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Design Space Identification of the Rotary Tablet Press

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ABSTRACT

The determination of the design space (DS) in a pharmaceutical process is a crucial aspect of the quality-by-design (QbD) initiative which promotes quality built into the desired product. This is achieved through a deep understanding of how the critical quality attributes (CQAs) and process parameters (CPPs) interact that have been demonstrated to provide quality assurance. For computational inexpensive models, the original process model can be directly deployed to identify the design space. One such crucial process is the Tablet Press (TP), which directly compresses the powder blend into individual units of the final product or adds dry or wet granulation to meet specific formulation needs. In this work, we identify the design space of input variables in a TP such that there is a (probabilistic) guarantee that the tablets meet the quality constraints under a set of operating conditions. A reduced-order model of TP is assigned for this purpose where the effects of lubricants and glidants are used to characterize the design space to achieve the desired tablet CQAs. The probabilistic design space, which takes into account interactions between crucial process parameters and important quality characteristics including model uncertainty, is also approximated because of the high cost associated with the comprehensive experiments.

Keywords: design space, tablet press, direct compression, pharmaceutical process, optimization

INTRODUCTION

The “quality-by-design” (QbD) paradigm put forward by the ICH Q8 guideline on pharmaceutical development states that quality should be built into the products instead of tested into them [1]. The QbD concept allows the practitioner to embrace a thorough and comprehensive approach towards pharmaceutical processes and product development. This leads to a more systematic understanding of the intricate relationships between material attributes, process parameters (CPPs), and product quality (CQAs) for the manufacture of new drugs. The manufacturer may get an advantage from this understanding and receive regulatory clearance to manufacture at any condition and within a broad operating regime if there is sufficient scientific proof that the process will produce a product of acceptable quality. Such an operational regime is called the design space and is also introduced in the ICH guideline. The regulatory approval provides the boundaries within which the material attributes and process parameters can be changed without further approval. However, changes beyond the design space values mandate a regulatory post-approval change process.

The most widely available literature for design space identification uses an empirical approach and generally follows the steps of: identifying the knowledge space; design-of-experiments (DoE) measuring the relation between the CPPs and CQAs within the knowledge space; using empirical regression methods to define boundaries of the design space; and validation experiments to confirm the design space [3]. The empirical approach is highly favorable when the model is complicated (e.g., multiple unit operations, integrated flowsheet model), and the design space analysis can be challenging due to the computational cost associated with the simulation of the process model.

However, in the presence of a relatively inexpensive computational model, the original model based on the mechanistic equations of the process can be directly used to characterize the design space. Instead of using experimental data to generate empirical relationships, the equations in these models are constructed from a series of presumptions about the physical system and

conservation principles of physics and chemistry. The degree to which these assumptions are true determines whether these models hold up when applied to novel situations. There are instances of mechanistic models being applied to the identification of design spaces; however, fewer examples exist for pharmaceutical processes [4-5].

The design space concept has been based on empirical relationships since its beginning; however, the current practice is to evolve by using models that are more mechanistic. The discussion remains about how much experimental evidence is necessary to establish the design space, which changes across regions and application scenarios. There are three broad approaches to identifying design spaces that result in desirable quality attributes: optimization methods, Bayesian inference, and knowledge space sampling. Optimization techniques help identify operational parameters, which ensures that the process acquiesces to a constraint set by performing the flexibility analysis [6]. Bayesian approaches use limited process data and variability and can also incorporate prior knowledge about the process to define a design space that includes uncertainty [7]. Another alternative approach to identifying the design space is to generate a mesh of sample points in the process parameter space and perform simulations at each of those points to determine if the predicted product quality disobeys any constraint [8].

The current work contributes to this fast-evolving domain, where we investigate a steady-state mechanistic tablet press (TP) model [2]. For the purpose of using QbD methods in a direct compression tableting process—where the dry blended component materials are compressed into tablets—the TP model may be used to predict the CPPs and CQAs of tablets. The reduced-order TP model has been used previously to describe the effects of glidants and lubricants on tablet CQAs [2] and implement moving horizon estimation-based non-linear model predictive control (MHE-NMPC) for the tablet press at Purdue's pharmaceutical continuous manufacturing pilot plant [9]. In the current study, the mechanistic model is deployed for identifying the design space using explicit knowledge space sampling, and the importance of various process parameters is discussed based on the optimal areas of operation that follow a set of constraints. The study investigates the effects of glidants and lubricants and other process parameters on making desired quality tablets via two separate experimental campaigns and their probabilistic design spaces are characterized.

The paper is organized as follows: the next section explains the reduced-order model for the TP, where the role of glidants and lubricants on tablet quality is explained. Subsequently, the design of experiments and the parameter estimation of the mechanistic model are described. We then present the design space results and recommend the optimal areas of process operation to manufacture tablets of the desired quality. The robust design space is also determined when the process model includes uncertainty by performing Monte Carlo simulations for different probability values as acceptable minimum.

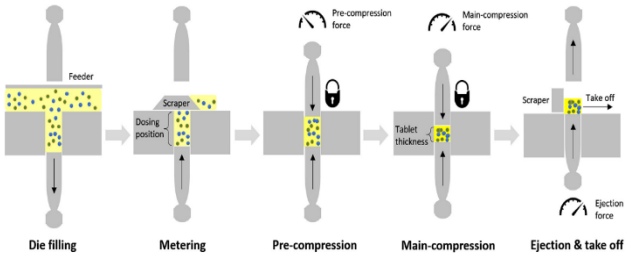


Figure 1. Steps in a rotary tablet press process (taken from [10])

TABLET PRESS MODEL

The tablet press is a multi-stage process that involves the following primary actions at each station: die filling, metering, pre-compression, main-compression, tablet ejection and take-off from lower punch. The metering stage adjusts the dosing position to change the amount of powder within the die after die filling the feed frame. The die is then locked between the upper and lower punches throughout the pre-compression and main-compression stage until tablet ejection and take-off takes place. While the main compression works to compact and solidify the powder into tablets, the pre-compression helps to release trapped air in the die and reorganize the particle packing.

In order to lower frictional losses and improve powder flow during die filling and the mechanical compression-formed solid tablet formation process, lubricants and glidants are essential components. Consequently, the porosity and tensile strength of tablets will be monitored and controlled using models for lubricant/glidant effects in die filling and compression operations. The effects of glidant and lubricant concentrations and mixing conditions are specifically captured by these mechanistic models.

The tablet weight, W, formed using NATOLI D-type tooling is affected by the process parameters such as dosing position (h_{fill}), turret speed (n_T), and diameter of the tablet (D) and is computed as

$$W = \rho_b V_{fill}\left(-\varphi_1 \frac{n_F}{n_T} + \varphi_2 \frac{h_{fill}}{D} + \varphi_3 \left(\frac{h_{fill}}{D}\right)^2\right) \qquad (1)$$

Where φ_1, φ_2, φ_3 refer to the model parameters (to be estimated using the experimental data) and V_{fill}, ρ_b, and nF is the die cavity volume, powder bulk density, and feed frame speed, respectively. The powder bulk density ρ_b is dependent on the glidant/lubricant concentration (c_l)

and mixing time (or shear imparted during mixing) (γ) which follows the asymptotic relationship as

$$\rho_b = \rho_{b,\infty} - \frac{\rho_{b,\infty} - \rho_{b,0}}{1 + C_p} \text{ with } C_p = \frac{c_l^{r_1}(\gamma + \gamma_0)^{r_2}}{r_3} \quad (2)$$

where $\rho_{b,\infty}$, and $\rho_{b,0}$ represent the bulk densities when the shear imparted during mixing is infinite and zero respectively, γ_0 is the initial shear imparted during pre-mixing, and r_1, r_2, r_3 are model parameters estimated from the experimental data. The bulk density in (2) increases with increase in concentration or mixing time of glidant/lubricant and reaches an asymptotic value. The die cavity volume is calculated as follows

$$V_{fill} = \frac{\pi D^2 h_{fill}}{4} + \frac{\pi h(\frac{3D^2}{4} + h^2)}{6} \quad (3)$$

where h is the cup depth. The main compression force (F_{main}) which is an important process variable can be estimated using the Kawakita equation [11] for the effect of silica (independent of the glidant conditions) by

$$F_{main} = \frac{\pi D^2(\rho_{in-die} - \rho_c)}{4b(\rho_{in-die}(a-1) + \rho_c)} \quad (4)$$

where a and b are the Kawakita parameters, ρ_c is the critical density of the powder and the in-die relative density, ρ_{in-die} is given by

$$\rho_{in-die} = \frac{W}{\rho_t V_{in-die}} \quad (5)$$

where ρ_t is the true density of the powder and V_{in-die} is the die-cavity volume with main compression thickness h_{in-die} given by

$$V_{in-die} = \frac{\pi D^2 h_{in-die}}{4} + \frac{\pi h(\frac{3D^2}{4} + h^2)}{3} \quad (6)$$

The lubrication conditions are found to affect the compression force for the MgSt blends and this is incorporated by modifying a as

$$a = a_\infty - \frac{a_0 - a_\infty}{1 + C_c} \text{ with } C_c = \frac{c_l^{p_1}(\gamma + \gamma_0)^{p_2}}{p_3} \quad (7)$$

where a_0, a_∞, p_1, p_2, and p_3 are model parameters. Here, the compaction force increases with increasing lubrication. The elastic recovery (ε_p) model which is part of the tablet ejection stage is insensitive to the glidant mixing conditions and can be calculated by

$$\varepsilon_p = \varepsilon_0 \frac{\rho_{in-die} - \rho_{c,\varepsilon}}{1 - \rho_{c,\varepsilon}} \quad (8)$$

However, the lubricant conditions affect the elastic recovery and an increase in the former increases the latter. This behavior is captured by modeling ε_0 as

$$\varepsilon_0 = \varepsilon_\infty - \frac{\varepsilon_\varphi - \varepsilon_\infty}{1 + C_\varepsilon} \text{ with } C_\varepsilon = \frac{c_l^{q_1}(\gamma + \gamma_0)^{q_2}}{q_3} \quad (9)$$

where ε_φ, ε_∞, q_1, q_2, and q_3 are model parameters. The tablet density ρ_{tab} can then be calculated using

$$\rho_{tab} = \rho_{in-die}(1 - \varepsilon_p) \quad (10)$$

The tensile strength (σ_t) of a tablet is a crucial CQA which affects the tablet dissolution along with the tablet weight W. Both lubricant/glidant concentration and mixing time affect the tensile strength and the relationship is governed by Kuentz and Luenberger, 2000 [12]

$$\sigma_t = \sigma_0 \left[1 - e^{(\rho_{tab} - \rho_{c,\sigma})}\left(\frac{1 - \rho_{tab}}{1 - \rho_{c,\sigma}}\right)\right] with\ \sigma_0 = \frac{\sigma_{0,\varphi}}{1 + C_\sigma}$$

$$\rho_{c,\sigma} = \rho_{c,\sigma,\infty} - \frac{\rho_{c,\sigma,\infty} - \rho_{c,\sigma,\varphi}}{1 + C_\sigma} \text{ and } C_\sigma = \frac{c_l^{b_1}(\gamma + \gamma_0)^{b_2}}{b_3} \quad (11)$$

Where $\rho_{c,\sigma,\varphi}$, $\rho_{c,\sigma,\infty}$, b_1, b_2, b_3 are the model parameters [13] and $\sigma_{0,\varphi}$ and $\rho_{c,\sigma,\varphi}$ represents the tensile strength and critical relative density when there is no lubrication, C_σ = 0. As a result of the tensile strength model, soft tablets with lower tensile strength are formed as the concentration or mixing time of glidant or lubricant in the formulation increases. However, the decrease in tablet tensile strength manufactured using silica blends is solely because of the variations in the blended material properties, but the lower tensile strength of tablets formed using Magnesium Stearate (MgSt) blends would in addition be due to the increased elastic recovery of lubricated tablets.

METHODOLOGY

Tablets are the most common oral solid dosage form that can be produced by direct compression or enhanced by either wet or dry granulation to meet specific formulation needs. The direct compression line in the pharmaceutical continuous manufacturing pilot plant at Purdue University was used for the studies in this work. The materials used in the current study include 10% w/w acetaminophen (APAP) as the API, microcrystalline cellulose Avicel PH200 (MCC) as the excipient, and glidant colloidal silica and lubricant Magnesium Stearate (MgSt) at different concentrations. Colloidal silica is an excipient which is useful for improving powder flowability and MgSt helps reduce internal friction during compaction and tablet-tooling friction during ejection. These excipients have a substantial impact on the powder's surface characteristics, such as the strength of the solid bridges created during compaction, as well as bulk properties, including bulk density, even when added in very small amounts [14]. This shift in the blend's characteristics naturally affects the tableting procedure and the final tablet's CQAs, including its dissolving profile [13, 15], which in turn affects the active pharmaceutical product's (API) bioavailability.

For the experimental campaigns, APAP and MCC were mixed in a tote blender with 0-0.2% w/w silica in the first experimental campaign and with 0-2% w/w MgSt in the second campaign for 10–30 minutes. The dosing

position and the in-die (main compression) thickness values were maintained between 7–11 mm (9-13 for lubricant MgSt) and at 3.1 mm, respectively, to manufacture tablets that have a wide range of relative densities. The design-of-experiments DoE was conducted separately for the two experimental campaigns to study the effects of silica and MgSt on tablet quality. The MATLAB function lhsdesign was used to build a Latin hypercube sampling (Viana, 2013) of turret speed, dosing position, concentration, and mixing time to generate 30 experiments for the silica blends and 20 experiments for the MgSt blends. Next, the powder blends were compressed into tablets using a NATOLI-NP400 tablet press using D-type tooling with shallow cup of depth 0.33 mm, which features a total of 22 punch-die stations with die-size 8 mm. A SOTAX AT4 tablet tester was utilized to measure the weight, hardness, diameter, and thickness of 50 tablets under steady-state manufacturing conditions for each run in the DoE. At the beginning of each experimental run, 0.5 kg of the mix was added to the tablet press hopper.

The TP model parameters are estimated by minimizing the least squares which is typically solved as an optimization problem where the objective is to minimize the sum of squared errors (SSE) between the model predicted and observed values.

$$SSE = \sum_{i=1}^{n}(y_{mod,i} - y_{obs,i})^2 \quad (12)$$

where $y_{mod,i}$ and $y_{obs,i}$ are the *ith* estimated value using the TP model and *ith* experimental data of the tablet CQAs (tablet weight, main compression force, and tablet tensile strength), respectively, and n is the number of experimental samples. The sum of squared errors is minimized, and the corresponding optimal values of model parameters and their uncertainty are stored for design space characterization.

There are 4 CPPs in the DoE namely turret speed, dosing position, concentration, and mixing time. In the tablet press, the feed frame speed gets automatically adjusted to be ~15 rpm greater than the turret speed. While high feeder to turret speed ratios can lead to uneven die-filling and tablet weight variability, the current DoE maintains low turret and feeder speeds, minimizing their impact on tablet weight. The dosing position (h_{fill}) determines the tablet weight, while the main compression thickness (h_{in-die}) affects the tablet density and hence the tensile strength of the tablet. Therefore, the crucial CPPs for the design space are the dosing position, main compression thickness, concentration, and mixing time and their realizable bounds are shown in Table 1. The main compression thickness is flexible enough to vary within operable limits and can be used to widen the useful design space regions. The tablet CQAs considered in this study include main compression force, tablet weight, and tensile strength, and the desired specifications are mentioned in Table 2. The compression force is essentially not included in the tablet CQAs but it helps in regulating the lower bounds of dosing position and main compression thickness that results in useful design space regions. Therefore, it is included as a quality constraint. The objective of this study is to identify the design space of input variables (h_{fill}, h_{in-die}, c_L, γ) such that the tablets are guaranteed to meet the quality constraints (W, F_{main}, σ_t) under the operating limits of the tablet press.

Table 1: The critical process parameters (CPPs) and their bounds

CPP	Low limit	High limit
Dosing position (h_{fill})	6 mm	11 mm
Comp. thickness (h_{in-die})	1.5 mm	3 mm
Silica conc. (c_l)	0.1 %	0.2 %
MgSt conc. (c_l)	0.1 %	2 %
Mixing time (γ)	10 mins.	30 mins.

Table 2: The critical quality attributes (CQAs) and their specifications

CPP	Low	High
Tablet weight (W)	125 mg	175 mg
Compression Force (F_{main})	2 kN	50 kN
Tensile strength (σ_t)	2 MPa	15 MPa

As previously stated, an explicit sampling of the knowledge space is used to identify the design space. For the deterministic design space, the process parameters are discretized by creating a fine mesh of sample points within their predefined bounds. To determine if the projected CQAs jointly observe the constraints for each discretized sample, simulations are performed for each of these discretized CPPs. A deterministic design space is the outcome of this mapping.

For the probabilistic design space, additionally, at each of the discretized CPPs, Monte Carlo simulations are executed on the full model N times using the model parameter values in the space of their uncertainty bounds. The uncertainty information is incorporated in the design space using the computed standard deviation values of model parameters from the least squares approach. The fitted model predictions against experimental data for different CQAs can be seen in Figure 2. Then, for each of the discretized process parameter samples, the probability of meeting the constraints jointly is estimated. The probability is computed based on the fraction of times the Monte Carlo simulations resulted in CQA values that complied with all the constraints. For each discretized sample, the probability is set equal to this fraction. This allows for the propagation of model uncertainty to the predicted CQAs, and the Monte Carlo simulation serves well in showing the possible values of the model prediction as explicit probability maps which

accounts for model variability and common cause variability.

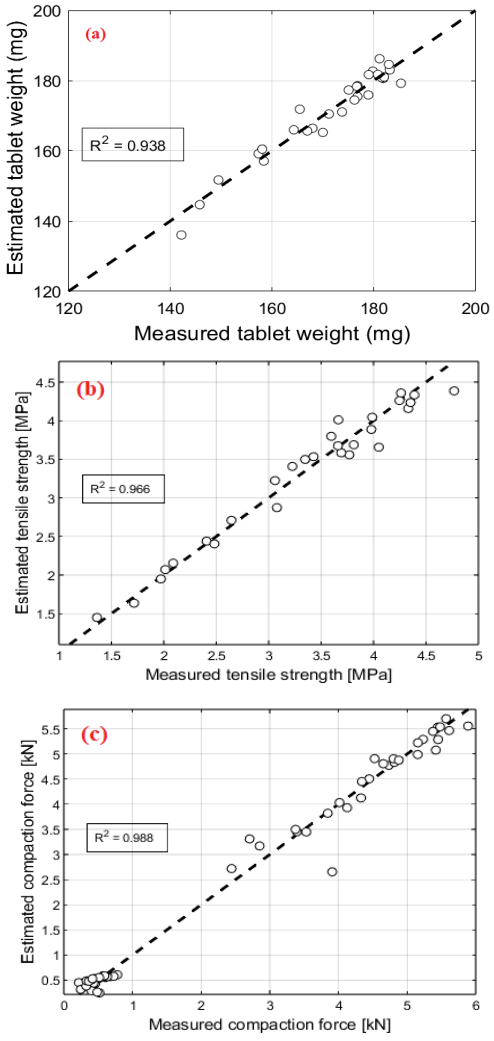


Figure 2. Fitted TP model predictions versus experimental data for (a) tablet weight, (b) tensile strength, (c) compaction force.

The explicit sampling method is effective in identifying the probabilistic design space, and the process parameter grid can be made finer through discretization, and there is no restriction on the sampling size of the uncertain parameters. It is worth mentioning that a major limitation of this approach lies in the large number of simulations that need to be performed, and the design of effective strategies for knowledge space sampling is an active research area but that is beyond the scope of this work. Despite the computational challenges, the explicit sampling method is the most straightforward approach to estimate even complex design spaces. However, the goal here is to recommend optimal areas of operation for the tablet press within the process parameter space that results in quality tablets utilizing the straightforward and effective explicit sampling approach.

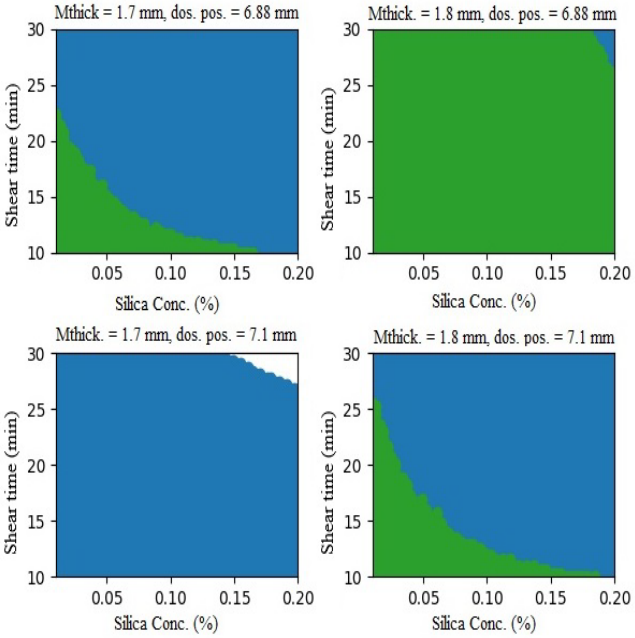


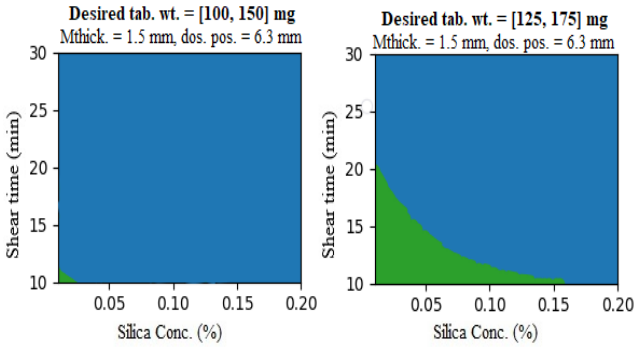
Figure 3. Design space plots for silica blends following CQA constraints mentioned in Table 2. Blue region is the deterministic design space (without accounting for model uncertainty) and green region is the probabilistic design space with 85% confidence.

RESULTS AND DISCUSSIONS

From the tablet press model described in the second section, it can be seen that the CPPs dosing position h_{fill}, lubricant or glidant concentration c_L, and mixing time γ, affect the CQA tablet weight W (from equations 1, 2, and 3). The main compression force F_{main}, which is another CQA, is additionally influenced by the main compression thickness (equations 4, 5, 6, and 7). The tensile strength σ_t is also dependent on all the CPPs (equations 8, 9, 10, and 11). Therefore, the tablet press model can be lumped into three equations: one for tablet weight, a second for main compression force, and a third for tensile strength. The equations have not been mentioned here due to their comprehensiveness. However, the equations can be used to solve for the design space variables within the bounds shown in Table 1, and the equations themselves would be constrained due to the limits specified in Table 2.

Figure (2) depict the multidimensional design space in simplified graphical form for the silica blends. Several simulations were performed for various combinations of process parameters and sampling model parameters within their uncertainty bounds in order to identify the multidimensional design space. For demonstration, 1000 Monte Carlo simulation realizations were used in this case, with an acceptable minimum probability of 85%.

The blue region is where the three quality constraints are met without accounting for the model uncertainty and the green region is where the probability of meeting all the quality constraints is acceptable. It is important to emphasize here that the lower feasible bounds of the dosing position and the compression thickness is regulated by the main compression force and their upper feasible bounds is controlled by the tensile strength constraint. From the design space plots of silica blends, it is observed that the closer you operate near the nominal value of compression thickness (~ 2.1 mm) and dosing position (~6.9 mm), wider would be the probabilistic design space. Although the comprehensive probability maps have not been shown here, but the variation in design space can be explained as follows: for lower dosing positions values (closer to lower bound in Table 1), lower thickness values are favorable and for high dosing positions values (closer to upper bound), higher thickness values are required for tablet quality to obey the constraints. This is only valid within the feasible limit of process parameters. The design space plots for the lubricated blends were found to very narrow and small even



for the deterministic case and are therefore not reported.

Figure 4. Design space plots for different tablet weight CQA limits. Blue region is the deterministic design space (without accounting for model uncertainty) and green region is the probabilistic design space with 85% confidence.

We also demonstrate the effectiveness of the TP model in capturing the design space boundaries by showing the design space plots with varying tablet weight limits. The other two CQA constraints remain unchanged as mentioned in Table 2. To illustrate the case, we have considered a new limit for tablet weight W = [100, 150] mg and compare it with the original case but the operating conditions on dosing position and compression thickness is kept fixed at (6.3 mm, 1.5 mm) and other constraints also remain unchanged. The silica blends are used for this case study. The change in feasible region boundary for the probabilistic design space is shown in Figure 4. Here the green region shrinks towards bottom left for smaller tablet weight CQA.

CONCLUSIONS

The study investigated the determination of design space for the tablet press operation to achieve desired tablet quality. The design space plots showed the effects of glidant or lubricant on the tablet quality. Tablets made from silica blends showed much promise where a design space point in a sufficient broad feasible region can be used to perform validation experiments. The efficacy of the TP model is also depicted in the case where the variation in probabilistic design space boundary is captured when the required tablet weight changes. An immediate future work includes performing the validation experiments based on the identified design space plots.

The future work includes various improvisation to the current study. First, the TP model needs to be tested against variations in measured tablet CQAs. Second, to develop design space plots for much smaller or larger tablets and to study the effect of die size on such tablets and how the TP model performs with such variations. Finally, an empirical approach such as Bayesian modeling based on the DoE can be used to explore the design space of the TP and compare its efficacy against the model-based methodology.

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