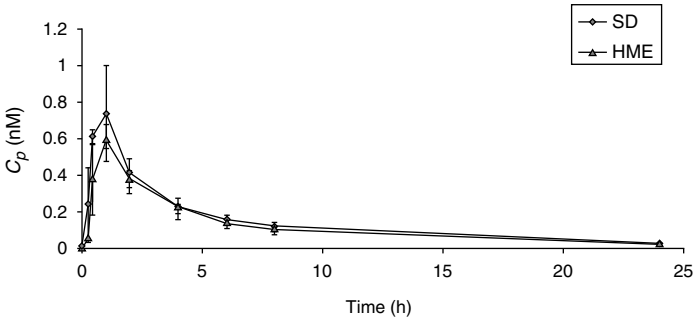


FIGURE 42.3 Comparison of identical solid solution formulations prepared by spray drying (SD) and extrusion (HME). Plasma concentration profile following oral administration of compound B in HPMC-AS-LF as tablets (male beagle dogs; $n = 6$; crossover; 50 mg dose).

of quality methodology [17]. This risk assessment exercise was not one of the tools explicitly outlined in the ICH Q9, however, it successfully managed the complexity of the hot melt extrusion process and delivered on the spirit of providing "transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and, sometimes, detectability of the risk." [18] The outcome of this exercise was a summary of clearly prioritized development targets focused on a manageable set of potential CPP's.

Development efforts aimed to generate a fundamental understanding of the system recognizing that the degree of regulatory flexibility attainable was predicated by depth of knowledge. Enhancing this fundamental understanding was a focus on scale-independent parameters rather than scale-dependent parameters. An example of achieving this more fundamental understanding of the extrusion process by studying scale-independent parameters is demonstrated here for the case of shear stress in the extruder. Shear stress is a key parameter thought to influence quality attributes including degradation, and the capacity to achieve a molecularly dispersed product. Shear stress (the scale-independent parameter) is primarily manipulated via screw speed, or rpm (the scale-dependent parameter). While rpm is an easily accessible parameter to incorporate into design of experiments (DOE's), only studying the influence of rpm on product quality would have resulted in at best a correlative understanding of the system. This type of understanding does not capture the added impact of the degree of fill, scale, equipment manufacturer, or the result of wear in the extruder; all of which can change the shear stress at a given rpm. Focusing on scale-dependent parameters (i.e., rpm) rather than scale-independent parameters (i.e., shear stress) would have limited the potential to apply findings broadly to both anticipated and unanticipated process changes.

Initial small-scale experiments were conducted via DOE and successfully identified one scale-independent parameter that had a disproportionate impact on the key product quality attributes. This also yielded supportive data for more definitive CQA and CPP definitions. The next stage of development sought to build empirical models for the relationship between key scale-independent and scale-dependent parameters. This was achieved through response surface mapping, which was needed due to the multidimensional and quadratic means by which scale-dependent parameters (e.g., rpm, degree of fill, clearance) influenced scale-independent parameters (e.g., shear stress). This DOE was conducted on

FIGURE 42.4 Direct-to-drug-product extrusion process train schematic, highlighting bulk feeders, precision loss in weight feeders, liquid injection, and calendaring of tablet between two chilled rolls.

commercial scale equipment incorporating in-line process analytical technology that facilitated evaluation of both product quality and process robustness. Robustness was assessed by introducing known perturbations at all processing conditions, and monitoring the system's capacity to dampen the upset. The combined understanding of quality attributes as a function of scale-independent parameters, the empirical models from response surface mapping and the PAT data on process robustness allowed definition of a design space that achieved balance between achieving target quality attributes and optimizing operating conditions including throughput and process stability.

42.2.2 HME Process Overview and Mapping

The intent of process mapping is to create an objective view of the extrusion process, and generate the set of potential process inputs to serve as the basis for risk assessment activities. Consider extrusion as a series of suboperations (1) material feeding, (2) powder conveying and degassing, (3) melting and mixing, (4) melt conveying and venting, and (5) pumping, shaping, and cooling. Each of these suboperations was mapped independently. The following sections include the map of process inputs and discuss some of the features of each suboperation.

42.2.2.1 Material Feeding Extruder feed systems in many ways ultimately control the content uniformity of product. While extruders offer some backmixing to dampen out high frequency feed rate perturbations, low frequency disturbances in material feed rates can result in compositional variations in the extrudate, and, hence, compromised product quality [19]. One route to decouple feeder performance from the extrudate compositional uniformity would be to preblend all of the feed streams. However, preblending requires an extra unit operation, presents a risk for segregation, and is generally complex when one or more components are liquids. Figure 42.5 is a process map outlining a subset of the potential process inputs for the material feeding process.

Solids feed to the extruder can be achieved via volumetric or gravimetric feeders. Volumetric feeders are best suited for applications where the materials flow well and control of the composition of the feed stream will not vary (i.e., for use with powder preblends). The applications presented here focus on

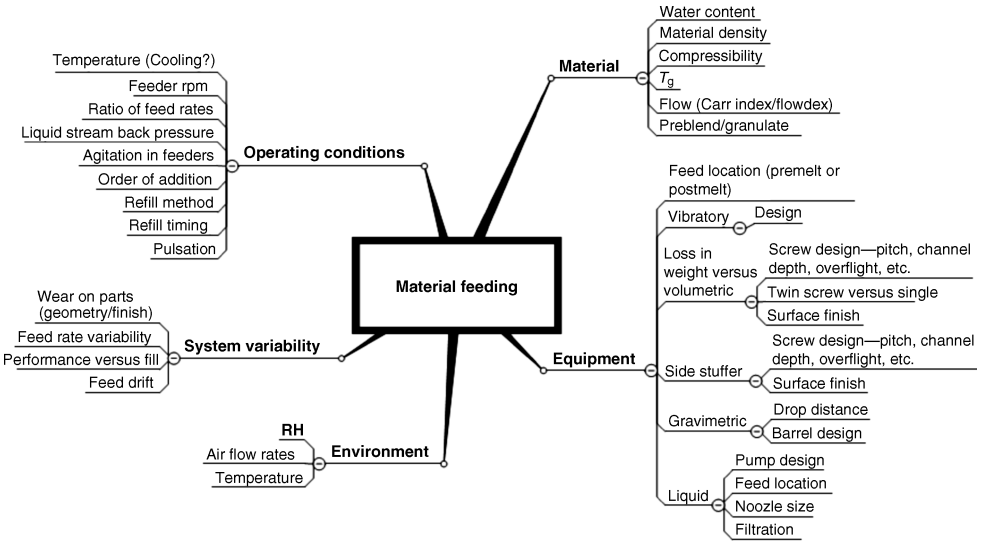


FIGURE 42.5 A summary of input parameters of the material feeding process.

gravimetric feeders. These feeders are often single or twin-screw feeders coupled to a load cell(s). Constant flow rates into the extruder are attained via loss in weight feedback control.

A key consideration when evaluating solids feeders is that flow rates from these units are never fully continuous. Intrinsic to powder conveying screws is some level of pulsing into the extruder, since the feed material is not a continuous media. For very poorly flowing material exhibiting strong propensity for avalanching, the frequency of the pulsing for a twin-screw feeder could be expressed by

$$\frac{\text{rpm}}{(2n-1)60} \tag{42.1}$$

where n is the number of flights in the feed screws. For example, for a twin-screw feeder with single flighted conveying screws feeding poorly flowing material, running at 60 rpm would result in a pulse every second. Similarly the concept of continual versus pulsed addition applies for liquids. At low liquid flow rates, any inconsistent flow, or dripping should be evaluated to ensure it is not occurring at a frequency undampened by the extruder's backmixing. This can be overcome by trying to achieve back pressure to deliver the liquid as a continuous stream.

Powder feeders can be coupled to the extruders such that material drops from the end of the feed screws into an open barrel section. A limitation of this approach is that incorporation of the powders into the extruder is limited to a fraction of the open barrel feed port where the extruder's down turning screw conveys material into the extruder [20]. The feeding of low bulk density powders can be particularly problematic and can significantly constrain the maximum attainable throughput. A common means to overcome flood feed limitations of low bulk density materials is via a side stuffer. Here, the loss in weight feeder delivers powder gravimetrically to volumetric (constant rpm) conveyors coupled to the side of the extruder. These conveying screws produce some predensification and force the powder into the extruder enabling higher throughputs for low bulk density powders. Successful densification in the side stuffer requires sufficient venting of entrapped air.

A consideration when designing feed locations are the disparities in shear stress, temperature, and mixing histories that materials experience. The highest viscosity that polymers transition through occurs at the melt onset, which is also the point of maximum shear stress. Active ingredients or liquids could be added upstream or downstream from this point. Adding the active downstream limits the total time at temperature and reduces the shear stress, however, it also potentially reduces the extent of mixing achieved. An additional consideration when determining the feed location are the difficulties in mixing materials having large viscosity differences. Lower viscosity materials can act as lubricants, reducing shear rates and mixing intensity [21]. In extreme cases, streaming of the low-viscosity material through the extruder may be observed. Special attention should be paid to the mixing sections of the screw profile when there is a need to incorporate materials having large viscosity differences.

42.2.2.2 Powder Conveying and Venting The next task that must be accomplished in the extruder is conveying the bulk powder to the melt zone. A list of process inputs to consider when feeding and conveying low bulk density powders is listed in Figure 42.6. In conveying sections, material passes through the extruder via drag flow with very little pressure generation. In an ideal conveying scenario, material would demonstrate perfect slip with the screw, and perfect friction with the barrel.

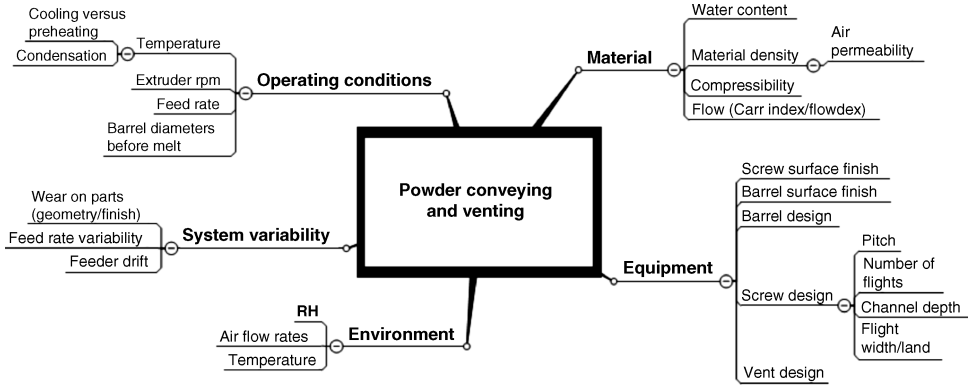
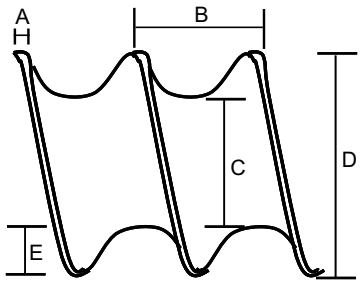


FIGURE 42.6 A summary of input parameters of the powder conveying and venting suboperations.

Figure 42.7 highlights aspects of screws with particular relevance to conveying. Increasing flight width results in greater pumping efficiency of the screws. Increasing flight pitch, or angle of the helix, generally results in faster material conveying per revolution, although low bulk density materials may not follow this trend. The internal (D_i) and external (D_o) diameters of the screw have numerous implications. The channel depth (D_o–D_i) sets the free volume of the extruder and largely determines the maximum feed rate (without the use of mechanical predensification via a side stuffer, etc.). The D_i generally limits available torque at small scales, although at larger scales the torque constraints of the drive motor may be limiting. Although a larger D_i enables greater torque, this generally reduces throughput by sacrificing free volume.

Conveying involves added complications for pharmaceutical applications because many of the feedstocks possess substantially lower bulk densities than commodity polymer extrusion operations based on 3 mm pellets. It is not uncommon for an API to have 0.2–0.4 g/cm^3 bulk density. Many of the pharmaceutical polymers and surfactants are also only available from manufacturers as powders (not pellets),



A: Flight width
B: Pitch
C: Internal diameter, D_i
D: External diameter, D_o
E: Channel depth (D_o–D_i)

FIGURE 42.7 A subset of the critical design components of conveying screw elements.

having bulk densities of 0.4–0.6 g/cm^3. As noted in the previous section, this low bulk density largely impacts the maximum feed rate achieved in the extruder due to flooding of the feed port. Increasing screw speed (in some cases) [22], employing a side stuffer, or increasing the free volume of the screws can enable higher feed rates. One way to achieve a higher free volume in the feed section is to use undercut, square channel screws in the feed zone [23]. While these are not self wiping, this may not be a concern since there is no molten material in the feed section, and this would not extend the heat history of the material.

A further challenge in feeding low bulk density powders involves the entrained air. Low bulk density feed materials undergo significant densification during extrusion because up to 80% of powder feed streams are entrained air. Effective venting mechanisms are essential to remove this air and maximize throughput [22]. In addition to venting air, moisture removed from the feedstock by heating in the extruder may condense on colder upstream barrel sections or feed powder in the feed zones [24]. Given these two considerations, proper venting in the feed section is critical.

42.2.2.3 Melting and Mixing Achieving a melt is generally accomplished through the input of energy by the extruder into the formulation. A generic free energy diagram (Figure 42.8) illustrates this principle. The formulation components, whether crystalline API or amorphous polymer, undergo a transformation to a more mobile and deformable state at higher temperatures. The melt extrusion process enables energy input through both thermal and mechanical means. Thermal energy input is typically achieved through electric or oil heating of the barrel, which is transferred to the formulation via conduction. This method can be efficient in small-scale extruders, although conductive heating alone is generally not a sufficient source of energy to achieve a melt due to the poor thermal diffusivity of polymers [25]. Relying heavily on conductive heating also poses scale up challenges since heat transfer is a function of surface area, while scale up to preserve key material properties generally occurs on a

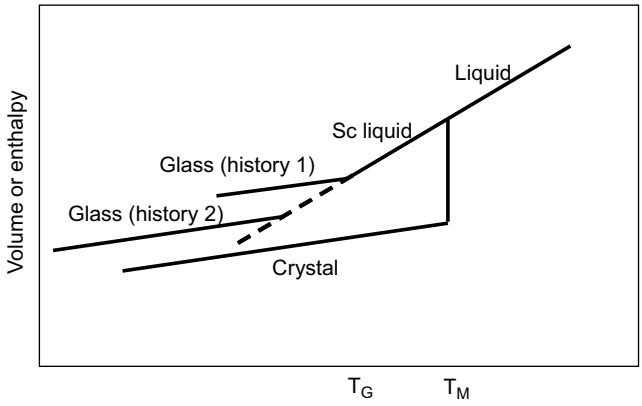


FIGURE 42.8 Behavior of glass forming single component material.

volumetric basis. Moreover, greater product temperature uniformity could be expected when minimal conductive heat is transferred from the barrel [26].

While conductive heat can contribute to the total energy input at smaller scales, melting is largely achieved by viscous dissipation via frictional forces (including interparticle, material/wall, and material/screw friction) [25, 27]. Some estimates suggest at least 80–90% of the energy to achieve a melt is supplied by the extruder's screws [28]. This energy is generally referred to as the specific energy, which is the ratio of mechanical energy (as measured by a wattmeter on the drive motor) to feed rate in units of kW h/kg. It is important to note that the wattmeter reading does not account for losses to the thrust bearing (which can be significant if high pressures are generated in the extrusion process), or drive motor efficiency at the given rpm, although these adjustments can be made. Mechanical energy input is achieved through deliberate design of the extruder screws to impart mechanical stress on the formulation, with specific energy often serving as a target to ensure process consistency upon scale up [29].

Extruder screws are generally modular and consequently allow for a number of different configurations, which have a direct impact on the specific energy, residence time distribution, and maximum shear stress among other process responses. The same formulation extruded under different conditions, therefore, may exhibit disparate levels of quality [30].

Pharmaceutical extrusion often features the use of double-flighted screws, creating three distinctly separate channels down the length of the extruder barrel. A configuration using only conveying elements would largely move material through the extruder in plug flow with minimal backmixing or material transfer between these three channels. The only mixing achieved in a pure conveying system would be laminar in nature, and would potentially be less than expected due to viscous polymers not following no-slip boundary layer conditions [31]. As such, under these conditions there is almost no high-frequency disturbance dampening, potentially leading to poor compositional uniformity. Compositional uniformity requires backmixing, and is achieved via screws designed to allow pressure flow to cause material movement between the channels. Here, the screw flights are opened, often taking the form of mixing blocks. Figure 42.9 attempts to show conceptually how conveying elements are discretized in a way that allows exchange of material via mixing blocks. While mixing blocks are the conventional means to achieve a melt and sufficient backmixing, other routes include blister rings [26], gear or turbine type elements [32], or simply staggering or offsetting conveying elements [20].

Mixing screw elements have been designed to ensure compositional uniformity. The axial width of a mixing paddle is an indicator of the magnitude of global pool capture (a region of the screw channel known for its high shear) and determines the extent to which mechanical energy will be imparted by a single mixing element. In plastics extrusion, wide mixing paddles reduce particle size through attrition (dispersive mixing), whereas narrow paddles and similar lower energy elements are utilized primarily to achieve compositional and thermal homogeneity (distributive mixing) [33]. Formulations consisting of miscible components benefit from both dispersive and distributive mixing to impart energy for melting, and create surface area for diffusion; thereby yielding uniformity at a molecular level [34, 35]. The number of mixing cycles (cycles of volume expansion and compression during screw rotation) may also serve as a measure of mixing intensity. This mechanism is analogous to kneading pizza dough as a method to incorporate and mix ingredients (Figure 42.10) [20, 33]. A full list of process parameters evaluated for the melting and mixing stage is highlighted in Figure 42.10.

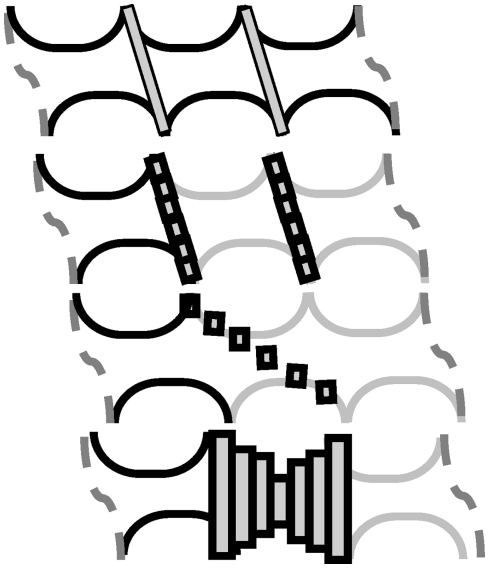


FIGURE 42.9 Illustration of the transition from conveying elements with a closed channel (*top*) to mixing elements with an open channel (*bottom*), to produce backmixing.

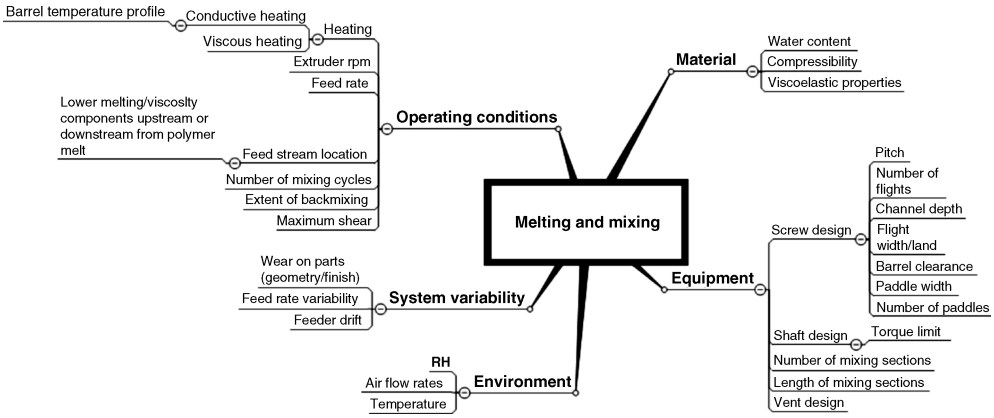


FIGURE 42.10 A summary of input parameters of the melting and mixing suboperations.

42.2.2.4 Melt Conveying and Venting Downstream of the mixing paddles, the aggregate material is in a molten state and any additional conveying before the die continues to constitute a formulation's time at temperature, which is the most relevant component of the residence time distribution as it relates to product quality (i.e., degradation versus homogeneity). The conveying screws are generally less than completely filled, and residence time is a function of screw speed. See Figure 42.11 for a list of process input parameters related to this stage. This is in contrast to residence time in full barrel sections (e.g., reverse conveying elements, neutral mixing sections) were residence time is a function of feedrate with minimal contributions from screw speed [23].

Venting is an important aspect of the melt conveying step. The melting of API and excipients liberates solvents (e.g., water) and without proper venting, even small quantities of water or other volatiles could result in bubbling/foaming as the melt exits the die and/or result in undesirable residual solvents in the extrudate that could impact product properties. Devolatilization is generally a mass transfer limited process, as volatile materials must diffuse through the melt. Key influencing parameters include temperature (with elevated temperatures increasing the diffusion coefficients), feed rates (which impact residence time), and the screw profile. The screw profile affects both the residence time in venting sections, and diffusion distances. Screws sections under the vent are typically designed to minimize local degree of fill using multiflight large pitch screws to maximize surface area and minimize diffusion distance [28]. Screw profiles can also be designed to enhance the surface renewal phenomena to further reduce the diffusion distances.

The extrusion of formulations containing API solvates is an intriguing application of venting to enable what has not been possible with conventional pharmaceutical processing. A given drug molecule can exist as any number of solvates, depending on its chemical synthesis route. Safety considerations prohibit the vast majority of solvates from moving into drug development despite their sometimes favorable physical properties (i.e., improved flow, enabling better control of feeding to the extruder and improved content uniformity of the extrudate). Using the melt extrusion process, an API solvate may be fed into the extruder, with the solvent removed upon melting. The final drug product should contain low levels of residual solvent, meeting ICH [36] specifications.

42.2.2.5 Pumping, Shaping, and Cooling The stage of extrusion most closely associated with its namesake is the pumping of molten extrudate through a die. Die geometry may play a role in the final product, such as in the production of transdermal films, which would require a slit die. The

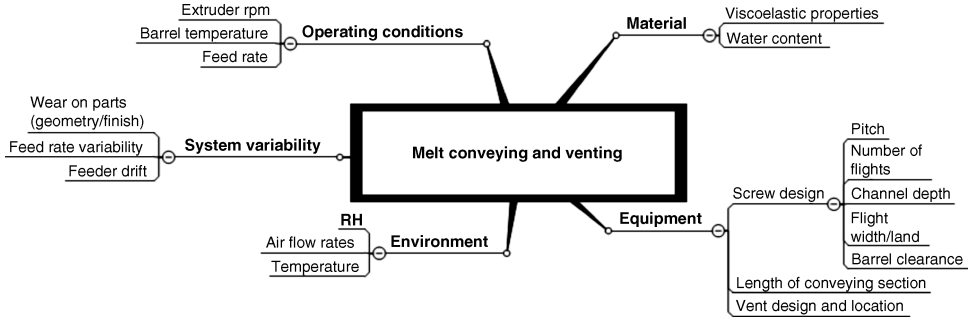


FIGURE 42.11 A summary of input parameters of the melt conveying and venting.

molten extrudate may also be processed downstream via conventional unit operations (i.e., milling and compression) and in this case precise die geometry is not critical. A common shape for pharmaceutical extrusion application is a circular die, with multiple strands facilitating more rapid quench cooling. In some cases, particularly for multiparticulate controlled release applications, the extrudate strand may be passed through a die face cutter resulting in small pellets [37]. Here, strand diameter plays a more central role in product quality, and is determined by the die geometry, viscoelastic properties of the formulation, process conditions (e.g., pressure) and material flow rates.

The extruder die can be roughly characterized as a resistance to material flow. Sufficient pressure is generated in the screw channels prior to the die to overcome this resistance. The pressure resistance can again be considered a function of the die geometry and the melt's viscoelastic properties. Significant pressure increases near the die may result in melt temperature increases due to viscous dissipation [38], resulting in the product's maximum melt temperature. For inviscid materials, additional heating during pumping out of the die may not be significant. In this case, the maximum product temperature may be achieved upstream of the die at some point after achieving a melt.

The extrudate can take many paths to a finished pharmaceutical dosage form following extrusion. The formulation is often quenched using such methods as passing along a conveyor belt with compressed air, or feeding through chilled stainless-steel rolls. Once cooled, the extrudate may be sized using conventional pharmaceutical mills, then compressed into tablets or filled into capsules. Alternative options for manufacturing finished pharmaceutical dosage forms include direct shaping methods of the extrudate. Directly formed tablets may be created by calendaring [39] or injection molding [40]. Figure 42.12 shows an example of a directly shaped dosage form. Molding enables production of complex shapes with features such as embossing to improve patient compliance, enable branding opportunities, and prevent counterfeiting. Molding also has the potential to reducing the need for fillers and compression aids. See Figure 42.13 for a list of input parameters related to this process stage.

FIGURE 42.12 Example of a directly shaped tablet following a melt extrusion process illustrating the ability to form complex shapes, such as the Merck corporate logo (image weight ca. 200 mg).

42.3 RISK ASSESSMENT

42.3.1 Quality Attribute Definition

Multiple processes and process conditions can produce material with similar *in vivo* responses (as demonstrated in Figure 42.3) provided the process achieves a true solid solution. In the case of extrusion, heat generally drives miscibility unless the enthalpy of mixing is very unfavorable at high temperatures. Miscible formulations produced by extrusion will be homogeneous provided sufficient mixing, time, and heat.

While the bulk of extrudate properties can be explained by the heat history and energy input, relaxation state and particle physical attributes (e.g., particle size) may also impact formulation performance. The relaxation state can be varied systematically by changing quench rate. Figure 42.8 is a common illustration of how different quench rates of a single component system can lead to materials of different relaxation states and properties.

HME processing conditions are generally constrained at one end by the maximum throughput. This operating limit is usually characterized by low specific energy, short residence time, low product temperature, and/or limited mixing (Figure 42.14). An extreme case for a low energy limit would be to employ conveying elements, no barrel heat, and no die restriction [41]. With more conventional compounding screw profiles, it is possible that the low energy limit resulting in unacceptable product quality will lie outside of the accessible operating space (e.g., a torque limit may be encountered before inhomogeneous product is produced).

The upper end of HME processing conditions as shown in Figure 42.15 may be constrained by thermal degradation. Efforts to circumvent thermal degradation in HME include the use of plasticizers with the goal to process at low barrel temperatures and/or with a less aggressive screw profile [42]. Incorporating antioxidants during extrusion [43] and nitrogen blanketing can effectively stabilize oxidatively sensitive drugs. Elucidating degradation mechanisms for the polymers and developing analytical characterization methodologies is more complex compared to thermal degradation of small drug molecules for which stability indication assay method and LC-MS are commonly used.

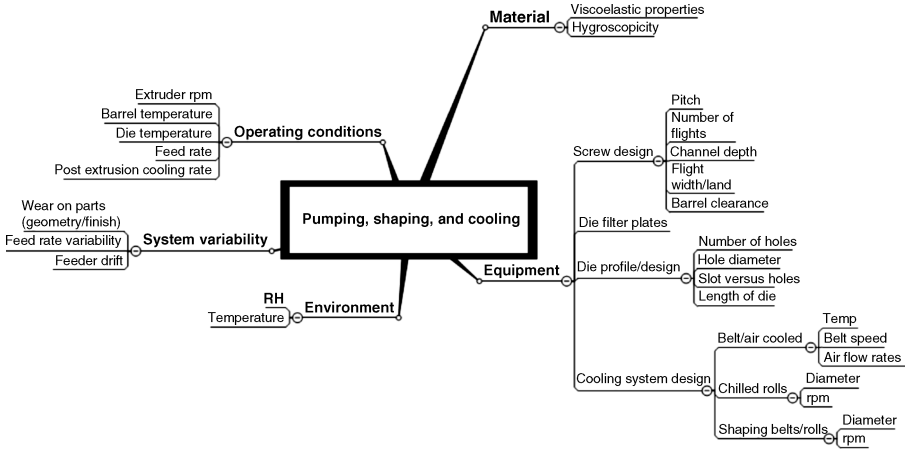


FIGURE 42.13 A summary of input parameters of melt pumping, shaping, and cooling.

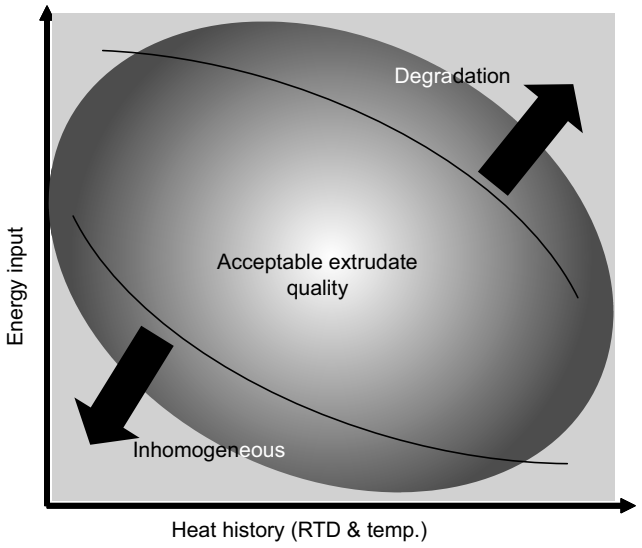


FIGURE 42.14 A schematic showing the balance of energy input and heat history, with the extreme combinations of these resulting in either degradation or inhomogeneous material.

The implication of polymer degradation is twofold (1) potential safety concerns of the degradation products at levels exceeding the ICH qualification threshold and (2) potential impact on polymer functionality (e.g., stabilizing high energy amorphous drug in solid state and/or enhancing solubilization of poorly soluble compounds during *in vitro* drug release).

Hydroxypropyl methylcellulose acetate succinate (HPMC-AS) is a widely used polymer for making solid solutions owing to its unique physical and chemical properties including high T_G, ample solubility in organic solvents, and potential for diversified molecular interactions with a broad range of poorly soluble drugs. HPMC-AS is a linear polymer consisting of $\beta(1 \rightarrow 4)$ linked substituted D-glucose units. Three possible reactions could occur after thermal stress: (1) the dissociation of substitution groups, (2) the breakage of glycosidic linkages, and (3) rearrangement of the polymer backbone via intramolecular reactions (Scheme 1). A detailed understanding in degradation chemistry involves polymer characterization using an array of analytical techniques such as TGA, GC-MS, size exclusion chromatography (SEC), NMR, IR or mass spectrometry.

TGA is an effective tool for monitoring polymer breakdown products as a function of temperature. It has been routinely used to derive activation energy associated with polymer decomposition [44]. TGA analysis of HPMC-AS showed a modest volatile formation (2%) at temperatures ranging from 175 to 250°C (linear ramp in 5 min). Headspace GC-MS analysis showed the volatiles mostly consist of CO_2, formic acid, acetic acid, succinic acid, and other unidentified small molecular species. The volatiles are likely the by-products of dissociation of side chains from the polymer backbone. The TGA/GC-MS results are consistent with those from variable temperature IR, where an increase in OH signal was observed, indicative of the loss of R groups. At representative HME processing temperature (e.g., <230°C), the loss of R groups is believed to dominate the reaction pathway leading to polymer degradation. TGA was also conducted for a series of other polymers including HPMC-phthalate, HPMC-trimellitate polyvinyl pyrrolidone, and polyvinyl pyrrolidone–polyvinyl acetate copolymer (PVP–PVAc). The polymer decomposition rate appears to increase in the order of PVP < PVP–PVAc < HPMC-AS < HPMC-T, and HPMC-P.

Thermally induced glycosidic bond breakage could lead to depolymerization or cross-linking of the polymer, which could potentially compromise polymer functionality. SEC results of HPMC-AS processed at several extrusion conditions suggest polymer breakdown or cross-linking is not likely to occur at typical operating temperatures (e.g., 170–230°C). This is consistent with biorelevant dissolution of HME extrudate samples in which typical process

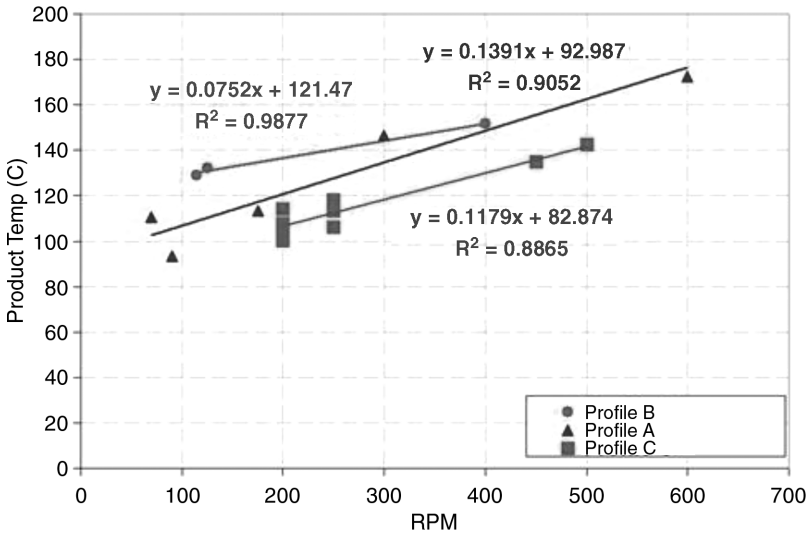
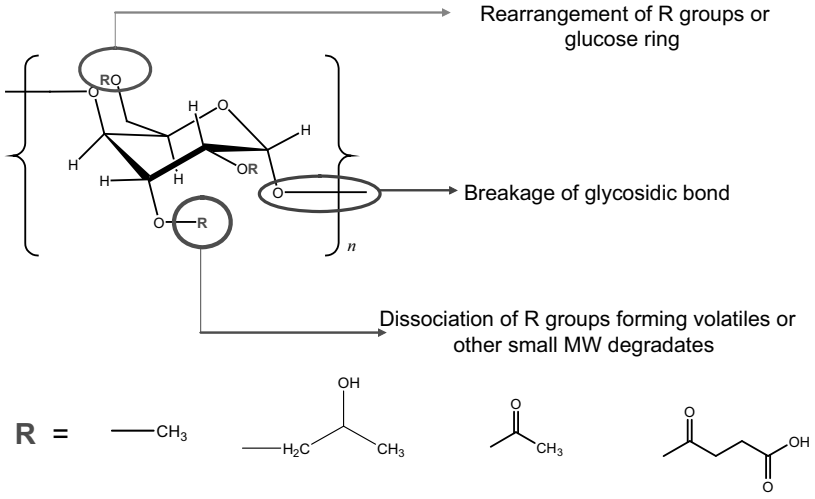


FIGURE 42.15 Impact of rpm and screw profile on the product temperature. Screw profiles varied from modest to aggressive: B → C → A.



Scheme 42.1

conditions had minimal impact on dissolution rate and apparent drug concentration. Under extreme processing conditions (e.g., 220°C barrel temperature coupled with an aggressive screw profile), polymer cross-linking is evident, as shown by a significant drop in polymer aqueous solubility. The nature of the cross-linked polymer is not clear and remains the subject of further investigation. The polymer cross-linking could significantly compromise *in vitro* performance of solid dispersions due to the entrapment of drug molecules by cross-linked polymer networks.

42.3.2 Risk Assessment Tool

The foundation of risk assessment began with existing knowledge of how the extrusion process conditions would likely influence product quality. The quality attributes of the extrudate include achieving a molecularly dispersed glass having micro- and macroscale compositional uniformity and no degradate products. The critical process parameters to achieve this molecular dispersion include delivering appropriate thermal driving force without degrading any of the components, and coupling this thermal driving force with sufficient time and adequate surface area for molecular diffusion to occur. Ensuring macroscale compositional uniformity requires process conditions optimized to minimize sensitivity to feed rate disturbances.

A series of scale-independent parameters were understood to influence each critical quality attribute. Formulation dependent parameters such as viscosity and glass transition temperature are also important, however, due to the limited

ability to adjust these; their discussion is not included in detail here. Thermal driving force was influenced by the specific energy, maximum product temperature, and product temperature distributions. Sufficient time at temperature was influenced by the residence time and cooling rate. The surface area for diffusion was influenced by effective expansion/compression mixing cycles, mixing intensity, and the shear stress profile. The process robustness, or the ability to dampen feed input perturbations, was influenced by the extent of backmixing and the residence time distribution.

The risk assessment efforts sought to prioritize process parameters and identify those that should be carefully evaluated. There are complex interactions between many of the scale-dependent parameters, scale-independent parameters, and quality attributes. The QFD tool was thought to better address these complexities compared to more traditional, linear risk assessment tools such as fault trees or failure mode effects and analysis.

42.4 ACHIEVING A DESIGN SPACE

Initial efforts focused on determining how scale-independent parameters impact quality attributes. Integral to this was identifying characterization methods indicative of patient relevant quality attributes. A battery of solid state and thermal characterization methods coupled with a DFSS driven measurement system analysis were used to identify a technique believed to be a good indicator of molecularly dispersed extrudate.

A quantitative assessment of the correlation between scale-independent parameters and quality attributes was evaluated within the framework of a DOE, with the scale-independent parameters set as the design factors. Constitutive equations and commercially available software based on one-dimensional solutions to heat, mass, and momentum balances were an integral part of this design. These models were used to determine how to adjust scale-independent parameters (screw profile, rpm, throughput, barrel temp, etc.) to achieve low and high factor level set points for scale-independent parameters (residence time distribution, specific energy, shear stress, mixing, etc.). Analysis of the result focused on quantitatively linking variations in the quality attributes to the scale-independent parameters.

While scale up of extrusion processes is well understood [23, 25, 28], and achieving comparable product quality attributes upon scale up is certainly feasible, it is unrealistic to expect all scale-independent parameters will be equivalent upon scale up. For this reason, it was particularly important to have a deep understanding of which scale-independent parameters most influence quality attributes, and where to focus scale up efforts.

Results from these experiments indeed suggested that variations in the key measurements of quality could be attributed to a single scale-independent parameter. This greatly simplified which scaling rules to apply, how to approach scale up, and how to define scale up success.

Initial experiments also highlighted that while constitutive equations, and the modeling software provided a reasonable first approximation, they did not sufficiently explain the relationship between scale-dependent parameters and scale-independent parameters. Statistically designed experiments were used to generate empirical models for this purpose.

Figure 42.15 illustrates one case of observed multifactor interactions between dependent variables used to describe independent variables. During these experiments, feed rate, barrel temperature, screw speed, and screw profile were manipulated to achieve targeted responses in the scale-independent parameters. Figure 42.15 shows how the response for the product temperature (scale-independent parameter) can be largely explained just by the screw profile and screw speed (scale-dependent parameters). Attempts were made to generate this correlation in one comprehensive empirical equation via DOE; however, the screw profile had too large of an impact and required a multiple linear regression approach to effectively describe the observed behavior. The product temperature dependence is a stronger function of screw speed as the aggressiveness of the screw profile is increased (Figure 42.15).

Further response surface mapping experiments sought to capture factor interactions and curvature. Figure 42.16 shows contour lines for the mean residence time as a function of barrel temperature and feed rate. This illustrates the nature of the barrel temperature feed rate interaction and that a quadratic model was necessary. Here, lower feed rates resulted in longer mean residence times. This is expected since lower feed rates would equate to more backmixing per unit mass. Longer residence times were observed at higher feed rates when the barrel temperature was decreased from 160 to 120°C. This could be due to the impact of lower barrel temperatures achieving lower product temperatures, and hence higher viscosity. This would increase backup lengths in filled sections, effectively extending residence time. Similar figures and empirical models were generated for the other key scale-independent parameters.

Understanding curvature and parameter interactions enabled a multifactored optimization of processing conditions. The resulting equations also made a detailed definition of the design space possible. The models provided insight into how quality attributes could be influenced in regions outside the space explored by the DOE. Several points were included outside the space of the DOE where a specific combination of operating conditions could achieve higher throughputs. This high throughput could not be universally achieved such that it could not have been a high factor setting in the DOE. Using the empirical model built via the DOE, the quality responses at these extreme points were predicted accurately.

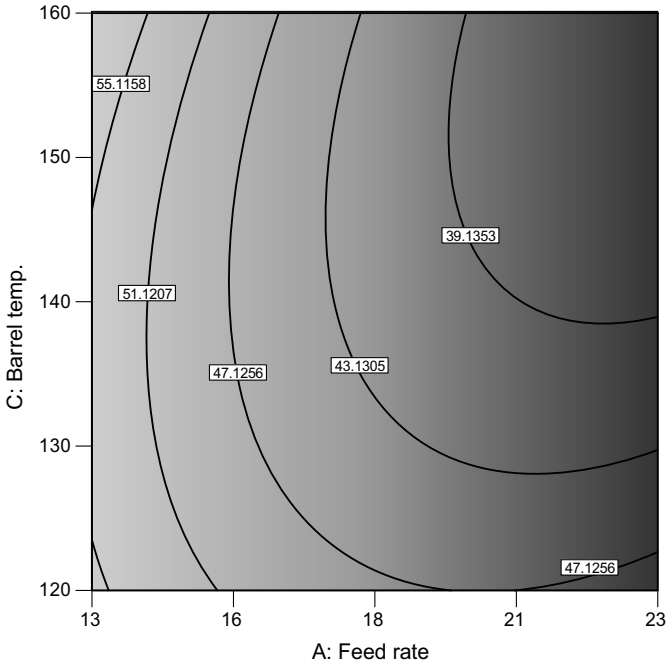


FIGURE 42.16 Impact of feed rate (kg/h) and barrel temperature (°C) on mean residence time.

42.4.1 Process Robustness

42.4.1.1 Introduction The extrusion process is the integration of the mass feeding systems with the extruder itself, and when operated with multiple feed streams, an understanding of the overall system dynamics is vital to ensuring product quality. The compositional homogeneity of the extrudate is dependent on performance and stability of each independent mass feeding system. Process upsets and perturbations as well as unstable mass feeder operation and degrading mass feeder performance threaten product quality.

In this work, PAT, was used as a key enabler for holistic process understanding and quality control. An in-line transmission near infrared measurement system was developed and implemented to monitor the composition of the multicomponent melt stream exiting the extruder in real time. Real time measurement of product composition during operation enables an operator to verify that the process is stable, identify process upsets, and ensure the targeted set point is realized. This PAT tool was also used to develop a dynamic model of the process to both pulsed and stepped inputs. The process model was then used to understand the disturbance dampening capabilities of the process and to inform performance requirements for the mass feeding systems.

42.4.1.2 System Identification A series of system identification tests were conducted, that consisted of both pulsed [45], and step change inputs. Pulsed inputs were achieved by rapidly introducing preweighed amounts of API into the feed throat of the extruder. Step change inputs were achieved by changing the mass flow set points on the feeder controllers. The dynamic response of the process to the input signal was measured in each test case. The process responses to the compositional step change identification tests were fit to a first order plus dead time (FOPDT) model equation (42.2), where $I(t)$ is the component concentration as a function of time, K is the process gain ($K = 1$, mass flow changes are fully realized), Δx is the magnitude and the direction of the step change, $u(t–t_0)$ is the unit step change with dead time, t is time, t_0 is dead time, τ is the process time constant, and $I(0)$ is the concentration of the component before the step change. More sophisticated models were considered [46, 47], but in this case the FOPDT model was found to adequately describe the data. The best-fit global FOPDT model parameters are shown in Table 42.1. The process time constants are similar for all three components in the formulation. This is consistent with expectations, because the extruder acts as a CSTR-PFR model in the sense that all mass elements will experience the same environment as they pass through the extruder. The processing environment is fixed by the extruder process parameters (screw profile, barrel temperature profile, mass flow rate, screw speed) and the formulation rheology. The process dead times are also similar, but their variation is consistent with the location in which they are introduced into the process. Example model fits are shown in Figure 42.17 (panels a, b, and c are the responses for each formulation component). The high speed of data acquisition of the spectrometer (one prediction every 1.31 s) was well suited for model parameter identification, in particular the process dead time.

$$I(t) = K \cdot \Delta x \cdot u(t-t_0) \cdot (1-\exp(-(t-t_0)/\tau)) + I(0) \tag{42.2}$$

42.4.1.3 Process Disturbance Rejection Capability Disturbance rejection capability of the process can be assessed by calculating the periodogram of the time derivative of the identified process model. The periodogram [48] is defined as the absolute value of the square of the finite Fourier transform (FFT) versus a frequency vector as described by equation 42.3, where U is the FFT of the time series $u(t)$, N is the number of elements in the time series, ω is the frequency

TABLE 42.1 First Order Plus Dead Time Model Parameters

Model Parameter	API	Surfactant	Polymer
τ (time constant, s^{-1})	11.1	10.5	10.3
t_0 (dead time, s)	59.4	66.2	62.2

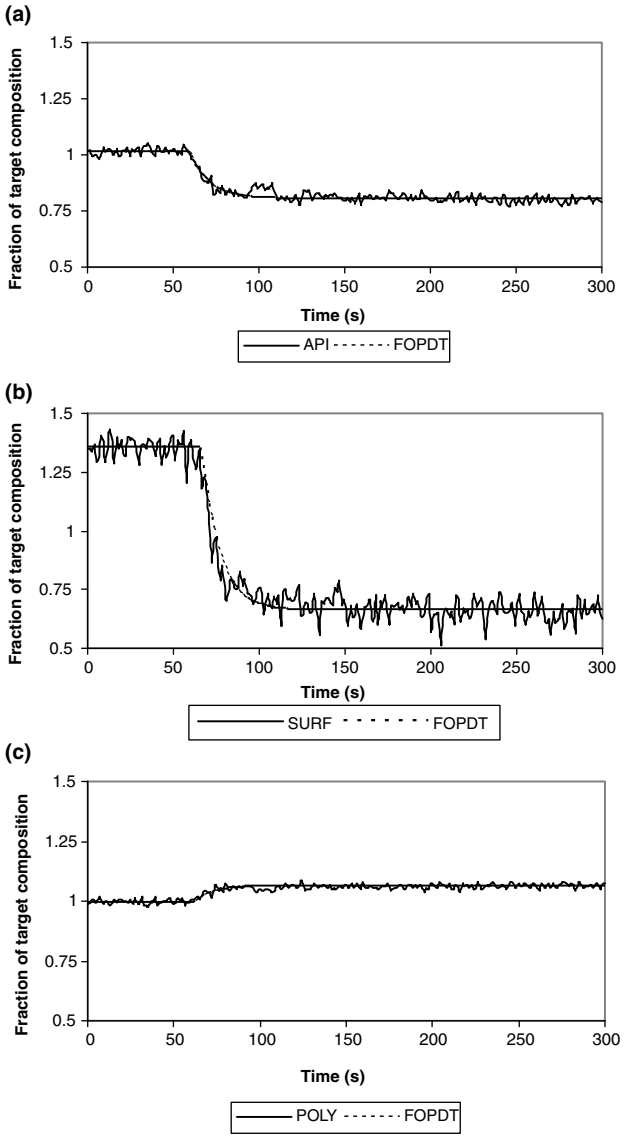


FIGURE 42.17 Example FOPDT model fits of the extruder process response to simultaneous mass feed rate step changes in API (upper), surfactant (middle), and polymer (lower) as measured by in-line transmission NIR.

in inverse time, i is the square root of negative one, and t is time.

$$|U_N(\omega)|^2 = \left| \frac{1}{\sqrt{N}} \sum_{t=1}^{N} u(t) e^{-i\omega t} \right|^2 \qquad (42.3)$$

The time derivative of the identified process model is an estimate of the finite impulse response function for the process. The periodogram, which is a plot of signal power versus frequency, is the frequency response function of the process. Figure 42.18 shows the periodogram of the process model. This plot describes the extruder's ability to dampen mass feeder input disturbances and shows that the extruder acts as a low pass filter. Specifically, input signals that contain energy content at frequencies above 0.05 cycles/s will be nearly entirely damped. Conversely, input signals that contain energy content at frequencies below 0.05 cycles/s will pass through the extruder virtually undamped and will affect product uniformity. Additionally, the amplitude of the instantaneous variability in mass flow rate is essentially irrelevant as long as the variability frequency is above the critical frequency (ca. 0.05 cycles/s in this work) and that the mean flow rate is on target. This knowledge can be used to either set mass feeder performance specifications or could be used to redesign the extrusion process (screw profile, or screw speed, total mass flow rate) to be compatible with known mass feeder performance. The mass feeder performance is highly dependent on the feed material properties that could vary from lot–lot including particle size, Carr index, and compactability. A possible control strategy for monitoring mass feeder performance would be numerically calculating the periodogram from the real time mass flow rate data (from loss on weight) over a moving window (1 min, for example) that would trigger an alarm when the time series has frequency contributions below the critical frequency or a defined threshold value.

The process model can also be used for real time predictive process monitoring. This could be achieved by numerical convolution of the differential form of the process model with the time discretized mass flow rate data coming from the mass feeders calculated over a moving window. This enables predicting the extruder outlet composition one mean residence time in the future and triggering quality control actions in a feed forward manner.

42.4.1.4 The Future of Quality Control and Process Understanding for HME The future of quality control and process understanding is the integration of PAT tools and model based process knowledge. Large progress toward process understanding can be made during development, but additional information required to increase robustness and optimize the process can only be addressed in the supply phase. For example, during the product and process development cycle, it is not practical to study every factor with design of experiments. Additionally, the full range of raw material variability has not been experienced by the process, as development typically involves only a few lots of API. Lastly, unmeasured disturbances can pose a threat to product quality. PAT tools that include process sensors to measure physical and chemical information in real time together with the implementation of multivariate data analysis techniques can be used to enhance process understanding.

Multivariate statistical process control (MSPC) provides an efficient way of reducing all of the real time process data streams into one convenient control chart that also captures

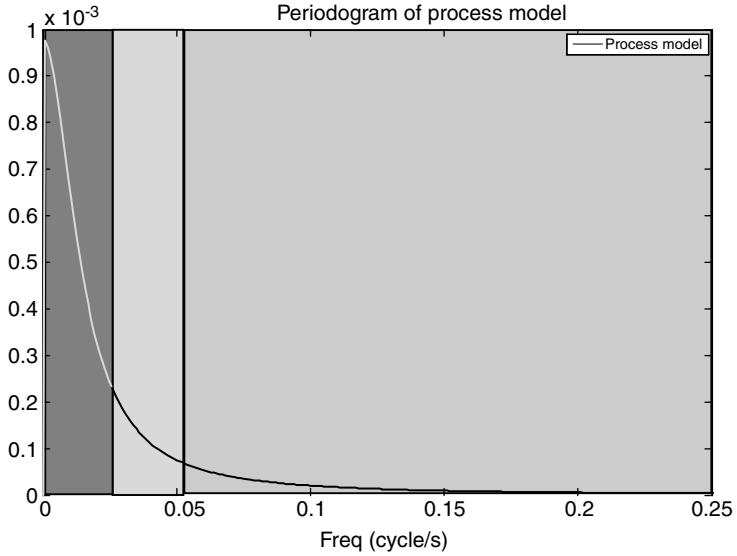


FIGURE 42.18 Periodogram of the process model showing that the process acts as a low pass filter capable of rejecting high frequency noise, but that input disturbances with a frequency of 0.05 cycles/s and lower will pass through the process potentially impacting product quality.

all of the variable interactions as well. MSPC models the covariance pattern of the real time process data and signals an alarm when the base covariance pattern is broken. When faults and deviations are detected, the variables causing the breakdown in the covariance pattern are identified. The implementation of MSPC to a manufacturing line can improve process robustness in several ways. MSPC can detect both sensor faults and deviations from normal process behavior. Early detection of sensor faults and process abnormalities improves process robustness by enabling

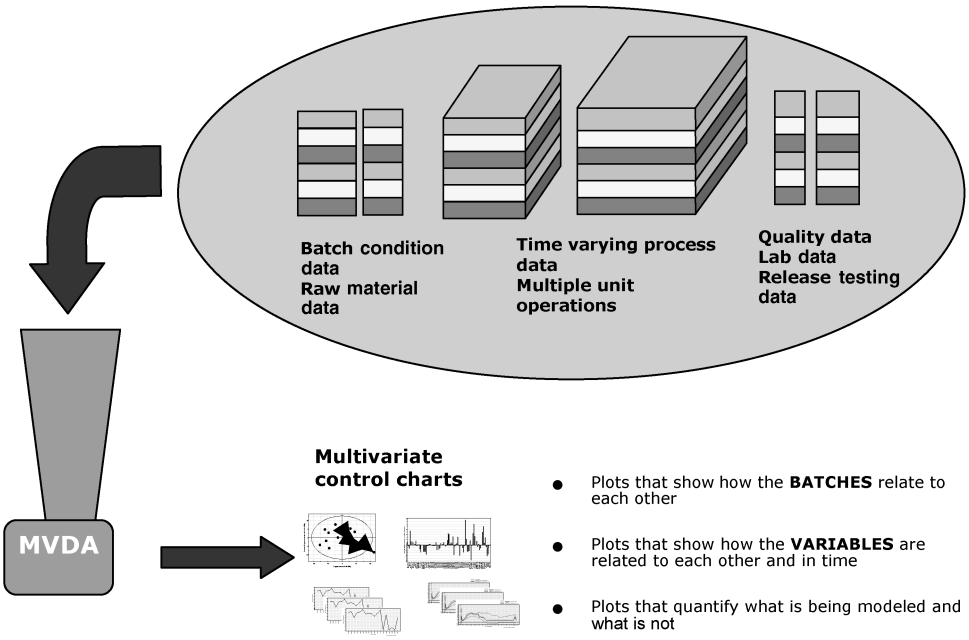


FIGURE 42.19 Overview of applying multivariate data analysis for holistic process analysis. MVDA techniques enable fast and efficient analysis of large and complex data sets.

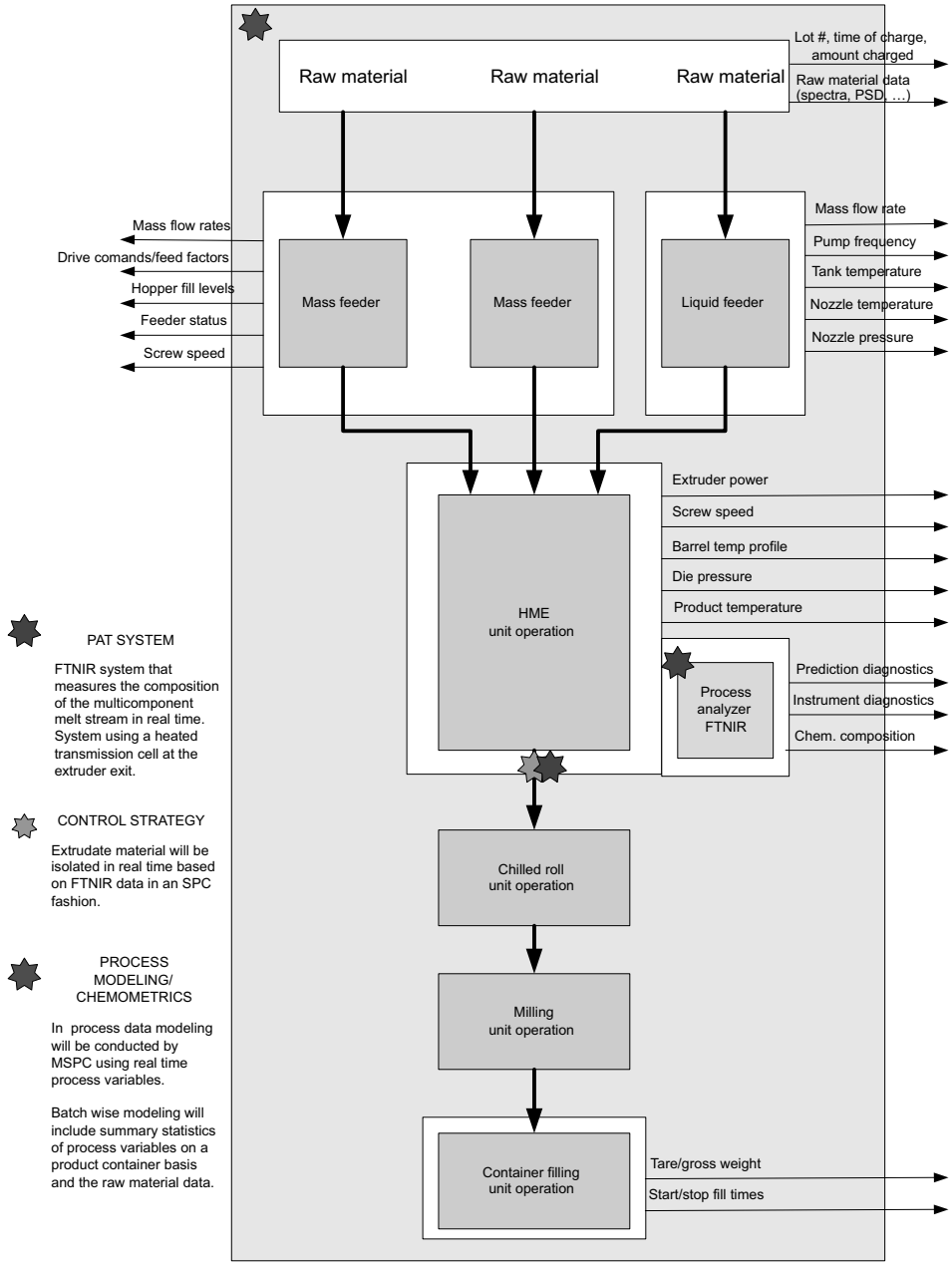


FIGURE 42.20 Material and information process flow diagram for an HME process train that depicts the use of a PAT analyzer to trigger an automated waste diverter and the implementation of multivariate statistical process control for fault detection and isolation as well as holistic process analysis that compares process performance on a batch-to-batch or campaign-to-campaign level.

intervention and rapid root cause identification. The extrusion process contains a multitude of sensors that could potentially fail, and monitoring each sensor individually is impractical, making it a good fit with MSPC.

Holistic process analysis consists of aggregating all of the data sources related to the process and the product and analyzing the data with multivariate tools. This type of data aggregation and analysis will detect any existing correlations between process inputs such as raw materials or equipment used and process outputs such as product quality or process performance. This type of analysis is also capable of detecting process drifts and differences on a batch-to-batch and a campaign-to-campaign basis. To facilitate holistic process analysis, it is necessary to have an IT infrastructure capable of aggregating raw material data, real time process data from multiple unit operations and process trains, in process

testing, PAT data, equipment status and system suitability data, and quality testing and product release data. These IT systems need to be able to trace material and product genealogy as well. Figure 42.19 shows an overview of the holistic analysis process and Figure 42.20 shows a process flow diagram for an extrusion intermediate production process. The process depicted contains (1) a PAT system that measures the composition of the extrudate in real time and triggers a diverter system to isolate off-specification material, (2) a multivariate statistical process control system for sensor and process fault detection, and (3) a PAT-IT system that aggregates raw material data, lot/batch genealogy, process data, and release data for post batch holistic multivariate analysis. The implementation of these tools in manufacturing facilitates expanding the process knowledge space by detecting process upsets and deviations in real time and providing that data and information to rapidly identify correlations between process inputs and process performance. A logical progression of process understanding is identification of correlations, establishing causation, and model-based understanding. Ideally, model based process understanding will be based on first principles, but empirical, hybrid, and statistically based models can often be sufficient for improving product quality and rejecting process disturbances. Identified process models can be used to develop feed forward control systems that make processes robust to measured input variability.

This work describes the application of QbD principles and design space development to one unit operation in a pharmaceutical process train. A more complete process design space needs to be holistic, going from raw materials all the way to the final product image, with model based process knowledge describing the relationships between process inputs, process set points, and final product attributes.

42.5 CONCLUSION

Extrusion is a pharmaceutical process technology that meets a growing need to enable oral delivery of insoluble candidates and is particularly well suited to the quality by design approach. The application of DFSS methodology helped manage the technical complexity of developing the hot melt extrusion process and deliver on QbD. The knowledge gained from this development exercise facilitated process optimization and clear definition of a robust design space. The integration of PAT enabled added process robustness, process understanding, and derivation of a multifactor quadratic model of the process parameters most responsible for influencing the CQA's. The future of pharmaceutical extrusion will include fully integrated process analysis and control beyond single system PAT approaches and the continuous delivery of final drug product via a small footprint seamless process.

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