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Quality-by-design in hot melt extrusion based amorphous solid dispersions: An industrial perspective on product development

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Abstract

An industrially feasible approach to overcome the solubility and bioavailability limitations of poorly soluble active pharmaceutical ingredients is the development of amorphous solid dispersions (ASDs) using hot-melt extrusion (HME) technique. The application of Quality by Design (QbD) had a profound impact on the development of HME-based ASDs. The formulation and process optimization of ASDs manufactured via HME techniques require an understanding of critical quality attributes, critical material attributes, critical process parameters, risk assessment tools, and experimental designs. The knowledge gained from each of these QbD elements helps ensure the consistency of product quality. The selection and implementation of appropriate Design of Experiments (DoE) methodology to screen and optimize the formulation and process variables remain a major challenge. This review provides a comprehensive overview on QbD concepts in HME-based ASDs with an emphasis on DoE methodologies. Further, the information provided in this review can assist researchers in selecting a suitable design with optimal experimental conditions. Specifically, this review has focused on the prediction of drug-polymer miscibility, the elements and sequence of QbD, and various screening and optimization designs, to provide insights into the formulation and process variables that are encountered routinely in the production of HME-based ASDs.

Graphical Abstract

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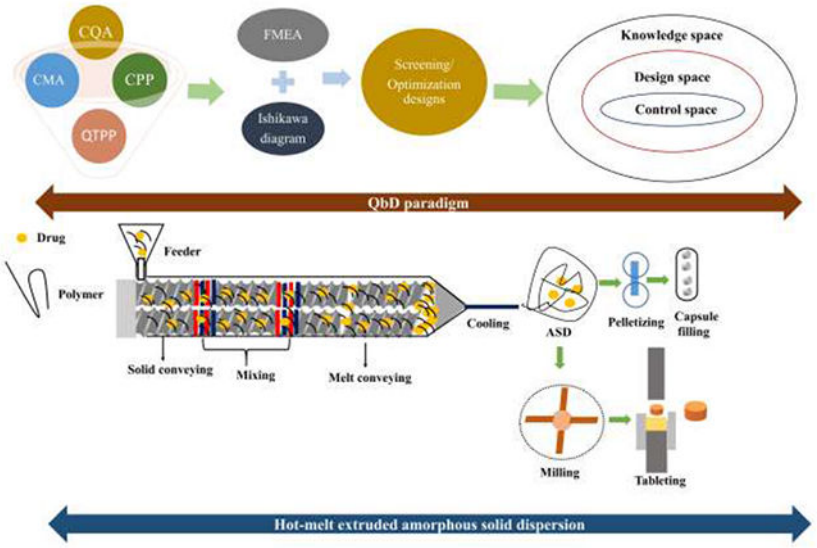
Conflicts of Interest

The authors declare no conflict of interest.



Keywords

Amorphous solid dispersion; Hot-melt extrusion; Quality by Design; Design of Experiments; Control strategy

1. Introduction

The International Council for Harmonisation (ICH) guidance documents ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System) provide directions for the application of Quality by Design (QbD). Thus, pharmaceutical manufacturers employ the principles of ICH guidance to design a drug product that consistently meets all the required quality standards (Badawy et al., 2016; Food and Drug Administration, 2009; Lionberger et al., 2008). The implementation of these guidance documents during product development enhances product and process understanding and builds quality into the product, rather than merely testing the end product before release into the market (Bastogne, 2017).

The Design of Experiments (DoE) methodology for the screening and optimization of experimental parameters can be applied to enable the development of quality amorphous solid dispersion (ASD) formulations using robust and reliable processes. Thus, the use of DoE in the field of ASD development has increased steadily over the past few years; however, the selection of suitable design with optimal factors and responses is still ambiguous and requires a thorough understanding of the formulation and process variables. Nevertheless, researchers have applied DoE in the development of ASDs for employing hot-melt extrusion (HME) technology. The implementation of DoE in the development of ASDs offers advantages over a one-factor-at-a-time approach from the perspectives of conserving resources and minimizing the number of experimental trials required to produce a quality product. However, identification of potential factors and establishment of validity,

replicability, and reliability of the experimental design are some of the main concerns encountered when implementing DoE (Beg et al., 2019b).

Successful implementation of QbD requires an understanding of quality target product profile (QTPP) and the critical quality attributes (CQAs) of the product; moreover, the relationship between CQAs and critical material attributes (CMAs) and critical process parameters (CPPs) should be considered. In practice, the linking of CQAs to CMA and CPPs requires previous knowledge and experience and necessitates discussions and agreement among the group of people working on the project (Lionberger et al., 2008; Yu, 2008; Yu et al., 2014). This review provides a roadmap for the implementation of QbD with the emphasis on DoE in the development of ASDs manufactured via HME technology. To the best of our knowledge, no published review has provided a comprehensive overview of QbD with a focus on the DoE in the development of HME-based ASDs. This review has focused on prediction of drug polymer miscibility, the elements and sequence of QbD, and various screening and optimization designs. Case studies of ASDs utilizing DoE have been presented and the CMAs and CPPs during the implementation of QbD in ASD formulations have been considered.

2. Hot-melt extrusion

The application of HME in the pharmaceutical industry has grown since the late 1990s; successful implementation has been achieved in the development and manufacturing of numerous drug delivery systems such as ASDs, implants, ophthalmic delivery, controlled, sustained release drug delivery, granules, cocrystals, and taste-masking formulations (Bandari et al., 2020; Butreddy et al., 2020b, 2020a; Sarabu et al., 2019; Schenck et al., 2019; Tiwari et al., 2016). HME is a proven continuous manufacturing process for the development of ASDs with commercially available marketed formulations (Haser et al., 2018). The HME process involves feeding, conveying, mixing, melting, and pressurization of the physical blend within the barrel to produce ASDs (Brown et al., 2014; Patil et al., 2016). The main components of the extruder are the barrel, feeder, and screw elements (Thiry et al., 2015). The barrel of the extruder comprises a feeding section, venting, and closed segment configuration (Martin, 2016). Each section of the barrel can be heated to soften or reduce the viscosity of the polymer. The feeder aids in the transfer of the material to the barrel. The starve feeder with a screw speed independent of feed rate is most commonly used in the HME process. Screw elements (conveying and kneading) help with mixing, transporting, and subsequently pushing the melt through a die. The arrangement of screws facilitates the setup of different screw configurations to achieve either low or high shear. The conveying elements help to push the solid material within the barrel, whereas kneading elements are used for mixing, dispersing, and to apply mechanical shear to the solid material (Brown et al., 2014; Patil et al., 2016) The basic theory and historical and technical perspective of HME is provided by Martin et al (Martin, 2016).

The key mixing mechanisms that occur inside the barrel are distributive and dispersive mixing. Distributive mixing ensures the homogenous distribution of the active pharmaceutical ingredient (API) throughout the polymer matrix. In contrast, dispersive mixing acts to break down the solid material or any agglomerates to the molecular level

owing to the greater shear stress generated by the screw elements present in the mixing zone (Kolter et al., 2012; Tan et al., 2018). Typically, a combination of distributive and dispersive mixing is desired to develop the ASDs (Thiry et al., 2015). Further, in the HME process, thermal and mechanical energies are applied to the physical blend of drug and polymer owing to the presence of the heated barrel and rotating screws. As a result, crystalline API is dissolved in the polymer and or molecularly dispersed within the molten polymer (Haser et al., 2017).

3. Amorphous solid dispersions

Over the last few decades, ASDs have been reported as the most effective strategy to enhance the solubility, dissolution rate and consequently, the oral bioavailability of poorly water-soluble drugs (Vasconcelos et al., 2007). ASDs enable the oral delivery of drugs with poor aqueous solubility because the increased apparent solubility in ASDs leads to a concomitant increase in apparent permeability (Hancock and Parks, 2000; Miller et al., 2012a). In contrast, in other solubility-enhancing strategies, such as complexation and co-solvent approaches, the increase in apparent solubility may hamper bioavailability because of a resulting decrease in permeability that limits the oral absorption (Miller et al., 2012b). The APIs in the ASDs exist in higher energy state, which results in increased kinetic solubility and a greater dissolution rate than for the crystalline API (Haser et al., 2017).

ASDs are a single-phase system that contain drug molecules dispersed or dissolved in one or more polymeric carriers. The addition of polymeric carriers offers several advantages, such as long-term storage stability and better dissolution properties, compared with pure amorphous drugs (Kanaujia et al., 2015). Different methods to improve the dissolution and stability of ASDs include drug-polymer interactions, the maintenance of supersaturating conditions by delaying recrystallization, and adjustment of the water uptake properties of hydrophilic polymeric carriers during dissolution (Huang and Williams, 2018; Schittny et al., 2019; Školáková et al., 2019). Several techniques are employed to produce ASDs, including HME, spray drying, co-precipitation, and KinetiSol® dispersion (Figure 1); however, the utilization of these techniques depends on properties of the API, desired product characteristics, and suitable processing window (Hou et al., 2019; Huang and Williams, 2018; Mendonsa et al., 2020; Tran et al., 2019).

The ASDs manufactured via HME have garnered increased attention owing to the clinical and commercial success of numerous products available in the market (LaFountaine et al., 2015; Repka et al., 2018). Three types of ASDs (Figure 2) can be formed via using HME processes, such as crystalline glass suspension, amorphous glass suspension, and solid glassy solution depending on the state of crystalline drug being dispersed (molecular, amorphous, nanocrystaline) in the polymeric carrier (Ma et al., 2013).

The ASD formation depends on the degree of miscibility and solubility of the drug in the polymeric carrier, and molecular level interaction between the drug and polymer (Kolter et al., 2012). The ASDs manufactured via HME are physically stable if the amount of drug in the polymer is below its solubility in the polymer at the given storage conditions. However, during storage the drug product may take up water leading to a decrease in solubility of the

drug in the polymer and thereby increasing the risk of recrystallization and phase separation (Haser et al., 2017).

3.1. Drug-polymer miscibility prediction

For development of ASDs via HME, adequate understanding of miscibility between the drug and polymer and the solubility of a drug in the polymer carrier is crucial. Different predictive models have been used, such as Flory–Huggins (F–H) theory and the Hansen solubility parameter, to evaluate the drug–polymer miscibility and solubility, respectively. The performance of ASD formulations depends on the molecular interactions, i.e., dispersion or dissolution of drug molecules in the polymeric carrier. Such types of interactions depict the physical stability and supersaturation kinetics of ASDs. The relevant tools used to predict the drug-polymer miscibility and or solubility are discussed below.

3.1.1. Flory–Huggins theory and interaction parameter—The prediction of drug-polymer miscibility is prerequisite during the early stage of development to obtain stable ASDs. The lattice-based Flory–Huggins (F-H) theory predicts the thermodynamic miscibility and molecular interaction between the drug and polymer. The Flory–Huggins interaction is expressed in equation (1): (He and Ho, 2015; Jog et al., 2016)

$$\frac{\Delta G}{RT} = \frac{\Phi_{drug}}{\left(m_{drug}\,.\,\ln \Phi_{drug}\right)} + \frac{\Phi_{polymer}}{\left(m_{polymer}\,.\,\ln \Phi_{polymer}\right)} \chi \cdot \Phi_{drug} \cdot \Phi_{polymer} \quad (1)$$

where ΔG is the free energy difference between the crystalline and amorphous forms, R is the molar gas constant, T is the testing temperature, Φ_{drug} is the volume fraction of drug, m_{drug} is the ratio of the volume of the drug to the lattice site, $\Phi_{polymer}$ is the volume fraction of the polymer, $m_{polymer}$ is the ratio of the volume of the polymer to the lattice site, and χ is the F–H interaction parameter. The F–H interaction parameter (χ) can be determined by two approaches: i) the solubility parameter, ii) the melting point depression approach; according to the solubility parameter, χ is determined from equation (2):

$$\chi = \frac{V\left(\delta_{drug} - \delta_{polymer}\right)2}{RT} \quad (2)$$

where R and T are the same as in Eq. (1), V is the volume per lattice site, d_{drug} and d_{poly} are the solubility parameters of the drug and the polymer, respectively; the χ parameter according to the melting point depression approach is presented in equation (3) (Jog et al., 2016):

$$\left(\frac{1}{Tmix\ M} - \frac{1}{Tpure\ M}\right) = -\frac{R}{\Delta H\ fus}\left[\ln \Phi_{drug+}\left(1 - \frac{1}{m}\right)\Phi_{polymer} + \chi \Phi^{2}{}_{polymer}\right] \quad (3)$$

Where Tmix M is the melting temperature of the drug in the presence of the drug-polymer physical blend, Tpure M is the pure drug melting temperature, ΔH_{fus} is the heat of fusion of the pure drug, Φdrug and Φpolymer are the same as in Eq. (2). As per the F-H lattice theory, at a given temperature, the interaction parameters >0, ~0, and <0 are indicative of very poor,

poor, and strong miscibility, respectively, of the drug and polymer (Verma and Rudraraju, 2014).

3.1.2. Solubility parameter—The physical and chemical properties of the polymer, drug, and their potential interactions are critical for the development of ASDs. The experimental determination of drug miscibility in the polymeric carrier is always challenging. However, drug-polymer miscibility can be estimated qualitatively using the Hansen solubility parameter (Baghel et al., 2016; Marsac et al., 2006). The solubility parameter (δ) is a measure of energy from dispersion forces, intermolecular forces, and hydrogen bonds. The solubility parameter calculation by the Hoftyzer and Van Krevelen method is depicted by the following equations, by considering the group contribution from the chemical structure of drug and polymer (Mendonsa et al., 2020; Verma and Rudraraju, 2014).

$$\delta^2 = \delta^2_{\mathrm{d}} + \delta^2_{\mathrm{p}} + \delta^2_{\mathrm{h}} \tag{4}$$

$$\delta_{\mathrm{d}} = \frac{\Sigma\, \mathrm{F_{di}}}{\mathrm{V}} \tag{5}$$

$$\delta_{\mathrm{p}} = \frac{\left(\Sigma\, \mathrm{F^2_{pi}}\right)^{1/2}}{\mathrm{V}} \tag{6}$$

$$\delta_{\mathrm{h}} = \left(\frac{\Sigma\, \mathrm{E_{hi}}}{\mathrm{V}}\right)^{1/2} \tag{7}$$

where δd, δp, and δh are the contributions from the dispersive forces, polar forces, and hydrogen bonding, respectively, δ^2 is the total solubility parameter, F_{di} and F_{pi} are the molar attraction constants due to dispersion and the molar component, E_{hi} is the hydrogen bonding energy, and V is the molar volume. A difference of $\delta^2 \leq 7$ $MPa^{½}$ indicates miscibility between the drug and polymer, whereas a difference > 10 $MPa^{1/2}$ indicates immiscibility (Baghel et al., 2016; Haser et al., 2018).

3.1.3. Perturbed-chain statistical associating fluid theory (PC-SAFT)—PC-SAFT is a thermodynamic model to estimate the solubility of a drug in the polymeric carrier. According to PC-SAFT theory, spherical segments present in the chain of each molecule can interact with the segments of other molecules through various types of interactions such as hydrogen bonding, ionic and polar interactions (Medarević et al., 2019).

In PC-SAFT model, the residual Helmholtz energy (a^{res}) of a drug and polymer system is calculated as the sum of hard-chain contribution (a^{hc}) accounting for repulsive interactions between the molecules, contributions due to dispersion (a^{disp}) accounting for van der Waals attraction forces and a contribution due to association (a^{assoc}) accounting for hydrogen bonding interactions.

$$a^{res} = a^{hc} + a^{disp} + a^{assoc} \quad (8)$$

Within the PC-SAFT framework, the following parameters are needed for calculating the contributions due to hard-chain repulsion, dispersion and association: segment chain number and segment diameter, dispersion and association energy parameter and the association volume. Additionally, the number of association sites (electron acceptors and donors) based on molecular structure is required particularly for drugs and polymers potential to form hydrogen bonding interaction. A detailed calculation and description of different contributions (a^{hc}, a^{disp}, a^{assoc}) can be found in the literature (Gross and Sadowski, 2001; Iemtsev et al., 2020; Lehmkemper et al., 2017; Medarević et al., 2019; Prudic et al., 2014).

The PC-SAFT method has been successfully used to predict the solubility of drugs such as artemisinin and indomethacin in different molecular weights of poly ethylene glycol as a function of temperature and are in close agreement between predicted results and experimental data (Prudic et al., 2014). This approach could also be utilized to evaluate the influence of relative humidity on the drug recrystallization, phase separation (amorphous-amorphous) and to predict the long term stability of the active in binary and ternary solid dispersions. The PC-SAFT model require less experimental work and is an alternative to Flory-Huggins method, particularly for mixtures showing hydrogen bond interactions (Dohrn et al., 2020).

3.2. Physical stability

Physical stability is the most challenging issue in development of ASDs. The factors that can affect the physical stability include Tg of the amorphous APIs and polymers, miscibility and solubility of API and polymer, molecular mobility of APIs, molecular weight of APIs, fragility index of amorphous APIs, storage conditions (temperature and humidity). Therefore, in development of ASD formulations, it is suggested to select high Tg polymer and high drug-polymer solubility should be considered to enhance the physical stability. The physical stability of ASDs is assessed from thermodynamic and kinetic perspectives (Ivanisevic, 2010; Lin et al., 2018; Pandi et al., 2020; Qi et al., 2013).

From the thermodynamic perspective, the physical stability of ASDs is related to the miscibility and solubility of drug in the polymeric carrier. Therefore, the ASDs formulation can be thermodynamically stable if the drug load is below the solubility of active in the polymer. The Tg and interaction between API and polymer are kinetic factors that affect the physical stability of ASD. Hence, an ASD formulation is kinetically stable if the Tg of the ASDs is greater than the storage temperature, which limit the molecular mobility of amorphous material in the polymer (Lin et al., 2018; Ojo and Lee, 2020).

4. Quality by design

QbD is a step-by-step systematic approach in pharmaceutical product development that begins with a predefined objective and emphasizes bridging between product and process understanding based on sound science and quality risk management (Zhang and Mao, 2017). QbD is a regulatory-driven approach that builds and ensures the quality of the product,

rather than establishing quality by merely testing the end product. The principles and goals underlying QbD include (Lionberger et al., 2008; Mockus et al., 2011; Yu et al., 2014):

- Risk assessment and root cause analysis to identify the formulation and processing factors affecting product quality;
- Systematic experimental approach with an intent to increase product development and manufacturing efficiencies by setting meaningful limits on the key formulation and process variables;
- Identification of design spaces for formulation and process variables by increasing the understanding of the product, process design, and control;
- Utilization of knowledge obtained from the design space for post-approval change management.

As per ICH Q8, Q9, and Q10, the general framework for the implementation of QbD principles requires knowledge and understanding of key elements that serve as pillars of the QbD for systematic product and process development (Beg et al., 2019a). The pillars and key elements of QbD are presented in Figure 3.

4.1. Quality target product profile

QTPP serves as the basis for product development and is usually defined or established before the design or development of drug product (ASD). QTPP starts with a prospective summary of the quality characteristics of the drug product to be designed, to ensure the desired quality drug product by considering the safety and efficacy (ICH Q8 (R1)). An ideal QTPP should contain the properties of the formulation or dosage form (type, route of administration, and strength), drug product quality attributes (assay, degradation products, water content, and content uniformity), pharmacokinetic parameters, and microbial attributes. The successful implementation of these parameters helps to meet the end product quality requirements (Bastogne, 2017; Riley and Li, 2011). The elements of QbD-involved HME-based ASDs are presented in Figure 4 (Evans et al., 2019; Gupta and Khan, 2012; Patwardhan et al., 2015; Rathore, 2009; Schenck et al., 2019; Simões et al., 2019; Thiry et al., 2015).

4.2. Critical quality attributes

CQAs are a subset of the QTPP and are defined based on the QTPP. CQAs provide a greater mechanistic perspective about the product and process understanding compared with the QTPP. After defining the QTPP, the next step in drug product development or ASD is the identification of the CQAs. ICH Q8 (R1) defines a CQA as a physical, chemical, biological, or microbiological properties or characteristics that should be within the appropriate limit, range, specification, or distribution to achieve the desired product quality (Lionberger et al., 2008). The CQAs of the drug product are essentially influenced by material (drug substance, excipients) and manufacturing process (HME) parameters. CQAs represent the attributes of the final drug product (ASD); hence, monitoring the CQAs throughout the formulation or product development ensures consistency in product performance and process robustness. Thus, the use of a prior product or process experience and literature reports can help in better understanding and identification of CQAs during the early stage of product

development or ASDs (Riley and Li, 2011). The most important predefined CQAs of ASDs manufactured by HME include residual crystallinity, impurities, assay, dissolution, and moisture content (Evans et al., 2019; Gupta and Khan, 2012; Park, 2015; Patwardhan et al., 2015).

Residual crystallinity: The residual crystallinity of a drug product determines the amount of API miscible or soluble within the polymer after the extrusion process. The free available API may contribute to increased or decreased *in vivo* performance. The CMAs and CPPs should be optimized to obtain crystalline free ASDs.

Impurities: The degradation of the API is an important CQA of ASDs, particularly for thermosensitive APIs because the degradation profile can affect patient safety and efficacy. In most cases, degradation of the API in ASDs may not occur until the API is completely solubilized or miscible in the polymer matrix, leaving no residual crystallinity.

Assay: The assay is an important quality attribute as it can affect the safety and efficacy of the developed ASDs.

Dissolution: The dissolution profile of ASDs in many cases influence the in vivo oral bioavailability due to the precipitation potential of the released drug in the gastrointestinal fluid. This is because of the high kinetic solubility of API in the polymer matrix, which exceeds the API supersaturation level.

Moisture content: The moisture content of the drug product can affect the physical and chemical stability of the ASDs.

The particle size and bulk density of ASDs are key parameters during downstream processing. The CQAs of ASDs with respect to downstream processing are bulk density, flowability, compressibility, and compactibility. However, these parameters can be controlled by the addition of appropriate extra granular components, such as diluent/filler, disintegrating agents, glidant, and lubricant (A. Agrawal et al., 2016; Grymonpré et al., 2017; Vig and Morgen, 2017). Hence, these parameters were not considered further as potential CQAs of ASDs. The continuous monitoring of these CQAs from early stage development and stability testing stage to large-scale manufacturing is essential to ensure that the drug product retains these CQAs, which are necessary for patient safety, efficacy, and regulatory approval.

4.3. Critical material attributes

CMAs are properties of active and inactive input raw materials that have a direct influence on the CQAs and are considered an essential element in regulation of product quality. The identification and screening of these CMAs are the basis for their critical nature in the CQAs of the drug product. This criticality is generally accomplished by using risk assessment tools. The choice of right material in optimal quantity enables successful extrusion process with a broad formulation and process design space and optimal product quality. Knowledge of the CMAs and their relationship with and influence on drug product CQAs is

fundamental to the successful implementation of QbD in product development or ASDs (Beg et al., 2019a; Zhang and Mao, 2017).

In the development of HME-based ASDs, knowledge and understanding of thermal and rheological properties of API and polymer materials are essential. For HME-based ASDs, the CMAs include API and polymer particle size and powder flow; polymer type (immediate release vs sustained release and pH-dependent or pH-independent) and nature (amorphous, crystalline or semi-crystalline); API and polymer Tg; API and polymer degradation temperatures (Td); and polymer melt viscosity as a function of temperature, shear rate, and moisture content of the polymer and API. The investigation and characterization of these parameters provide information in the identification of CPPs of HME (Evans et al., 2019; Islam et al., 2014; Simões et al., 2019). However, these parameters may vary from product-to-product depending on the concentration and type of input raw material used in the ASDs.

4.4. Critical process parameters

CPPs are related to the HME technology used in the manufacture of ASDs. Variability of the CPPs can affect process performance and the CQAs of ASDs. The selection of CPPs requires prior process knowledge and literature data. The CPPs considered in HME processes include barrel temperature, screw speed, feed rate, and screw design (Islam et al., 2014). HME process parameters can be considered either continuous or step-change parameters. The continuous parameters, such as screw speed and feed rate, can be altered during the HME process; the step-change parameters, such as the barrel and screw design, require the process to be interrupted (Leister et al., 2012).

For the manufacture of HME-based ASDs, barrel temperature should be optimal to provide miscibility and interaction between API and polymer and achieve optimal melt viscosity. These properties are required to operate the extrusion process without blockage or interruption. The presence of at least one kneading zone is necessary to provide sufficient mixing and shear to ensure optimal homogenization between the API and polymer. The screw speed and feed rate employed should be desirable or high to decrease the residence time and to provide high throughput (Thiry et al., 2015). These CPPs can be identified by a formal risk assessment approach and are monitored and controlled throughout the product development (ASDs) to ensure process consistency and product quality.

4.5. Risk assessment

After the CQA, CMA, and CPPs are identified, linking of the CMAs and CPPs with the CQAs is performed through risk assessment methodologies; this is required for qualitative risk analysis. The most commonly used risk assessment tools in HME-based ASD product development are the Ishikawa fish-bone diagram (Figure 5) (cause-and-effect relationship) and failure mode effect analysis (FMEA) (Buttini et al., 2018). The primary goal of risk assessment methodology is to identify, analyze, and evaluate the potential risk associated with each CMA and CPP, and their influence on the product CQAs. The Ishikawa diagram is a graphical tool to highlight all possible variables and the potential risk of CMAs and CPPs on the CQAs of a drug product (Suryawanshi et al., 2019).

Based on the published literature, process knowledge, and initial experimental data, the FMEA can be used to evaluate the modes, causes, and effects of each potential failure and their severity (S), occurrence (O), and detectability (D); such parameters are usually expressed on a scale of 1–10. Each failure is rated on a three-level scale, i.e., high (H), medium (M), or low (L). The output from the FMEA analysis is reported as a risk priority number (RPN) score and is calculated as S × O × D (Suryawanshi et al., 2019; Zhang and Mao, 2017). The parameters identified as high risk, with a high RPN, should be further evaluated through a DoE to reduce and/or to accept the risk as a part of quality risk management (QRM) (ICH Q9 (R1)).

Based on previous literature, prior formulation, and process knowledge, the linking of CMAs to CQAs and their impact on CQAs are presented in Table 1 and 2.

Based on the previous literature, prior formulation, and process knowledge, the linking of CPPs to CQAs and their impact on the CQAs are presented in Table 3 and 4. However, these CPPs may vary according to product quality requirements.

4.6. Design of experiments

Once the risk factors of CMAs and CPPs are identified, the next step is to conduct DoE to reduce the risk associated with CMAs and CPPs. A correlation between scale-independent input parameters (CMAs and CPPs) and CQAs was evaluated quantitatively within the framework of DoE. Generally, low-resolution (III–V) designs are suitable for the screening of various factors with minimal experimental trials, whereas high resolution (V–VIII) designs are used to optimize the formulation and process parameters (N Politis et al., 2017; Singh et al., 2005).

Randomization, blocking, and replication are the fundamental principles of experimental design, and govern the accurate prediction of response variables. Randomization refers to the allocation of individual experimental runs that are required to be performed randomly. The effect of uncontrollable/extraneous factors can be averaged out by randomizing the experimental runs. Blocking refers to the arrangement of experimental runs into groups that belong to similar experimental conditions; this minimizes the variability between groups and improves the precision of the estimation of variability between groups. Replication indicates the repetition of each experimental run, which allows the estimation of experimental error (Beg et al., 2019b; Vanaja and Rani, 2007).

In addition to the type of design used, general information about the experimental design and the obtained model can help the reader to understand and analyze the response variables. The validation of design space is necessary to evaluate whether the model predictions meet the individual response criteria. In general, higher values for the coefficient of determination (R^2), adjusted R^2, and predicted R^2, and lower standard deviation values depict the model suitability for any type of design. The coefficients of variation (CVs) represent the reliability of the experimental model; a low CV indicates high experimental reliability (Durakovic, 2017; Vanaja and Rani, 2007). Similarly, the measurement of precision of design using the signal-to-noise ratio dictates adequate model discrimination, and a signal-to-noise ratio of >4 is desired for any model to be valid. For any design, non-significant factors (p values of

>0.1) of the model can be excluded before proceeding with the subsequent steps to simplify and to improve the predictability of the experimental design (Mori et al., 2019). This could be beneficial to adequately improve the precision of the model corresponding to each response variable compared with the initial model (with both significant and non-significant factors). A center point in the experimental design is necessary, particularly for factorial designs, to understand whether the response is sensitive to input factor and further, to evaluate the reproducibility of the experimental design. In general, a curvature or steep slope in the perturbation plot of the response variable suggests that the response is influenced by the input variable (Mori et al., 2019; Singh et al., 2005). If the model shows significant curvature, the design should be augmented from factorial to response surface designs to estimate the quadratic effects.

The main objective in the execution of DoE is to screen and optimize the CMAs and CPPs to finally establish a design space during drug product development. ICH Q8 defines a design space as a multidimensional combination and interaction of CMAs and CPPs that need to be demonstrated to provide real quality assurance of the drug product. Within the design space, any change in CMAs and CPPs levels is not considered a change and does not require regulatory approval during post-approval changes (ICH Q8 (R1)) (Geigert, 2019; Rathore, 2009). To demonstrate a proper and valid design space, it is necessary to choose a design with adequate resolution and a suitable number of experimental runs along with the necessary knowledge and understanding of input product and process parameters. The sequence of steps involved in the selection and implementation of DoE is shown in Figure 6.

In DoE, factors (qualitative or quantitative) and their levels (two-level or three-level) influencing the CQAs are selected by considering the prior knowledge on product/process, the relevant literature, and the preliminary experimental information. Typically, determining the optimal levels of the factors can create the best experimental response with a valid design space. Thus, the selection of factors in the optimal levels plays a critical role in identifying the impact of factors on the responses. The selection of input factor is also crucial in identifying the interactions between factors, optimization of the model, and establishing the mathematical relationship between factors and response variables (Mousavi et al., 2018). DoE designs are categorized into screening and optimization designs.

The common screening designs include Plackett-Burman design (PBD), fractional factorial design (FFD), and Taguchi design (TD), and frequently used optimization designs (response surface designs) include factorial design (FD), central composite design (CCD), Box-Behnken design (BBD), D-optimal design (DOD), and mixture design (MD) (Dhoot et al., 2019; Singh et al., 2005). The objective of the screening design is to identify the critical factors and their levels. In contrast, optimization designs are mainly used for the identification of factors with the optimum level to achieve an optimum response. The selection of these experimental designs is based on the number of factors, and their levels, interactions to be studied, predefined objectives, effectiveness, and statistical validity of each design (Fukuda et al., 2018). In this review, common screening (PBD, FFD, and FD) and optimization designs (CCD, DOD, and MD) are utilized, and application of these designs in HME-based ASDs is discussed. The details of each of these designs are presented in Table 5.

4.6.1. Screening designs—Screening designs are useful to identify critical factors and their main and interaction effects on the response variables (Fukuda et al., 2018). In the early development stage, many parameters can affect the properties and performance of ASDs. Therefore, determining the actual effect of input parameters and screening of their levels reduces the potential risks during product/process development. Screening designs only allow two-levels (high and low) of input variables, and can therefore be used to predict the linear (first-order) response (Tye, 2004; Vanaja and Rani, 2007). The most common screening experimental designs employed are two-level FD, FFD, and PBD, owing to their cost-effectiveness and the reduced number of experimental runs required.

4.6.1.1. Full and fractional factorial designs: The two-level full factorial design is represented as 2^k, where 2 is the number of levels and k is number of factors. This design requires more experiments than PBD. A fractional factorial design (2^{k-1}) is one of the most widely used designs for screening, because this design enables the screening of a large number of factors with fewer number of experiments (Fukuda et al., 2018; N Politis et al., 2017; Palekar et al., 2019).

(Tian et al., 2018), employed a two-level FFD to screen and understand the impact of input factors such as screw speed, 90° mixing elements, 60° mixing elements on the drug-polymer miscibility, and residual crystallinity of felodipine-Soluplus® ASDs. The impact of the main effects and interaction factors was investigated on the response variables. A two-level FFD with no center points resulted in eight extrusion trials. The authors demonstrated the effect of screw configuration on the production of ASDs by incorporating 60° or 90° mixing elements, and the results suggested the formation of amorphous felodipine with both mixing elements. In contrast, crystalline felodipine was detected when full conveying screw configuration was employed during extrusion. The authors concluded that mixing elements (60° or 90°) has a significant impact on the residual crystallinity and drug-polymer miscibility (drug load) with the lower or moderate impact of the screw speed.

(Lang et al., 2014b), investigated the impact of extrusion process temperature, the ratio of surfactant (Poloxamer 407 and Cremophor® RH40), and the ratio of hydrophilic carrier polyethylene oxide (PEO N80 and PEO N10) on the dissolution of itraconazole-HPMCAS ASDs by employing a screening design. Although authors did not mention the type of design (FFD or FD) employed, based on the number of experimental runs performed, it was evident that FD was utilized in the study. The results demonstrated that surfactant levels had a minor impact on the dissolution profile in both acidic and neutral pH media, and the level of hydrophilic carriers showed increased dissolution in acidic medium and a decreased dissolution trend in the neutral pH medium. The reduced dissolution in neutral pH medium was attributed to precipitation or recrystallization of itraconazole. This provided evidence of the role of CMAs in the development of ASDs.

(Grymonpré et al., 2017), applied FD to study the impact of process variables, such as barrel temperature, screw speed, throughput, and a formulation variable drug load on the extrudate properties and tableting behavior of celecoxib-Soluplus® ASDs. A 2^3 full FD with three center point replicates resulted in 19 experimental runs. The response variables investigated were process torque, specific mechanical energy (HME process), moisture content, particle

size distribution, glass transition temperature, true density (extrudate properties), and plasticity factor, out-of-die elastic recovery, tensile strength, and Heckel yield pressures (tablet properties). The authors have successfully implemented FD with the intent to screen the impact of formulation and process parameters on the tableting of ASDs. The results demonstrated that drug load had a significant influence on the extrudate properties and tableting behavior, with minimal impact on the process torque and the specific mechanical energy. The process variables had minimal impact on the extrudates and tableting properties.

(Verreck et al., 2003), applied FD with two center points to investigate the effect of critical process parameters on the quality attributes of itraconazole-HPMC ASDs. The independent factors selected were: feed rate and screw speed, whereas the other process parameters, such as screw configuration and orifice diameter, were kept constant during the DoE runs. The response variables studied were: glass transition temperature, melting point, and intrinsic dissolution. The outcome of the study indicated that extrusion process parameters had no significant impact on any of the studied response variables. However, the results of the DoE demonstrated the robustness of the HME process towards ASD product characteristics. The above studies indicated the significance of CMAs and CPPs on the CQAs of amorphous solid dispersions. Further facilitation of the selection of appropriate factors and parameters should be considered in the manufacture of ASDs.

4.6.1.2. Plackett–Burman design: Plackett–Burman design (PBD) can be used to identify the main effect with a minimal number of experimental runs by assuming that all other interactions are negligible (Vanaja and Rani, 2007). In PBD, the number of experimental runs required must be at least k+1, where k indicates the number of input variables (Mousavi et al., 2018). This design can produce 12 experimental runs with a minimum of 11 factors without the need for center points. This design facilitates the screening of up to 27 factors with 28 experimental runs (Beg et al., 2019b). The major limitation of PBD is that two-factor interaction effects are partially confounded with the main effects, whereas in the case of resolution III FFDs, two-factor interaction effects are indistinguishable from the main effects (Singh et al., 2005).

(Patwardhan et al., 2015), employed a PBD to screen and study the effect of formulation and process parameters on the quality attributes of ibuprofen-Eudragit® E PO ASDs. The independent factors selected were: drug load (X1), screw speed (X2), extrusion temperature (X3), feed rate (X4), premixing type (X5), processing aid (PVP 25) (X6); the response variables studied were processing torque (Y1), glass transition temperature (Y2), and assay (Y3). A two-level PBD with six independent factors and two center points resulted in a total of 14 experimental runs. The results showed that the variables X1, X2, and X3 were found to affect the response variables significantly. Further, they investigated the potential interaction between the independent variables (X1, X2, and X3), along with an additional independent factor, i.e., level of Eudragit® E PO, by employing a custom-designed response surface design. This optimization design resulted in an additional 16 experimental runs. The authors successfully implemented both screening and optimization designs in a single study to understand the effect of process and formulation parameters during the development of ASDs. This type of study indicates the importance of screening and optimization design to manufacture the ASDs to produce reproducible products with regulatory acceptance.

4.6.2. Optimization designs—Critical factors (those ranked with high RPN) identified from both risk assessment and screening designs can be optimized by using response surface designs. The experimental runs produced with these designs can identify both the main effect and the interaction effects of each input variable. Optimization designs allow modelling of the quadratic response (second-order) by using three levels (high, medium, low) for each input variable (Beg et al., 2019b).

4.6.2.1. Central composite design: CCD is one of the most widely used response surface designs to optimize the product and process parameters. This design can use up to five levels (low, medium, high, axial low, and axial high) for each input factor with a reduced number of experimental runs (Pierlot et al., 2008). The design consists of an embedded full factorial (2^k) or fractional factorial design (2^{k-1}), a center point, and an additional star design (axial points) for the optimization of two or more variables (Hibbert, 2012). This design can be also employed when trials from previously performed factorial design experiments detect curvature in the data and thus require augmentation from factorial (linear) design to CCD (quadratic) to estimate the curvature in the experimental data (Fukuda et al., 2018). The number of experiments (N) required in CCD is according to $N = 3^k + cp$ where k is the number of input factors and cp is the replicate number of the center point (Bezerra et al., 2008).

(Xue et al., 2019), used a 3^2 factor CCD to optimize the ratio of Plasdone™ S-630 and HPMCAS-HF in ziprasidone hydrochloride ASDs. The independent variables used for the CCD design were concentration of Plasdone™ S-630 (X1) and HPMCAS-HF (X2), with a total of 13 runs. These variables were assessed to understand the performance of drug release at 10 min (Y1) and drug content (Y2). The results indicated that slower drug release was observed in the pH 1.2 dissolution medium with an increase in the amount of HPMCAS-HF, which was due to the formation of an enteric coating layer on the surface of a drug. Higher drug content results were observed with a higher amount of HPMCAS-HF and higher amount of Plasdone™ S-630 with a fixed amount of HPMCAS-HF. The final formulation ratio of Plasdone™ S-630 and HPMCAS-HF was optimized using the numerical function.

(Banerjee et al., 2016), employed a 3^2 CCD to optimize the levels of copovidone and hydroxypropyl cellulose (HPC) in the preparation of ziprasidone hydrochloride ASDs. The authors designed the experiment with three center points, and the response factors measured were disintegration time (DT), drug release in 10 minutes (Q10), and total impurities. The outcome of the study revealed that increasing the levels of HPC resulted in a decrease in the DT and an increase in the concentration of copovidone resulted in an increasing trend in DT owing to the high binding ability of copovidone. The impurity levels in the drug product were found to be increased with an increase in the concentration of copovidone, which was attributed to the peroxide levels in the copovidone. The authors investigated the quadratic interactions between HPC and copovidone and their impact on the response variables.

(Pawar et al., 2018), studied the effect of concentrations of Soluplus® and HPMCAS-HF on the solubility and dissolution profile of efavirenz ASDs. The authors have not specified the type of response surface design being used; however, based on the number of input variables

studied, it was understood that CCD was used in their studies. A user-defined response surface design with a full quadratic model resulted in 18 experimental runs. The results indicated that the concentration of both polymers showing significant impact on the solubility and dissolution rate of efavirenz with a maximum dissolution rate was observed at a ratio of 60:20 (Soluplus® and HPMCAS-HF). The above CCD studies indicated the importance of optimization designs to understand the performance of ASDs manufactured via HME. This process accelerates the development of the desirable optimized ASDs product.

4.6.2.2. D-Optimal Design: D-Optimal Design (DOD) is an algorithm-based model that requires an accurate model, a fixed number of design points, and variable space for design optimization (Mishra et al., 2018). Unlike other designs, DOD is model dependent; thus, the researcher must specify the model (i.e., first-order/quadratic/cubic) before a computer can generate the experimental runs. This type of design is of particular importance when both qualitative and quantitative factors are used in the same design, previously performed experiments are required to be included in the design, the number of experimental runs has to be reduced, or the experimental region (design space) is constrained (Grangeia et al., 2020; Heckert et al., 2002; Hibbert, 2012).

(Djuris et al., 2014), used a D-optimal mixture design to investigate the effect of formulation parameters on the quality attributes of carbamazepine ASDs. The independent variables selected were amount of carbamazepine, Poloxamer 407, and Soluplus®, and the response variables studied were crystallinity and drug release after 15, 30, 45, 60, and 90 min. The authors have applied additional constraints for each independent factor to ensure that the amount of drug present in the design space is therapeutically relevant. In total, 12 experimental runs were performed, nine model fitting runs and three runs to estimate the lack of fit. The quantification of main effects and the interaction between independent factors were analyzed with a quadratic regression model. The findings demonstrated that the interaction and quadratic effects between carbamazepine and Soluplus® play a significant role in the drug release. In addition, the inclusion of Poloxamer 407 positively influenced the drug release.

(A. Agrawal et al., 2016), applied a DOD to identify the type of polymer used, with their levels and extra granular components, during tableting of immediate release ASDs tablets. A level IV optimal design was employed with the intent to investigate both categorical and continuous factors. In total, six independent factors were selected: three categorical factors, namely type of polymer (HPMCAS-LF, PVP VA64, Soluplus®), filler (microcrystalline cellulose, lactose, dicalcium phosphate anhydrous), and disintegrant (crospovidone, croscarmellose sodium, sodium starch glycolate) and three continuous factors, namely levels of polymer, filler, and disintegrant. The response (dependent) factors analyzed were tablet disintegration time, tensile strength, compression force, and dissolution. The design model consisted of six factors with reduced quadratic and main effects, resulting in a total of 34 experimental runs. Center points and replicate runs were included in the design to evaluate the curvature effect of the chosen model. The three-way and four-way interactions were excluded from the design because of the increased number of runs; hence, only the main effects and the two-way interaction of the response variables were investigated. The study

results indicated that type of polymer had a significant influence on the quality of the tablet with respect to tensile strength and compression force. The findings confirmed that the maximum intragranular level of 60%–70% was acceptable while preparing HME-based ASD tablets and that the level of extrudates in the tablet composition had a major impact on the disintegration time of the tablets. The type of filler has an effect on the tensile strength of the tablet for each studied polymer. Thus, the employed optimal design enabled them to screen and optimize the ASD formulation components with the intent to develop an immediate release tablet dosage form. Further, the DOD design employed in this study was helpful in the development of the final drug product (immediate release tablet) with a minimal number of experimental runs to meet scientific and regulatory requirements.

4.6.2.3. Mixture design: Mixture design (MD) is a type of RSM in which the independent factors are a proportion of several components or ingredients, and the response is affected by the proportion of different components in the mixture. The objective of the mixture design is to predict or optimize the response for combination of ingredients in the blend or mixture. In mixture design, the total proportion of input factors remains constant as 100%, or the sum of component proportion must be 1 (Buruk Sahin et al., 2016; Medarević et al., 2016). Typically, while developing ASDs, different excipients or polymeric blends are mixed to obtain optimal characteristics of ASDs, such as dissolution and physical stability. In some cases, a mixture design approach would consist of a set of mixture of ingredients that may require optimization of the composition to obtain the desired performance of the ASDs.

(Mori et al., 2019), used MD in the development of ternary ASDs of indomethacin (IND) with low-hydrolyzed polyvinyl alcohol (L-PVA). They performed DoE for both formulation compositions (levels of IND, L-PVA, and sorbitol) and process variables (extrusion temperature and screw speed), and the responses studied were processing torque, residual crystallinity, residual ratio, and area under the dissolution curve (AUDC). The design model consists of three factors and two continuous factors, which resulted in 36 experimental runs. The mixture and process design factors were combined by applying a user-defined design mode. The influence of each independent variable on the response factors was determined by using ANOVA. Findings from their study suggested that sorbitol and screw speed had a positive and negative impact, respectively, on the process torque. The presence of a high level of sorbitol had a negative impact on the degree of residual crystallinity and AUDC of IND. The process temperature significantly impacted the residual crystallinity of IND. The authors successfully validated the design space for all the response variables.

(Thiry et al., 2016), employed MD to simultaneously optimize the formulation and process parameters of itraconazole ASDs prepared with four different polymers, namely Kollidon® VA64, Kollidon® 12PF, Affinisol™ HPMC, and Soluplus®. The mixture design consisted of a combination of three mixture design factors and two continuous factors each at three levels, and resulted in a total of 24 extrusion runs. The independent factors selected were the composition of formulation, i.e., percentage of bicarbonate (X1), Poloxamer (X2), Soluplus® (X3), and the extrusion process parameters included temperature (X4) and screw speed (X5). The response variables studied were crystallinity (Y1), thermoformability (Y2), and in vitro dissolution (Y3). The results of the study indicated that extrusion temperature had significant impact on the in vitro dissolution, whereas the screw speed had only a low

impact. An increase in the levels of Poloxamer had a negative impact on the thermoformability of the extrudates, and the amorphous nature of all the formulations showed that input factors had no effect on the crystallinity. The authors have determined the design space after the optimization of response variables, and an additional five experiments were conducted to establish the design space. The DoE employed successfully optimized the process and formulation factors within the established design space.

(Dinunzio et al., 2012), applied MD to investigate the use of highly compressible microcrystalline cellulose grades (Ceolus™) in the development of rapidly disintegrating tablets of indomethacin-Kollidon® VA64 ASDs. The authors have performed preliminary trials to set the fixed levels of milled extrudates (50%), superdisintegrant (10%), and lubricant (1%) during the DoE trials and investigated the impact of Ceolus™ grades on the characteristics of the finished dosage form. The independent variables selected were type of Ceolus™ (PH-102, UF-711, KG-802, PH-301), and the responses measured were hardness, flowability, and dissolution rate. The findings confirmed that use of all grades of Ceolus™ provided advantages in terms of greater compressibility and rapid drug release. Thus, the additive levels or a combination of Ceolus™ grades suggested an effective strategy for the improvement of compressibility and drug release characteristics of the finished dosage form. An increase in Ceolus™ levels beyond a certain limit resulted in a decrease in tablet hardness. The aforementioned studies have provided insights into the use of appropriate screening and optimization designs to develop HME-based ASDs. In addition, these investigations indicated the development of an appropriate design space for the ASDs manufactured via HME technology.

The summary of experimental designs, design objectives, independent variables (drug, carriers) and different response variables applied in the HME-based ASDs are presented in Table 6.

5. Control strategy and continuous improvement

The knowledge gained during the formulation and the process development of ASDs assists in the establishment of a control strategy, which is required to produce a consistent quality product during the manufacturing process. A control strategy comprises CQAs/CPPs, controls on raw material, components, drug product specifications, design space of unit operations, and process analytical technology (PAT) tools used for real-time process monitoring and control (Repka et al., 2018). The implementation of PAT tools, such as Raman and near-infrared spectroscopy, during HME process development enhances the process and product understanding. With the implantation of PAT tools, CQAs such as drug content and crystallinity, and in-process controls, such as extrudate temperature and residence time, can be monitored in real time (Ghebre, 2018). The development of a control strategy can be accompanied with conclusions from the risk assessment, process understanding, and design space considerations. The elements of the control strategy in the manufacturing of ASDs via HME are presented in Figure 7. Continuous improvement is the final step in the QbD process. Upon drug product approval, the performance of the manufacturing process will be monitored throughout the product lifecycle to ensure product quality. The additional knowledge gained during product development will be utilized for

process improvement, product quality improvement, variability reduction, and quality system enhancements through the implementation of ICH Q10.

6. Conclusion

HME is a well-established technique for the development of ASDs owing to its robust processing, improved product stability, and the advanced control strategies. Mechanistic understanding of the QbD elements provides insights related to the key formulation and process variables. The use of DoE methodology for the screening and optimization of product and/or process parameters is pivotal in the development of ASDs. The CQAs, CMAs, and CPPs of ASDs and the relationship between these QbD elements discussed in this review will help researchers to identify the main formulation and process parameters that can affect the performance of ASDs. Amongst the various DoE models, D-optimal, factorial, and mixture designs were most commonly used in the development of ASDs by the HME technique. Further, the overview and summary of different experimental designs presented in this article demonstrate the selection criteria and implementation of DoE during the development of the ASDs via HME.

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Abbreviations

ICH	international council for harmonization
QbD	quality by design
DoE	design of experiments
ASDs	amorphous solid dispersions
HME	hot melt extrusion
QTPP	quality target product profile
CQA	critical quality attributes
CMA	critical material attributes
CPP	critical process parameters
F–H	flory–huggins
Tg	glass transition
PBD	plackett-burman design
TD	taguchi design

FD	factorial design
CCD	central composite design
DOD	D-optimal design
MD	mixture design
PC-SAFT	Perturbed-chain statistical associating fluid theory

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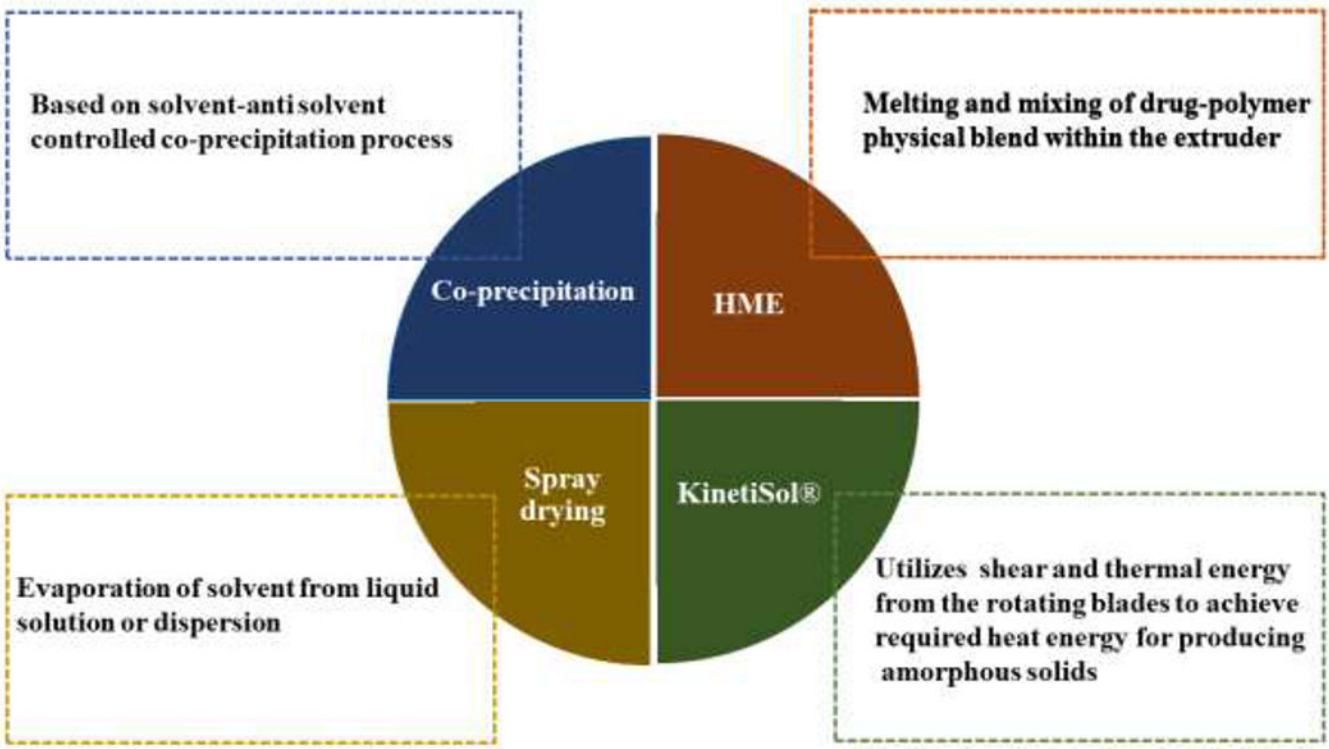

Figure 1.
Different commercially viable techniques to produce ASDs.

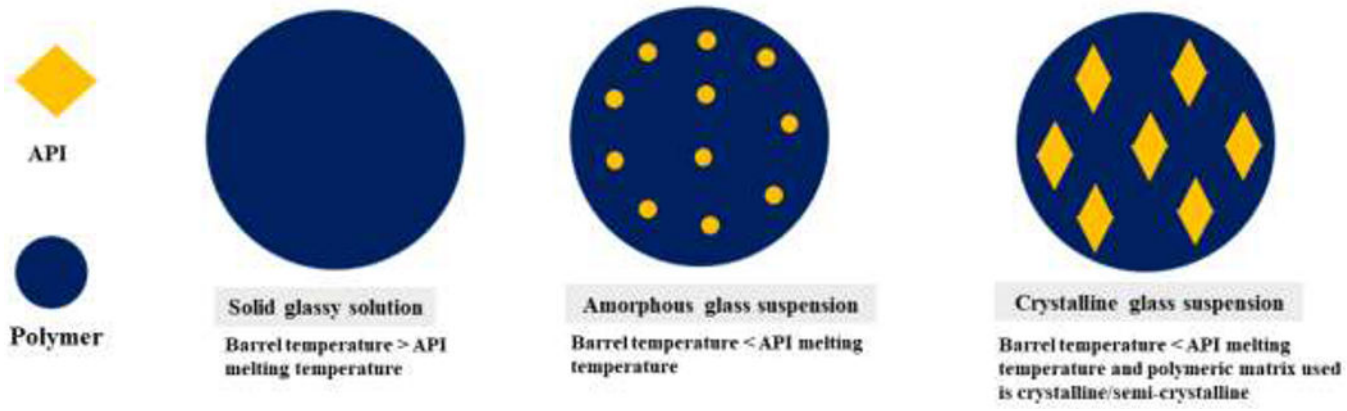

Figure 2.
Schematic representation of types of ASDs formed via HME

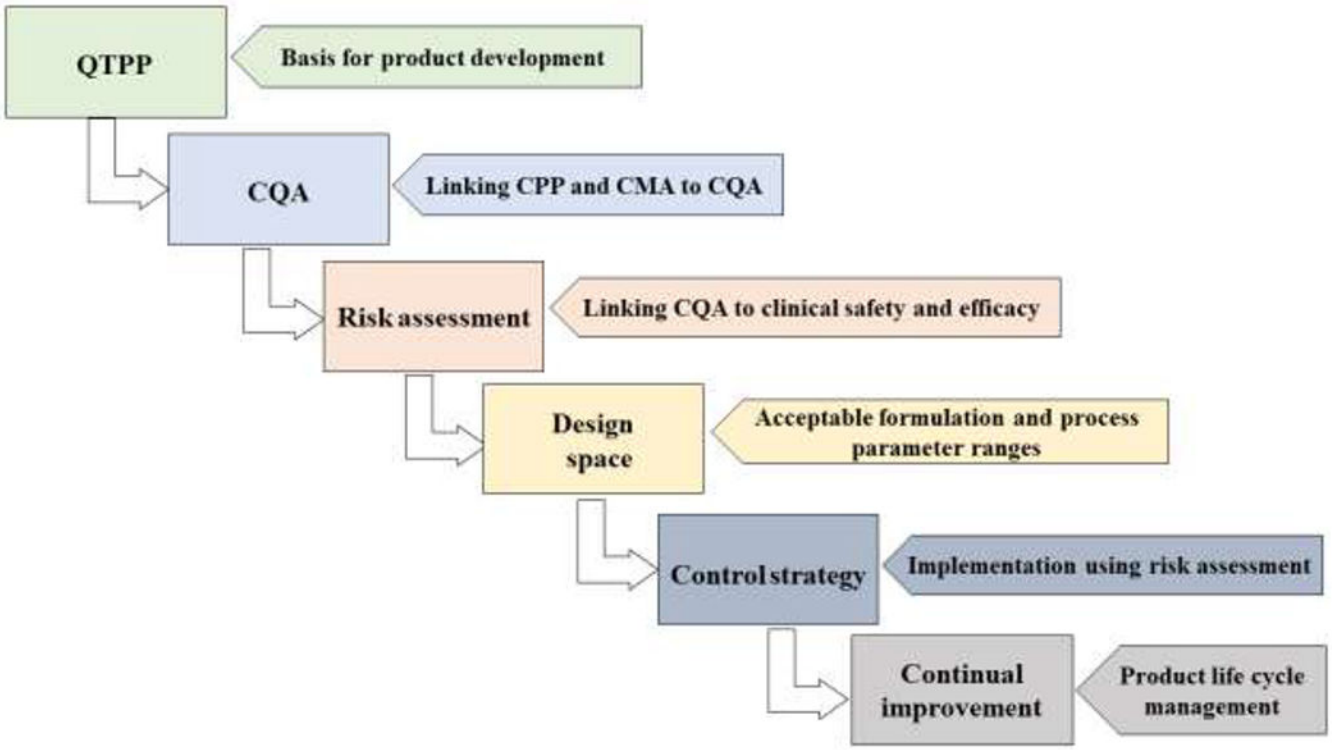

Figure 3.
Sequence and elements of the QbD paradigm in product development.

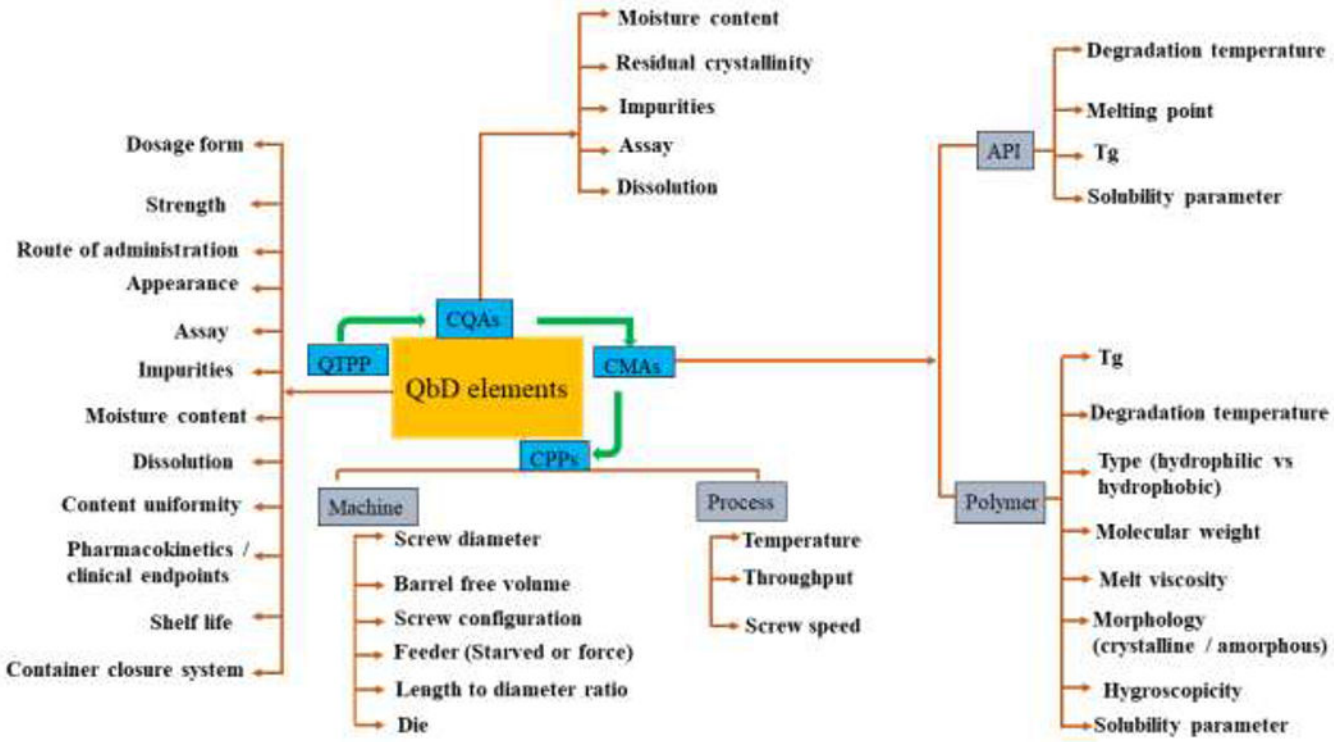

Figure 4.
Elements of QbD in the development of HME-based ASDs.

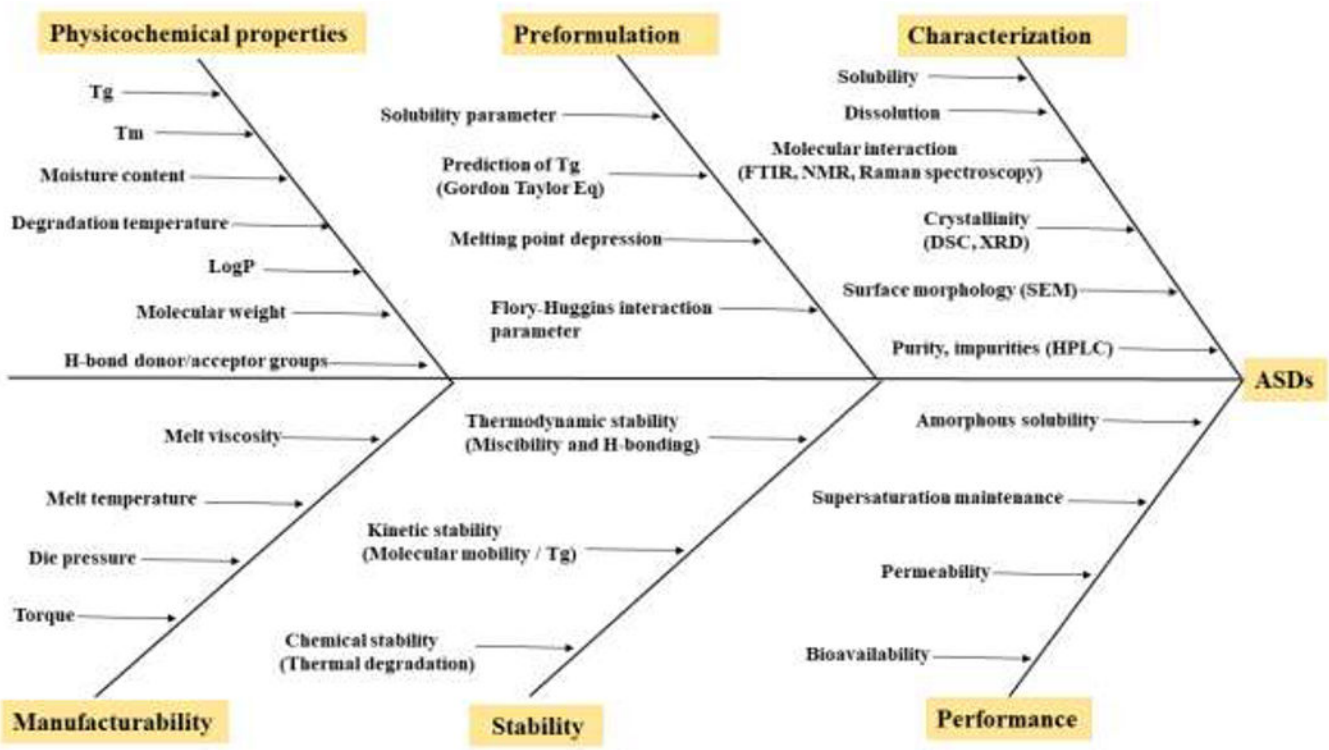

Figure 5.
Ishikawa diagram describing ASD formulation development.

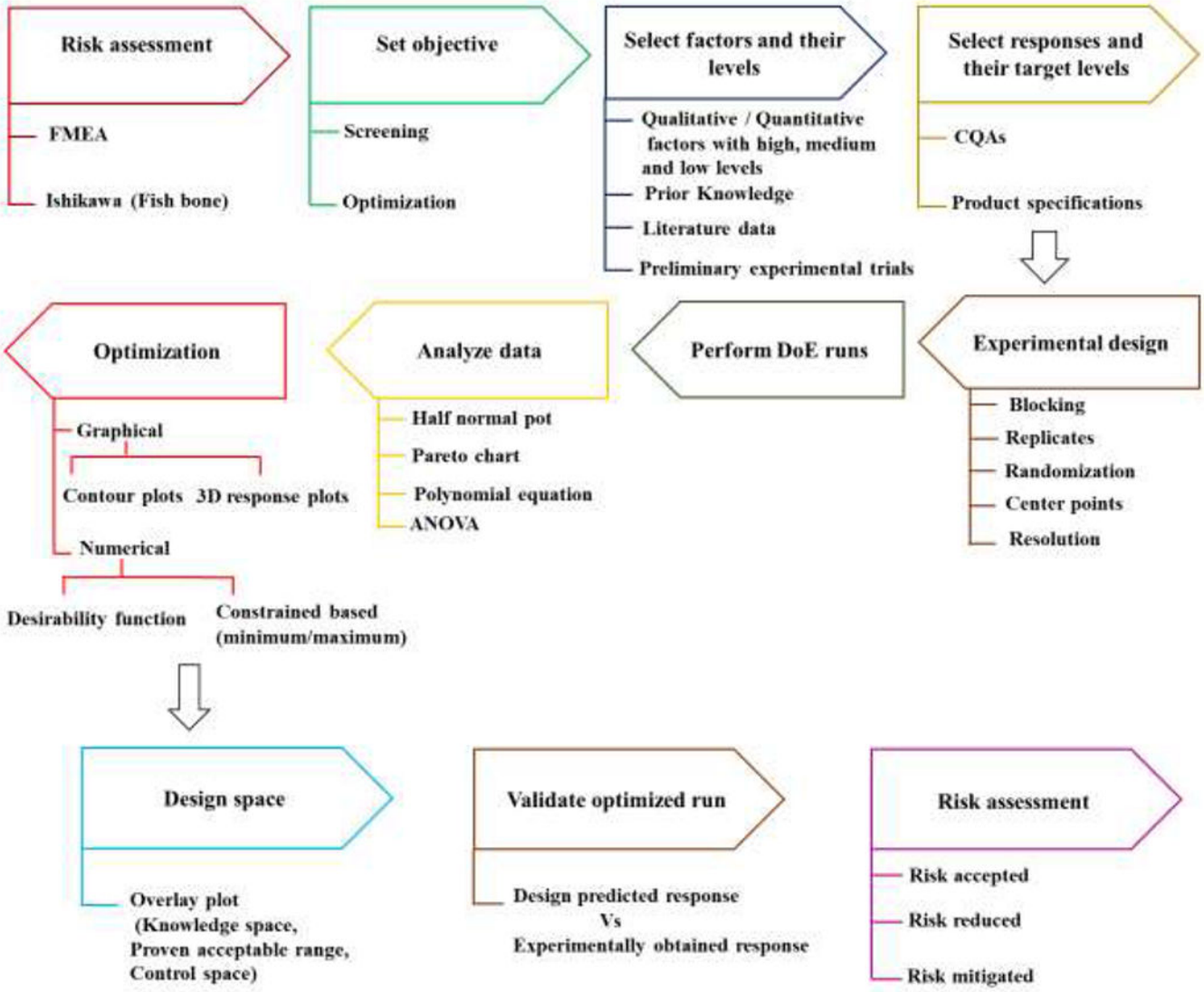

Figure 6.
Illustration of sequential steps involved in the DoE analysis.

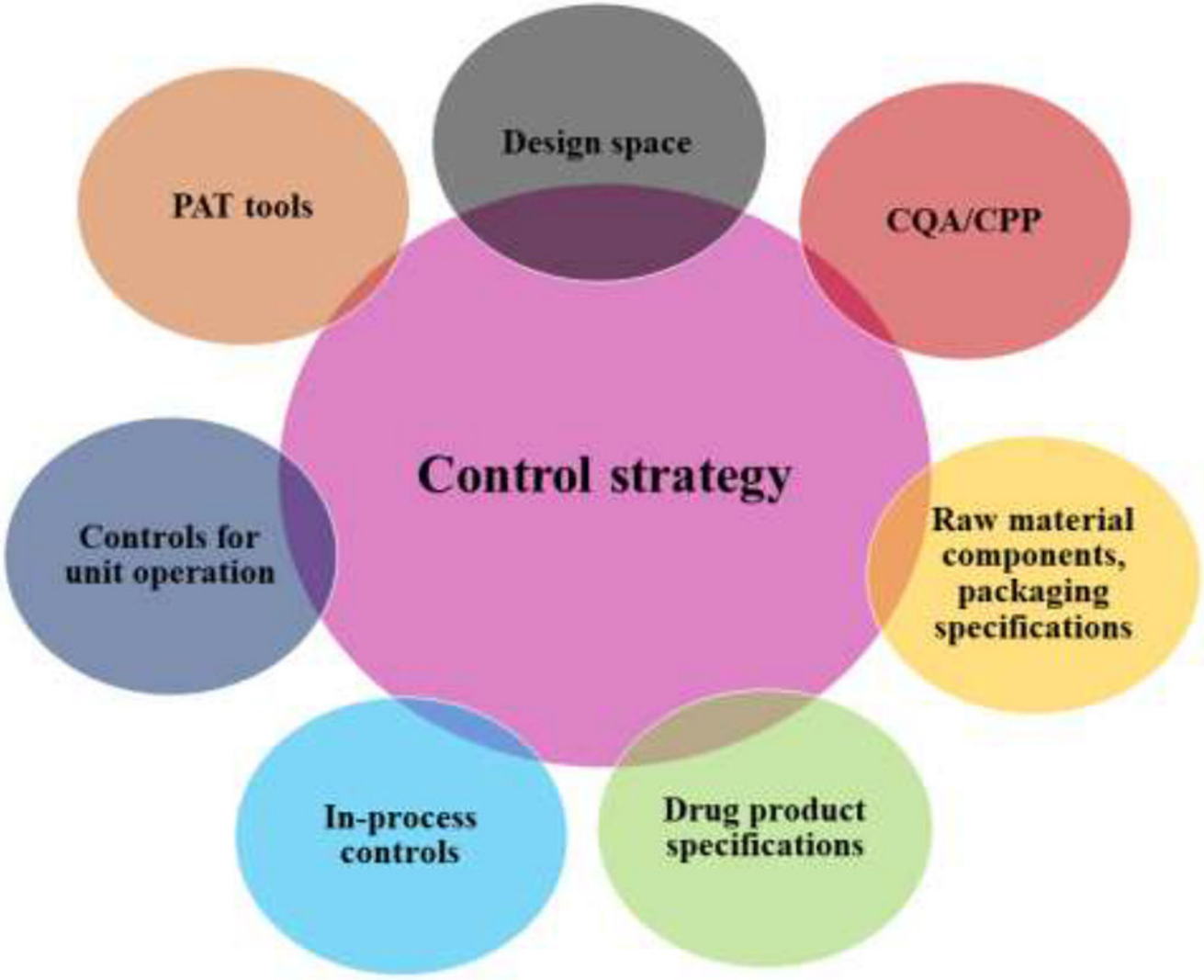

Figure 7.
Elements of control strategy in the QbD paradigm of HME-based ASDs.

Table 1.

Influence of various CMAs on the CQAs of HME-based ASDs.

CQAs	**Impact of CMAs on the CQAs**						
	Molecular weight & melt viscosity	Tg	Solubility parameter	Degradation temperature	Type of polymer	Hygroscopicity	API melting point
Crystallinity	High	High	High	High	High	High	High
Dissolution	High	High	High	High	High	High	High
Assay	High	High	Low	High	High	High	High
Impurities	High	High	Low	High	High	High	High
Moisture content	Low	High	Low	Low	High	High	Low

Table 2.

Impact of CMAs on the CQAs of HME based ASDs. (Capone et al., 2007; Censi et al., 2018; Dong and Choi, 2008; Ghebre, 2018; Kolter et al., 2012; LaFountaine et al., 2015; Lang et al., 2014a; Lu et al., 2018; Newman, 2015; Prachi et al., 2017; Sanghvi et al., 2010; Sarode et al., 2014; Schenck et al., 2019; Schver et al., 2020; Vig and Morgen, 2017; Zhang et al., 2017).

CQAs	CMA potential to impact CQA	Comments/Justification
Crystallinity & Dissolution	Molecular weight, Melt viscosity, Tg Melting point of API	The molecular weight of polymer determines the Tg. A high molecular weight polymer has higher Tg, and high Tg polymers can improve the physical stability of ASDs. The melt viscosity of the polymer is directly related to its molecular weight. Both the molecular weight and melt viscosity of polymer can affect the dissolution of ASDs. ASDs prepared with high molecular weight polymers result in diffusion-controlled drug release owing to the formation of a highly viscous diffusion layer around the ASD particles, whereas an ASD with low molecular weight polymers releases the drug rapidly owing to its rapid dissolution due to the lack of barrier surrounding the ASD particles. The polymer molecular weight impacts the crystallinity of ASD formulation. High molecular weight polymers in the ASD formulation may prevent the recrystallization owing to the higher Tg. The greater the amount of polymer, the lower will be the drug to polymer ratio; higher amount of polymer with a high molecular weight would potentially prevent drug crystallinity. The melting point (Tm) and Tg of both polymer and API can impact the crystallinity and physical stability of ASDs. The polymer and API with a higher Tg than the storage temperature will have less tendency to crystallize during the storage. Similarly, a higher Tg/Tm ratio of the API will result in less propensity to crystallize. The melting point of the API together with API solubility in the polymer and extrusion temperature dictates the physical state of the ASD (glass suspension or glass solution).
	Solubility parameter	The drug-polymer miscibility behavior can impact the crystallinity and dissolution of ASDs. A solubility parameter value of the polymer similar to that of the drug substance indicates the miscibility of drug and polymer. The degree of miscibility determines the maximum drug loading in the ASD formulations because excess drug above the solubility of the drug in the polymer may result in recrystallization during storage and can adversely affect the crystallinity and dissolution performance of ASDs.
	Type of polymer	The polymer type (hydrophilic or hydrophobic) is known to impact the dissolution and crystallinity of the ASDs. In ASDs based on water-insoluble polymers, the polymers affect the kinetic solubility and drug release behavior through their influence on supersaturation kinetics. Other polymer characteristics, such as miscibility with the drug, functional groups, hydrogen bond donors/acceptors, acidic/basic, nonionic/ionic, crystalline/semi-crystalline/amorphous nature, hygroscopicity, Tg, precipitation inhibition, and wetting properties also influence the dissolution behavior of ASDs.
	Degradation temperature	Extrusion processing at or above the polymer degradation temperature can affect the properties of the polymer such as molecular weight, rheological behavior and interaction potential (intermolecular interaction between drug and polymer) due to number of reactions include; polymer chain scission, and formation of crosslinks. These variations in the polymer characteristics can affect the performance of ASDs. Furthermore, degradation by-products in the polymer may be toxic or accelerate recrystallization of the amorphous drug. Thus, evaluation of changes in molecular weight, rheological behavior, and molecular interaction potential after processing below and above the polymer degradation temperature may provide evidence for extent of change in crystallinity and dissolution of ASD.
	Hygroscopicity	Hygroscopicity of the polymer has a major impact on the Tg of the ASD formulation. A decrease in Tg can be observed with an increase in the moisture uptake by the polymer, which enhance mobility of molecules within the ASD formulation. The continuous uptake of moisture upon stability may accelerate the crystallization of drug in the ASD formulation and recrystallization of the drug results in a lower dissolution rate.
Assay & Impurities	Molecular weight, Melt viscosity	The molecular weight of the polymer can influence the degradation rate. Thermal and oxidative stability of polyethylene oxide depends on the polymer chain length or molecular weight. A decrease in the molecular weight increases the degradation rate, which may compromise the assay and impurity of ASDs.
	Tg and API melting temperature	A polymer with higher Tg requires a high thermal and mechanical energy during the extrusion process, which may generate polymeric side chain reactions and leading to potential drug-polymer incompatibility. Hydroxy propyl methylcellulose acetate succinate (HPMCAS) may undergo hydrolysis and generate by-products succinic acid and acetic acid at a process temperature greater than 180°C. These by-products can form process related impurities due to the interaction with the drug substance. Similarly, with poly (vinyl alcohol), the thermal and mechanical stresses during HME process can induce the liberation of acetic acid due to side chain elimination reaction. Thus, Tg of the polymer indirectly impacts the assay performance and impurity profile of ASDs.
	Degradation temperature	The HME process temperature above the degradation temperature of polymer and API could impact the assay and impurity profiles. The high barrel temperature and shear rate that the HME process utilizes

CQAs	CMA potential to impact CQA	Comments/Justification
		may degrade both polymer and drug substances. When using the HME process, it is important to determine the extent of the chemical instability of the polymer and drug at elevated temperatures.
	Type of polymer	The chemical composition of the polymer includes peroxide (povidone, co-povidones), and free acids present in HPMCAS influence the assay and impurity profile of ASDs. Acidic impurities in HPMCAS may interact with the API by esterification and affect the quality of the drug product. Peroxide levels in povidone and co-povidone may interact with the tertiary amine group of APIs and induce oxidative degradation.
	Hygroscopicity	The assay performance and impurity profile of ASDs are impacted by the hygroscopicity of the polymer. Highly hygroscopic polymers may cause the long-term physical and chemical instability of ASDs. The chemical stability of ASD is impacted by moisture-mediated hydrolytic degradation. Although physical stability is influenced by decrease in Tg, an increase in molecular mobility is due to the presence of moisture. The moisture can act as a plasticizer in the ASD formulations, which can induce recrystallization and physical instability.
Moisture content	Hygroscopicity	The hygroscopicity of the polymer and API has direct impact on the moisture content of the ASD formulations. The high moisture levels present act as a plasticizer and affect the physical stability of ASDs, which further impact the quality of the product.

Table 3.

Influence of CPPs on the CQAs of HME-based ASDs.

CQAs	**Impact of CPPs on the CQAs**			
	Temperature	Throughput	Screw speed	Screw configuration
Crystallinity	High	High	High	High
Dissolution	High	High	High	High
Assay	High	High	High	High
Impurities	High	High	High	High
Moisture content	Low	Low	Low	Low

Table 4.

Impact of CPPs on the CQAs of the ASDs (A. M. Agrawal et al., 2016; Evans et al., 2019; Ghosh et al., 2012; Hanada et al., 2018; Haser et al., 2018; Henrist and Remon, 1999; LaFountaine et al., 2015; Lang et al., 2014a; Liu et al., 2012; Ma et al., 2019; Nakamichi et al., 2002; Reitz et al., 2013; Schenck et al., 2019, 2019; Shah and Repka, 2013; Simões et al., 2019; Six et al., 2003; Thiry et al., 2015; Van Renterghem et al., 2017; Vera-Sorroche et al., 2013; Verreck et al., 2003).

CQAs	CPP potential to impact CQA	Comments/Justification
Crystallinity & Dissolution	Temperature	The extrusion temperature plays a vital role in deciding the miscibility and solubility of API in the polymer. The process temperature should be optimized to enable thermodynamic miscibility between the drug and the polymer. In general, a process temperature above the Tg of the polymer and the melting point of a drug would ensure complete amorphization and result in low drug crystallinity. The barrel temperature influences the conversion of the API from a crystalline to an amorphous state. Incomplete amorphization may lead to a decrease in the kinetic solubility and dissolution rate.
	Throughput	The feed rate may affect the fill volume of the extrusion barrel. The balance between the screw speed and feed rate should be maintained in order to obtain amorphous extrudates because this correlation will determine the level to which barrel is filled with the feed material and residence time of the physical mixture in the barrel. Moreover, feed rate can affect both thermal and mechanical energy input to the physical mixture. An increase in feed rate results in an increase in the barrel fill level and decrease in residence time of mix in the barrel. The feed rate has a direct influence on the homogeneity, porosity, mechanical strength, and physical state.
	Screw speed	The screw speed impacts the crystallinity and dissolution rate of ASDs. A higher dissolution rate and reduced crystallinity can be observed when processing at lower screw speeds owing to the longer residence time. The mechanical energy/shearing forces generated by the screw speed of the extruder influence the dispersion and dissolution of the crystalline API in the polymer matrix. Change in screw speed may lead to varying level of mixing between the drug and the polymer. Thus, the high mechanical energy provided by the higher screw speed greatly enhances the miscibility/interaction between the drug and polymer, and provide homogeneous ASD, thereby Improves the amorphous characteristics of the extrudates. Further, a very high screw speed often led to generation of larger particles due to insufficient filling of the material in the barrel, this may result in slower drug release.
	Screw configuration	The type of screw elements, the number of kneading elements, and the position of mixing zones have an impact on the miscibility behavior and amorphization of the API. Generally, the high shear screw configuration with intense mixing should contribute to amorphization. Thus, the extent of amorphization had a direct impact on the crystallinity and dissolution rate.
Assay & Impurities	Temperature	The barrel temperature of the extruder can influence the degree of filling and residence time of the material within the barrel because of temperature dependent viscosity of the polymer. The increase in barrel temperature decreases the melt viscosity of the polymer, which allow barrel to fill more readily. Thus, a high barrel temperature can be attributed to a higher degree of filling and lower residence time and the lower residence time may have an impact on the potency and the degradation profile for drugs that are thermosensitive.
	Throughput	An increase or decrease in throughput/feed rate may significantly impact the barrel fill rate, melt viscosity, residence time, and mechanical energy of the material during the extrusion process. Further, increase in feed rate could greatly affect the residence time and energy deviations. Thus, changes in throughput influence the shear force, torque within the barrel, stopping the process, which can impact the assay performance and impurity profile of the APIs in ASDs.
	Screw speed	The higher screw speed during extrusion lead to a shorter residence time; conversely, lower screw speeds result in a longer residence time. When processing thermosensitive drugs, a low screw speed can induce longer residence time of the mix in the barrel, which may affect the degradation and assay of the drug substances. Higher screw speed of the extruder result in higher mechanical energy input to the formulation, which can induce thermal degradation. Hence, the screw speed must be optimum to reduce the thermal degradation of the thermolabile APIs.
	Screw configuration	The number and position of mixing zones can influence the residence time of the material within the barrel, which can affect the potency and degradation of the drug substances. In as study, (Ghosh et al., 2012), investigated impact of kneading element position on the degradation of Novartis pharma compound 1. The results confirmed that kneading elements positioned close to the feeding section resulted in degradation of the active, suggesting that active stayed longer in the barrel. In contrast, kneading elements positioned near the barrel end improved the active stability, which could be attributed to lower residence time and delay in melting of the active. Thus, the assay and impurity profiles are significantly affected by the screw configuration.

Table 5.

Summary of screening and optimization designs (Bezerra et al., 2008; Fukuda et al., 2018; Grangeia et al., 2020; Mishra et al., 2018; N Politis et al., 2017; Singh et al., 2005; Stalikas et al., 2009; Uhoraningoga et al., 2018; Vanaja and Rani, 2007).

Application	Experimental design	Model effects	Experimental runs	Salient features	Limitations
Screening	FD	Main effect, two factor interactions.	2^k	Applicable for screening and optimization design as well.	Design relies on a large Number of experimental runs when compared with FFD and PBD.
	PBD	Main effects (linear response).	N-1	Allows the study of N-1 input factors with N experiments (where N is multiple of 4).	Can only be used to screen the main effects.
	FFD	Main effect, Two factor interactions.	2^{k-1}	Useful design when the Number of input parameters is between 3 and 7.	Some of the main effects and interaction effects are aliased or confounded because of the fractionated design.
Optimization	CCD	Main effect, two-factor interactions, quadratic (curvature) effects.	3^k	CCD can use five levels of each input factor, and augmentation of an existing FD with appropriate star points is possible.	Can be used to study a smaller Number of input factors because an increased number of experimental runs is required.
	DOD		$N=k^2+k+C_0$	Minimizes the variance of parameters. Useful when factor space is constrained.	Researchers must specify the appropriate model, and this requires an understanding and practical knowledge of DoE.

2 or 3: level of factors, k: number of factors, C_0: number of center points.

Table 6.

Details of experimental designs, independent variables, response variables, experimental runs, and design objectives applied in HME-based ASDs

S.No.	Design name	Independent variables	Ranges studied	Response variables	Number of experimental runs[$]	Design objective	Reference
1	MD	Itraconazole	≤ 10%	Tg	17	Optimization of Soluplus® and HPMCCP combination for enhanced physicochemical properties, solubility and Stability of itraconazole ternary ASDs.	(Albadarin et al., 2017)
		Soluplus®	≤ 60%				
		HPMCCP	≤ 30%				
2	DOD	Itraconazole	20 – 50 %w/w	Torque, Tg, Solubility	15	Optimization of formulation for enhanced solubility of itraconazole ASD.	(Rambali et al., 2003)
		HPMC	10 – 60 %w/w				
		HP-β-CD	10 – 60 %w/w				
3	CCD	HPMCAS-HF	20 – 60 %w/w	Solubility, Dissolution rate	17	Optimization of ratios Soluplus® and HPMCAS-HF polymer combination for enhanced solubility and dissolution rate of efavirenz ASD.	(Pawar et al., 2016)
		Soluplus®	20 – 60 %w/w				
4	MD with a reduced design model	Type of polymer (PVP VA64, Soluplus®, HPMCAS-LF)	66.6% (constant)	Disintegration time, Tensile strength, Dissolution	34	Identification of optimal formulation composition for the development of immediate release ASD tablets.	(A. Agrawal et al., 2016)
		Type of filler (microcrystalline cellulose, lactose, dicalcium phosphate anhydrous),	60–80%				
		Type of disintegrant (crospovidone, croscarmellose sodium, sodium starch glycolate)	5–10%				
		Extrudate level	60–80%				
5	3^2 CCD	Level of copovidone	55 – 75 mg	Disintegration time, Dissolution in 10 min, Impurity profile	13	Optimization of the ratios of polymers in the development of ziprasidone hydrochloride ASD while Keeping other polymers (Soluplus®	(Banerjee et al., 2016)

S.No.	Design name	Independent variables	Ranges studied	Response variables	Number of experimental runs[$]	Design objective	Reference
						and Eudragit® EPO) at a constant level.	
		Hydroxypropyl cellulose	20 – 60 mg				
6	DOD	Carbamazepine	≤5% - ≤30%,	Solubility, Crystallinity	12	Study the Influence of formulation composition on the product characteristics of carbamazepine ASD.	(Djuris et al., 2014)
		Poloxomer 407	≤0% - ≤20%				
		Soluplus®	≤50% - ≤95%				
7	FD	Barrel temperature	160–200 °C	Torque Specific mechanical energy, Tg, Particle size distribution, Moisture content, True density, Tensile strength, Elastic recovery, Plasticity factor, Yield pressure	19	Investigation of impact of the HME process and formulation parameters on the CQAs of Soluplus®-celeco xib ASD.	(Grymonpré et al., 2017)
		Screw speed	50–200 rpm				
		Throughput	0.2-0.5 kg/h				
		Drug load	0–20%				
8	FD	Ratio of surfactants (poloxamer 407, cremophor® RH40)	0.3 – 0.7	Area under dissolution curve (drug release)	16	Investigation of impact of the type and level of surfactants and hydrophilic carriers on the dissolution profile of itraconazole-HP MCAS-L ASDs.	(Lang et al., 2014b)
		Ratio of hydrophilic carriers (PEO N80, PEO N10)	0.3 – 0.7				
		Extrusion temperature	60-100°C				
9	MD	Indomethacin	10–30%	Crystallinity, Residual ratio, Area under the dissolution curve	36	Investigation of effect of the formulation composition and process parameters on the physicochemical properties of indomethacin-PVA ternary ASDs.	(Mori et al., 2019)
		Low hydrolyzed PVA	50–90%				
		Sorbitol	0–40%				
		Process temperature	110–156 °C				
		Screw speed	20–100 rpm				

S.No.	Design name	Independent variables	Ranges studied	Response variables	Number of experimental runs[$]	Design objective	Reference
10	PBD	Drug Load	30 – 50 %	Torque, Tg, Assay, Drug release	14	Investigation of The most influential formulation and process parameters on the quality attributes of ibuprofen-Eudrag it® EPO immediate release ASDs.	(Patwardhan et al, 2015)
		Screw speed	75 – 150 rpm				
		Extrusion temperature	100 – 120 °C				
		Feed Rate	4 – 6 cc/min				
		Type of premixing (hand vs Turbula mixer)	0 – 10hand mixing, 10- 10 min tubula mixer)				
		Processing aid (PVP-25)	0 – 10 %				
11	Combined MD	Bicarbonate	0-5 wt.%	% Crystallinity, In vitro dissolution, Thermoform ability	24	Optimization of the formulation and process parameters in order to increase the dissolution rate of itraconazole ASDs.	(Thiry et al., 2016)
		Poloxamer	0-10 wt.%				
		Soluplus®	85-100 wt.%				
		Process temperature	125 - 155°C				
		Screw speed	50 – 100 rpm				
12	2^{4-1} FFD	No. 90° mixing elements	0-3	Drug-polymer miscibility, Crystalline content	8	Screen the impact Of critical formulation and process parameters on drug-polymer mixing and crystalline content of felodipine-Soluplus® ASDs.	(Tian et al., 2018)
		No. 60° mixing elements	0-3				
		screw speed	11-30 rpm				
		Drug load	50–70% w/w				
13	FD	Feed rate	1.0 – 2.0 (kg/h)	Tg, Intrinsic dissolution rate	10	To demonstrate the robustness of HME process on the product characteristics of itraconazole-HP MC ASDs.	(Six et al.,2003)
		Screw speed	200 – 400 rpm				
14	CCD	Amount of Plasdone™ S-630	45.86 – 70.00 mg	Drug release in 10 min (%), Drug content (%)	13	Optimization of ratios of the Plasdone™S-630 and HPMCAS-HF on the drug content and dissolution profile of	(Xue et al., 2019)

S.No.	Design name	Independent variables	Ranges studied	Response variables	Number of experimental runs[$]	Design objective	Reference
						ziprasidone hydrochloride ASDs.	
		Amount of HPMCAS-HF	35.86 – 64.14 mg				
15	BBD	Soluplus® ratio and Kollidon®V A64 ratio	30 – 70 %	Solubility, Dissolution rate	13 runs for each polymer type (total of 26)	Investigation of impact of the polymeric system and HME process parameters on the dissolution rate of efavirenz ASDs.	(Pawar et al., 2018)
		Screw speed	50 – 75 rpm				
		Processing temperature	70 - 140°C				
			30 – 70 %				
			50–75 rpm				
			70 - 140°C				
16	MD	Ceolus™ PH-102	Sum of 4 independent factors to 50% and the other 50% includes extrudates, Ac-Di-Sol and Magnesium stearate	Compression force, Hardness, Dissolution rate, Flowability	13	Investigation of impact of the microcrystalline cellulose grades (Ceolus™) and their levels on the critical product attributes of indomethacin-Kollidon® VA64 ASD tablets.	(Dinunzio et al., 2012)
		Ceolus™ UF-711					
		Ceolus™ KG-802					
		Ceolus™ PH-301					

[$]May vary depending on the number of center points and replicates