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To Design QBD (Quality-by-Design) Approach to Understand the Processing Factors Impact Melt-Extruded Solid Dispersions with an Instantaneous Release

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Abstract

Quality by Design (QbD) is a method for determining which patient-reported quality factors are most important, translating those factors into product attributes, and then determining how to consistently produce drug products with those attributes by varying key process parameters. For this purpose, it is necessary to identify sources of variability and create correlations between product features and factors pertaining to the formulation and manufacturing process, such as the properties of the medication ingredient and excipients, as well as process parameters. Using this information, a strong and adaptable manufacturing process is put into place, allowing it to consistently create high-quality products over time. Although hot-melt extrusion (HME) has been around for a while in the food and plastics industries, it wasn't until 1971 when El-Egakey et al. used it to pharmaceutical formulation. Different research organizations dug further into this method, honing it for use in the pharmaceutical industry.

Keywords: Quality by Design (QbD), pharmaceutical, organizations, extrusion, method.

Introduction

Quality by design (QbD) is at the heart of contemporary pharmaceutical quality systems, which aim to improve drug discovery and development. The appropriateness of a medicinal ingredient or medicinal product for its designated purpose is the essence of quality, according to ICH Q8. Qualities like authenticity, power, and innocence are included in this word. By noting, "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities," ICH Q6A highlights the significance of specifications. Quality by Design (QbD) in the pharmaceutical industry is a strategy to drug development that is methodical, scientific, risk-based, comprehensive, and proactive. It starts with goals in mind and places an emphasis on knowing one's products and processes inside and out and controlling those processes.

Developing and devising formulas and production procedures to achieve predetermined product quality goals is what this term refers to. Formulations with varying release kinetics, such sustained-release dose forms, may be made using HME, and it is also well-suited for solid

dispersion. Among this technology's many advantages are its adaptability to different instrument configurations, process parameters, polymeric matrices, and downstream equipment types, as well as its applicability for continuous production operations. Therefore, the processing parameters, excipients, and equipment configuration may be adjusted to suit the specific API(s) and the desired medication efficacy.

The pharmaceutical industry has shown increasing interest in HME technology as a result of the promising formulation opportunities it presents. Numerous formulations based on HME have entered the market since the 1980s, when the number of patents and scientific papers pertaining to HME technology began to climb. According to Wyttenbach et al.'s review of commercially available goods containing amorphous solid dispersions, HME technology is applicable to 42% of these items, 32% to those made using spray-drying, and 26% to those made using other methods. But, there are obstacles to this technology that must be surmounted. One crucial aspect is temperature. An amorphous solid dispersion can only be created by molecularly dissolving the API inside the polymer matrix. During the extrusion process, HME makes use of high temperatures and shear pressures to accomplish this. Each component's glass transition, melting, and degradation temperatures—including the API's—must be meticulously considered while establishing the process and selecting a polymeric matrix. Keep in mind that processing by HME puts heat stress on the API and excipient(s), and that local temperature spikes (e.g., owing to friction) may happen depending on the process setup. Additionally, an API that is sensitive to changes in temperature would not work well with a carrier polymer that has a high Tg. Some problems have been seen, especially when the Tg is near the Tdeg. A plasticizer, which reduces the Tg of the polymeric carrier and increases its processability, might be useful in certain situations.In [20], The release performance of the final formulations is largely determined by the choice of polymer. The polymer allows for either immediate or sustained release patterns. The small number of polymers available is a major limitation of this method, particularly for APIs that are heat sensitive or have a high melting point (Tm) more than 200 °C. Hydroxypropyl methylcellulose and hydroxypropyl methylcellulose acetate succinate are two examples of cellulose derivatives that are available polymers. Other examples are polyvinylpyrrolidone-co-vinyl acetate and a polyvinyl caprolactam-polyvinyl acetate-PEG graft copolymer.

Literature and review

Gajera, Bhavin & Shah, Harsh & Parekh, Bhavin & Rathod, Vishal & Tilala, Mitul & Dave, Rutesh. (2024) The spray-dry amorphousclotrimazole nanosuspension (CLT-NS) made of microcrystallinecellulose and Soluplus® was subjected to a Quality by Design (QbD) methodology in this research. The effect of input temperature, percentage aspiration, and feed rate on the key quality attributes (CQAs) of the clotrimazole spray-dried nanosuspension (CLT-SDNS) was systematically evaluated using the Box-Behnken Design. To build a prediction model for spray drying, this research used ANOVA and regression analysis to find important components and their interactions. After some fine-tuning, the CLT-SD-NS was analyzed using XRPD, FTIR, DSC, and in vitro dissolution tests. Inlet temperature, feed rate, and aspiration rate were identified as major factors influencing end product moisture content, redispersibility index (RDI), and yield. At a p-value of 0.05, the models developed for CQAs demonstrated statistical significance. FTIR showed that there were no interactions between the CLT and the excipients, while XRPD and DSC verified that the CLT in the CLT-SD-NS was amorphous. Due to the fast redispersal of nanosized amorphous

CLT particles, in vitro dissolution experiments demonstrated that the CLT-SD-NS had better dissolving rates, with a 3.12-fold increase in DI water and a 5.88-fold increase at pH 7.2 dissolution medium. Research that is both thorough and applied makes use of the Design of Experiments (DoE) framework.

Miller, Dave & Ellenberger, Daniel & Porfirio, Tiago & Gil, Marco. (2022) In this chapter, we will go over spray-drying technology and how it may be used to make medications that aren't very water-soluble. The first part of the chapter covers the basics of the process, including the theory behind it, the components of the process, the alternatives for equipment, the size of equipment, the different feeds, and the usual solvent systems. The chapter concludes with a discussion of spray drying as a potential method for improving the formulation of medications that are not very water-soluble. The use of spray drying in systems involving amorphous solid dispersion is highlighted in particular. You will find comprehensive information on the steps needed to create an amorphous spray-dried dispersion and transform it into a finished dosage form. The process's use as a formulation technique and its potential for commercial success are further shown by a number of examples drawn from both academia and industry. Lastly, the paper delves into the use of spray drying in inhalation as well as other developing applications, such as microencapsulation and spray congealing. This chapter delves further into the spray-drying process and how it may be used as a formulation method to improve medication delivery for chemicals that are not highly water-soluble. The present writers would like to express their gratitude to the prior writers for their substantial contributions to the first two editions.

Dohrn, et al (2021) One typical method for making amorphous solid dispersions (ASDs) is via spray-drying. The selection of process parameters has a significant impact on the final product's quality. Determining the spray-drying process design space is, consequently, a crucial step in developing medicinal products, in accordance with the quality-by-design methodology. Avoiding API crystallization and amorphous phase separation during drying is crucial for achieving a solvent-free and homogenous ASD. By taking into account thermodynamic driving factors for solvent drying, ASD-specific interactions between API, polymer, and solvent, and glass transitions, this paper offers a predictive technique to estimating the spray-drying process parameters. To determine the optimal spray-drying parameters, the ternary API/polymer/solvent phase behavior was determined by combining the results of mass and energy balances with the Perturbed-Chain Statistical Associating Theory. Spray drying poly(vinylpyrrolidone) or poly(vinylpyrrolidone-co-vinylacetate) from the solvent’s acetone, dichloromethane, or ethanol was chosen as the process design space for the ASDs of naproxen and ritonavir.

Strojewski, Dominik & Krupa, Anna. (2022) When it comes to making polymeric particles for use in pharmaceuticals, this study weighs the pros and cons of spray drying and nano spray drying. For a long time, the food, chemical, and pharmaceutical sectors have relied on spray drying to solidify liquids and create goods with consistent looks. Spray dryers are designed to atomize liquids into minute droplets, which greatly reduces processing time and guarantees a huge surface area for mass and heat transmission. By fine-tuning formulation factors and important process parameters, each droplet may be transformed into a unique solid microparticle with a unique set of characteristics. Numerous products in clinical use have successfully utilized spray drying technology to improve drug stability, enhance bioavailability, or control its release rate. This is due to the fact that spray drying is easy to scale up and can be used to

dry almost any drug in a solution or suspension. The idea of using nano spray drying technologies to make nanoparticles on a lab scale has been around for a while. At the beginning of the drug development process, when there are just a handful of novel chemical entities accessible, this method becomes quite attractive. Here, feed atomization is accomplished using the nebulization method, and mild drying conditions are ensured by laminar gas flow in the drying chamber. In addition, cyclone separators have been mostly superseded by electrostatic collectors, which guarantee very successful production of solid nanoparticles from very tiny volumes of material.

Mandpe, Shilpa & Kole, Eknath & Mujumdar, A. & Chatterjee, Aniruddha & Naik, Jitendra. (2023) Dried by spray Polymeric nanoformulation using eudragit L 100 and ethylcellulose loaded with flurbiprofen (FLB). After optimization, they underwent evaluation. Through the use of a nanoparticulate system and the design of experiments (DoE) method, this research ascertained the drug release percentage and the encapsulation efficiency percentage. Although it dissolves slowly in water, FLB has a limited oral bioavailability and is only minimally soluble in water overall. Polymeric nanoparticles loaded with FLBs were synthesized using spray drying and solvent evaporation. Screening and optimization using two distinct statistical approaches, namely Plackett-Burman and Centralcomposite Designs, were used to develop the nanoparticle formulation in this study. Drug release, surface morphology, X-ray diffraction (X-RD), percentage of encapsulation efficiency, and Fourier transform infrared (FTIR) spectroscopy were among the many attributes assessed for the polymeric nanoparticles. An effective incorporation of the medicine into the polymeric nanoparticles was determined by the X-RD analysis. Nanoparticles including FLB resulted in an 85-90% increase in drug release values and an EE ranging from 79 to 89%. When you mix ethylcellulose (EC) with eudragit L 100 (ED-100), a polymer, you get a great sustained release, or 14 hours. Finding the best formulation parameters for efficient encapsulation is made easier with these findings.

A Design of Experiment Approach For The Influence Of Processing Parameters On Melt-Extruded Solid Dispersions

Quality by Design (QbD) is a concept first outlined by quality expert Joseph M. Juran in publications, most notably Juran on Quality by Design. Designing for quality and innovation is one of the three universal processes of the Juran Trilogy, in which Juran describes what is required to achieve breakthroughs in new products, services, and processes. Juran believed that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned.

While Quality by Design principles have been used to advance product and process quality in industry, and particularly the automotive industry, they have also been adopted by the U.S. Food and Drug Administration (FDA) for the discovery, development, and manufacture of drugs.

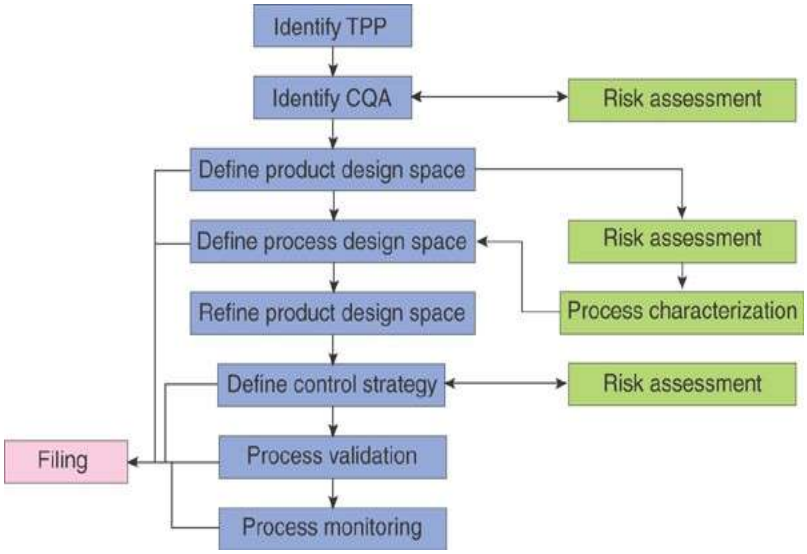

Figure 1 Key steps in implementation of QbD for pharmaceutical product

Pharmaceutical QbD requires a thorough understanding of the product and the process, along with the knowledge of the relationship between the critical quality attributes (CQAs) and the clinical performance of the product. With the concept of QbD, a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight can be achieved.

The effect of individual process parameters on the final product's CQAs is studied with the help of statistical design of experiments (DoE) through which an operational design space (DS) is established. As a result of this, a range of variability is defined for each variable under which the CQAs remain within the pre-established limits. Thus, a controlled DS is generated for the process. Although adapting QbD methodology could be cumbersome initially, it will eventually increase the robustness and quality of the product. It will also reduce overall waste produced during manufacturing, as well as allow efficient globalization for companies with manufacturing sites across the world.

In the QbD system, Design of Experiment (DoE) is most important part since the traditional changing of one factor at a time is not an efficient and economic strategy. The traditional experimental plan does not give any information about the position of the optimum and can, at its best, lead only to a local optimum of the system and is based on large number of experiments and often relies merely on the experience of the analyst. The one-at-a-time optimization also ignores interactions between factors and calls for unnecessarily numerous runs. With rapidly rising costs of experiments, it is very important that the development and optimization of any experimental plan is done with as few experiments and with as low costs as possible.

The present study was a Design of Experiment approach, or partial QbD (quality by design) approach to understand the effect of processing parameters on immediate release melt- extruded solid dispersions. The DoE approach was applied to melt extrusion and processing with Soluplus® for solubility enhancement using fenofibrate as a poorly soluble API.

Results and Discussion

During the hot melt extrusion processing, achieving the amorphous solid dispersion is the primary target. To convert the crystalline drug into amorphous state, the extrusion temperature should be near or higher than the melt temperature of the drug. If using temperature lower than the melting point of the drug, the screw

configuration and screw speed need to be optimized to generate enough shear for the high energy input for the drug. At same time, low extrusion temperature might cause failure of the processing due to high torque. If the extrusion temperature is close to or lower than the glass transition temperature of the binary formulation, the high viscosity could lead to high torque. However, if both high temperature and high shear are applied to the formulation, degradation could happen which would increase the impurities in the extrudate. Even the formulation is thermostable, too high extrusion could also result in liquidize extrudate or sticky formulations which is difficult to handle for the downstream processing.

- **The Design of Experiment method**

In this study, a Box-Behnken design was utilized to qualitatively and quantitatively evaluate the effect of different critical quality attributes on the product quality attributes. The Box-Behnken design is an independent quadratic design, not like other design methods, for example: fractional factorial design or central composite design, in that it does not contain any embedded factorial or fractional factorial design. The treatment combinations are at the midpoints of edges of the process space and at the center when using the Box-Behnken design. These designs are rotatable (or near rotatable) and require 3 levels of each factor. The designs have limited capability for orthogonal blocking compared to the central composite designs.

Select	Std	Run	Factor 1 A:feed rate g/min	Factor 2 B:temperature °C	Factor 3 C:screw spe... rpm	Response 1 disso %	Response 2 ME %
	16	1	15.00	120.00	100.00	55.3	77.1
	2	2	20.00	110.00	100.00	38.2	63.4
	10	3	15.00	130.00	50.00	70.8	68.9
	14	4	15.00	120.00	100.00	65.1	76.9
	13	5	15.00	120.00	100.00	65.1	76.9
	12	6	15.00	130.00	150.00	69.8	75.3
	9	7	15.00	110.00	50.00	40.7	70.3
	8	8	20.00	120.00	150.00	48.9	69.2
	4	9	20.00	130.00	100.00	71.5	74.8
	3	10	10.00	130.00	100.00	68.7	89.5
	15	11	15.00	120.00	100.00	57.1	76.9
	11	12	15.00	110.00	150.00	67.9	67.1
	1	13	10.00	110.00	100.00	58.4	71.6
	5	14	10.00	120.00	50.00	59.7	79.2
	7	15	10.00	120.00	150.00	68.2	87.7
	17	16	15.00	120.00	100.00	65.1	76.9
	6	17	20.00	120.00	50.00	49.2	73.2

Figure 2 Experimental layout by Box-Behnken Design

Table 1 Intermediate Product Quality Profile

Product Attribute	**Target**
Content uniformity (CU)	Conforms to USP<905> Uniformity of Dosage Units
Percentage of crystalline API	0% (100% amorphous)
Degradation product	Total impurities: NMT 1.0%

Table 2 Target Product Quality Profile.

Product Attribute	**Target**
Content uniformity (CU)	Conforms to USP<905> Uniformity of Dosage Units

Dissolution behavior	NLT 80% of label amount released at 30 min
Degradation product	Total impurities: NMT 1.0%

The milled solid dispersion particles serving as an intermediate product for the target product should meet the target profile, like total impurities no more than 1%, immediate drug release, content uniformity (Table 1). In the R1: disso ANOVA table, values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, C, BC are significant model terms which means feed rate, temperature, screw speed and interaction between temperature and screw speed are significant. However, the p value for screw speed was very close to 0.05 which means the impact of this factor is statistically significant but not huge. The 3D response surface also indicated that temperature was more significant.

Table 3. ANOVA for response surface quadratic model for response value 1

Response 1 disso

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	1575.81	9	175.09	7.08	0.0086	significant
A-feed rate	*278.48*	*1*	*278.48*	*11.25*	*0.0122*	
B-temperatur	*714.42*	*1*	*714.42*	*28.87*	*0.0010*	
C-screw spe	*147.92*	*1*	*147.92*	*5.98*	*0.0444*	
AB	*132.25*	*1*	*132.25*	*5.34*	*0.0540*	
AC	*19.36*	*1*	*19.36*	*0.78*	*0.4058*	
BC	*198.81*	*1*	*198.81*	*8.03*	*0.0252*	
A^2	*69.75*	*1*	*69.75*	*2.82*	*0.1371*	
B^2	*12.60*	*1*	*12.60*	*0.51*	*0.4986*	
C^2	*3.96*	*1*	*3.96*	*0.16*	*0.7010*	
Residual	173.21	7	24.74			

Table 4. ANOVA for response surface quadratic model for response value 2

Response 2 ME

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	649.02	9	72.11	7.91	0.0062	significant
A-feed rate	*280.85*	*1*	*280.85*	*30.79*	*0.0009*	
B-temperatur	*162.90*	*1*	*162.90*	*17.86*	*0.0039*	
C-screw spe	*7.41*	*1*	*7.41*	*0.81*	*0.3973*	
AB	*10.56*	*1*	*10.56*	*1.16*	*0.3175*	
AC	*39.06*	*1*	*39.06*	*4.28*	*0.0773*	
BC	*23.04*	*1*	*23.04*	*2.53*	*0.1560*	
A^2	*24.35*	*1*	*24.35*	*2.67*	*0.1463*	
B^2	*86.02*	*1*	*86.02*	*9.43*	*0.0180*	
C^2	*17.18*	*1*	*17.18*	*1.88*	*0.2123*	
Residual	63.84	7	9.12			

The effect of HME processing parameters on the dissolution rate

- The temperature showed more significant effect on the 30 min's dissolution when the feed rate is high comparing with the low feed rate runs. And the feed rate exhibited more significant effect on the 30 min's

dissolution when temperature is low. This is because that when feed rate is low, even low temperature can provide enough energy input to completely melt the API and polymer carrier, so that the drug is easier to be dispersed homogenously into the whole polymeric matrix. The evenly dispersed system can avoid the existing of drug rich zones in the solid dispersion which could avoid the amorphous drug recrystallization during the dissolution.

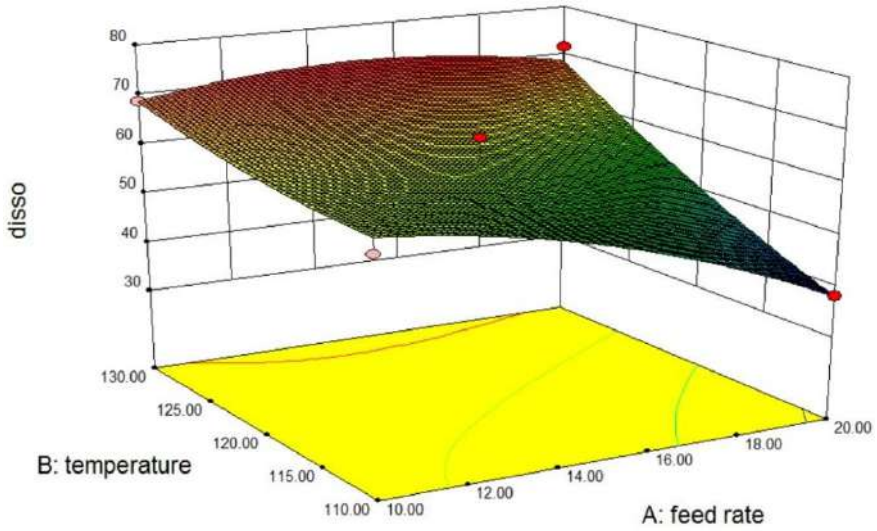

Figure 3 The 3D response surface of feed rate and temperature for response value R1

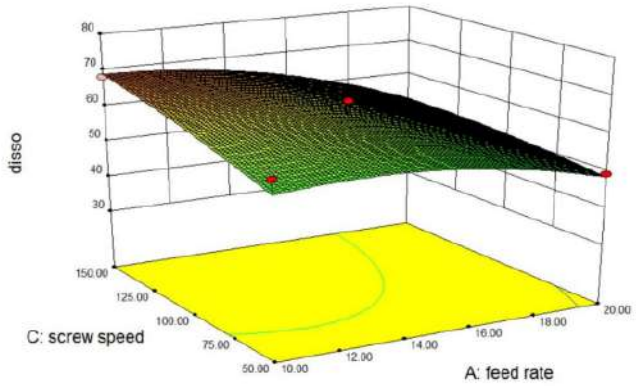

Figure 4 The 3D response surface of feed rate and screw speed for response value R1

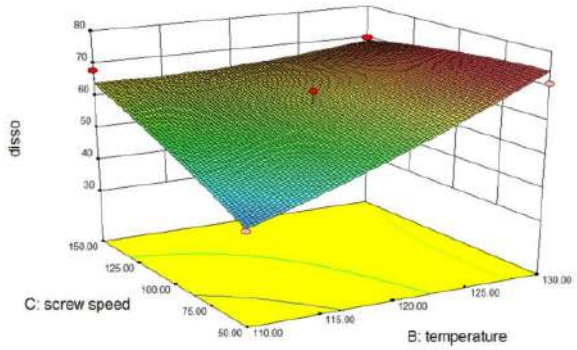

Figure 5 The 3D response surface of temperature and screw speed for response value R1

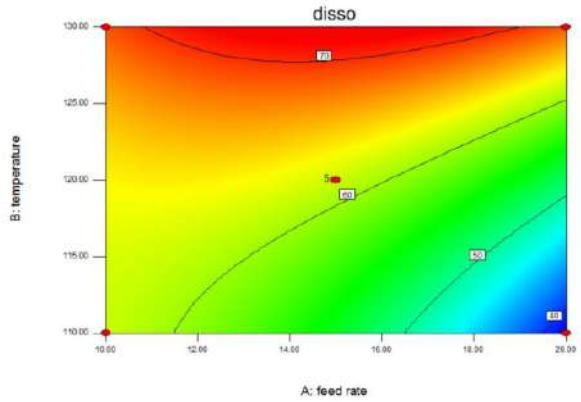

Figure 6 The 2D design space of temperature and feed rate with screw speed at 100 rpm for response value R1

Conclusion

A Design of Experiment approach, or partial QbD (quality by design) approach to understand the effect of processing parameters on immediate release melt-extruded solid dispersions. The DoE approach was applied to melt extrusion and processing with Soluplus® for solubility enhancement using fenofibrate as a poorly soluble API. The feed rate and temperature were found to have more significant effect on the milling efficiency and dissolution at 30 min.

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