DERIVATION OF DESIGN SPACE FOR BLEND HOMOGENEITY FOR ROBUST TABLET MANUFACTURING BY AN INTEGRATED QBD APPROACH

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Abstract

Oral dosage form is a maximally prescribed formulation amongst all possible pharmaceutical products. Formulation of tablet is multistep process where each step has meaningful effect on quality of final product. So, it is necessary to identify the important unit operations in process of tablet manufacturing which significantly affect the efficacy and safety of formulation. In present work, the blending step is elaborated in detail to check the impact of the same on the quality of tablet dosage form. The concept of QbD was employed on blending process with identification of QTPP and CQAs. In risk estimation matrix various independent factors were finalized having impact on CQAs of blending. Further, screening of critical factors was done using placket burmann design. Full factorial design (3*2) was used further to check the relation of identified critical factors (blending speed and blending time) on selected CQAs (blend uniformity & RSD). From overlay plot, control space was outlined and the range of risk free processing parameters was fixed. So, if blending of drug-excipients blend is performed in these specified conditions, the quality of blend (uniform mixing) can be assured. This blend can be charged further into granulation step.

Key words: QbD, Blending, Placket burmann design, Blend uniformity, %RSD

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1. Introduction

Powder mixing has been the subject of substantial research. This is motivated by applications in a variety of industrial sectors, which include pharmaceuticals, food, ceramics, catalysts, metals, and polymer manufacturing. Understanding mixing mechanisms and identifying critical process and material parameters is often a crucial step during process development. Content uniformity problems have four main root causes: (a) powder stream flow properties (Portillo, Ierapetritou et al. 2008), (b) poor equipment design or inadequate operation, (c) particle segregation due to differences in particle properties, and (d) particle agglomeration (Li and McCarthy 2003), driven by electrostatics, moisture, softening of low melting point components, as well as other factors.

Scale-up of mixing operations continues to present a concern to the pharmaceutical development process. The reliable scaling of a process requires an understanding of the effects that processing parameters may illicit on intermediate- and finished-product properties. Generally, processing conditions are thoroughly examined at small scales during process development of powder formulations. The design and scale-up of blending operations is a multivariate issue; the relative magnitudes of shear, dispersion, and convective forces may be altered as the process is transferred to larger scales (Mehrotra, Chaudhuri et al. 2009). A problem with the current scale-up philosophy is a failure in addressing several critical variables. Shear rate and total strain have been shown to affect blend microstructure (Delogu, Gorrasi et al. 2017), which may consequently affect the degree of ingredient agglomeration, blend flow properties, tablet hardness and final product dissolution, which may ultimately result in failures during the scale-up process. An example of this includes blend over-lubrication resulting from the increase in shear (per revolution of the blender)(Arratia, Duong et al. 2006). In a separate study, blender rotation rates were found to affect the relative standard deviation (RSD) plateau of a given system. Powder cohesion properties also affect the velocity gradient, where inter-particulate forces dilate the powder bed density. This may have further implications on downstream processing. Optimization of the blending process requires an understanding of blending mechanisms and critical variables(Dunber, Hickey et al. 1998). Although modifications to powder cohesion, blender size, and geometry may not be feasible due to other constraints, operating conditions such as rotation rate and fill level are easier to alter. An understanding of the interactions among these variables is essential.

Historical practices in pharmaceutical process development have largely involved univariate (OVAT, "one variable at a time") approaches, where the effects of a single variable are examined for a few conditions selected based on prior experience from a "safe" subset of the permissible design space. A value of the first variable is then selected and kept constant as a second variable is examined, and so forth. However, as suggested in the Process Analytical Technology (PAT) Guidance (Munson, Freeman Stanfield et al. 2006), the OVAT approach does not effectively address the effect of interactions between multiple process variables. As a result, unless the effects of all variables are nearly independent of one another, the optimal conditions for operating the process will not be determined. The pharmaceutical industry has recently focused substantial effort on improving its understanding of key unit operations and developing statistical, instrumental, and fundamental methods for characterizing and controlling sources of variability in product performance(Alford 2006).

Beginning with the introduction of the PAT Guidance in 2003 and continuing with the quality by design (QbD) initiative (for which draft guidance exists in ICH Q8 (Berridge 2004), Q9 (Elder and Teasdale 2017), and Q10 (Guideline 2008)), the industry is transitioning from OVAT approaches to a more multivariate statistical method for assessing the effects of process variables on product quality. The "process understanding" that is considered a keystone of the PAT and QbD initiatives enables the process control that facilitates the manufacture of quality products meeting desired performance specifications. As mentioned, this paper outlines a QbD strategy for the design of batch blending operations. In the next section, we discuss the experimental method. This provides the scope of experimental conditions investigated and the details behind the variable parameters, and optimization of design space.

1. Material and Method

The following pharmaceutical materials were used as received for this study, without further processing or purification prior to the powder mixing: USP 70 grade Paracetamol (Albemarle Corp., LA); USP/NF Microcrystalline Cellulose (MCC) and Sodium Starch Glycolate (SSG) (JRS Pharma LP, Cedar Rapids, Iowa).

2.1. Method

a. Quantification of Paracetamol

A double beam UV spectrophotometer (UV-1800, Shimadzu, Japan) was used to measure PCM in bulk samples and all *in vitro* studies. A known amount of PCM (1mg/mL) was dissolved in suitable solvents, followed by filtration and kept in quarts cell for analysis against solvents as blank reading. Suitable dilutions were prepared (5-30µg/ml) and linearity was observed. Samples were prepared and checked for 3 days for inter and intraday variability. λ_{max} for PCM was observed at 276 nm and drug content in bulk and *in vitro* studies was analyzed at this wavelength. A standard curve was prepared, and linearity function was applied.

b. Blending unit operation

The blender used in this study is shown in Fig. 1. They have a fixed geometry comprised of a rectangular bin blender and a pyramidal hopper that forms the tote. This design was selected for several reasons, including: (1) it is common, (2) it is available in our lab in three sizes, (3) it has been thoroughly examined in previous studies, and (4) a good working knowledge of the critical-to-performance variables is available. Baffles were used since they have been shown to improve mixing performance(Talebjedi, Ghazi et al. 2021) by increasing axial flow.

c. Powder Materials

A ternary blend system was investigated. The blends examined contained PCM (Paracetamol), SMCC (Silicified Microcrystalline Cellulose) and SSG (sodium Starch glycolate)

d. Powder Loading

The method by which materials are initially loaded into the blender vessel is a parameter that has been shown to affect the mixing performance of tumbling blenders. Two particular loading patterns previously examined are the top-to-bottom and left-to-right starting configurations. The top-to-bottom loading resulted in significantly faster mixing rates than left-to-right loading. Thus, the top to-bottom loading was used for this study.

e. Characterization of Blend

Blend Uniformity

CGMP (21 CFR.211.110) requires an in-process testing of powder blends to demonstrate adequacy of mixing, but it does not state that the blend has to be directly assessed for uniformity. It was on this premise that the original draft stratified sampling guidance document allowed the use of in-process dosage unit data as a surrogate to demonstrate dosage unit uniformity during routine manufacture(HARAPANHALLI 2009), in current study five points were selected for performing blend uniformity as already depicted in Figure 1.

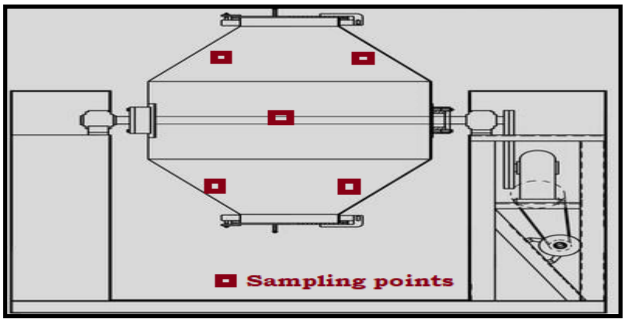

Figure 1. Random sampling location in double cone blender

***Determination* of %RSD**

Once you have determined the mean, you will then have all the information you need to calculate the relative standard deviation using the following formula:

(S x 100)/x = relative standard deviation.

2. Application of Quality by design approach for optimization of blend homogeneity

2.1 Development of Quality target product profile

A patient centric QPTT was developed considering safety, efficacy and quality of product as a target (Table 1).

Table 1 depicts the derived quality target product profile for the development of uniform blend

QTPP Element	Target	Justification
Drug Product attributes Physical Appearance Colour Odour Texture	White Odourless Uniformly mixed powder	Mixing is a precursor step for the tablet manufacturing in all the methods adopted. Physical appearance of powder doesn't significantly affect product quality. Further, the physical appearance depends on the material attributes of API and excipients. Physical appearance is required to achieve pharmaceutical equivalence.
Identification Assay	Positive for API 100% W/W of labelled claim	Identification and assay are important parameters to ensure pharmaceutical equivalence. Assay is considered significant for confirmation of claimed drug present in dosage form which finally affects proper therapeutics response.

Blend Uniformity	99-100%	Ideal limit of blend uniformity is 98-102%. The powder obtained after mixing has to undergo further processing steps like granulation and compression hence the limits of blend uniformity were constricted further.
RSD	< 2%	%RLD value has to be below 2% in order to ensure no demixing between API and Excipients. Relative standard deviation of a mix is indicative of blend homogeneity.
Dissolution Parameters	> 80% drug release in 30 min.	To ensure pharmaceutical equivalence. It must meet the same compendial standards of IR tablets.
Other Parameters **1.** Degradation products **2.** Residual Solvents **3.** Water Content **4.** Microbial Limits	Long term stability	Degradation products, residual solvent can impact the safety and must be controlled based on compendial requirements of RLD. It is required to maintain product safe and effective during its shelf life.

3.2 Development of Critical Quality Attributes

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. The derived critical material attributes and critical process parameters responsible for critical quality attribute are shown in the Table 2 along with their justification.

Table 2 Critical Quality Attributes

Quality Attributes of drug Product	Target	Is this a CQA?	Justification
Physical Appearance	Should be acceptable to patient	No	Physical appearance is not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
Identification	Positive for API	Yes*	Though identification is critical for safety and efficacy this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variable do not impact identity.
Assay	100% W/W of labelled claim	Yes*	Assay is considered significant for safe and effective delivery of API from the dosage form.
Blend Uniformity	99-100%	Yes	The FDA indicated that there is a strong need for routine blend uniformity testing following process validation to ensure content uniformity within the blend. It is insufficient to show that adequate distribution of the drug is obtained in the final product; it must be demonstrated within the blend also. For blending as a pre-step of granulation, the standard for the Blend uniformity can be kept as 99-100%. The powder obtained after mixing has to undergo further processing steps like granulation and

			compression hence the limits of blend uniformity were constricted further.
%RSD	< 2%	Yes	%RLD values has to be below 2% in order to ensure no demixing between API and Excipients. Relative standard deviation of a mix is indicative of blend homogeneity
Dissolution	NLT 80%at 30 min.	Yes*	Failure to meet the dissolution specification can impact bioavailability. Process variables and formulation variables can affect the dissolution profile. Dissolution can be managed if the blend uniformity is achieved hence, it will not be considered for current unit operation.
Micromeritical Properties	Angle of repose < 25 Carr's Index < 5-15	Yes*	Micromeritical properties of powder are important for further unit operations like granulation and compression for content uniformity and assay. The Micromeritical properties can be managed by addition of glidants hence this will not be considered critical.
* These parameters are critical, but they can be managed hence will not be evaluated further.			

3.3 Risk assessment

According to the ICH-Q9 guideline, risk identification and analysis should be performed to identify the highest risk variables. Subsequently a complex design strategy should be established to define the product or process design space. The first step in the risk assessment was to systematically gather up all the possible factors that could influence product quality. The risk assessment was performed in qualitative as well as quantitative way as described in the following sections.

3.4 Qualitative risk assessment

As a part of qualitative risk assessment an Ishikawa diagram was prepared. In order to identify the possible factors literature review was carried out, along with those past experiences and data of preliminary studies were used to organize a hierarchically using an Ishikawa diagram. For the identification of formulation and the process parameters regarding the given manufacturing method and for the evaluation of their potentials to influence the CQAs, an Ishikawa diagram was constructed to establish a potential cause-effect relationship among the factors (CMAs & CPPs) and CQA employing MS VISIO® software.

3.5 Quantitative risk assessment

Further quantification of risk factors was carried out using Failure Mode and Effect Analysis (FMEA). In order to detect the plausibility of failure modes associated with drug product FMEA was carried out.

Using FMEA(Ebrahemzadih, Halvani et al. 2014), the failure modes can be prioritized for a product or process for risk management process according to the seriousness of their consequences (effects), how frequently they occur and how easily they can be detected. The relative risk that each drug substance attributes can present was ranked according to risk priority number (RPN). Those attributes that could have a high impact on the drug product attributes needs to be studied in detail while those attributes that have lower impact on drug product attributes required no further investigation.

The RPN can be calculated using the equation (4), mentioned below.

RPN= Occurrence (O) *Severity (S) *Detectability (D) ……………………..(1)

3. Factor screening using Plackett Burman Design

Factor screening studies were further carried out on the input variables short-listed using REM and FMEA analysis to finally embark upon CMA and CPP employing Plackett Burman Design(Arora, Thakkar et al. 2020). An 8 factor-12 run Plackett Burman (Software: Minitab) design was used for the factor screening studies to identify the effect of each critical material attributes and critical process parameter on the CQAs.

Table 3. Screening variables and their levels in Plackett Burman Design

Sr. No.	Independent Variables	Code	Level used, Actual (Coded)	
			Low (-1)	High (+1)
1	Blend particle size distribution	**A**	Narrow	Wide
2	Humidity & Temperature	**B**	30%RH & 20°C	40%RH & 25°C
3	Fill volume	**C**	50%	90%
4	Blending time	**D**	5 min	50 min
5	Moisture content	**E**	Low	High
6	Flow properties	**F**	Poor	Excellent
7	Weight ratio of API to Excipient	**G**	1:1	1:4
8	Blender Speed	**H**	5 rpm	50 rpm

Derivation of design space using 3^2 full factorial design

In the present study, the 3*2 full factorial design was performed in Design Expert (Ver.10) software using Blending speed (X1) and Blending Time (X2) as independent variables while % blend uniformity (Y1) and %RSD(Y2) were selected as dependent variables (Kusumorini, Nugroho et al. 2021).

Table 4 Layout of full factorial design along with response value

Batches	Coded Value		Actual Value		Responses	
	X1 (Speed)	X2 (Time)	X1 (Speed)	X2 (Time)	Y1 (BU)	Y2 (%RSD)
B1	-1	-1	5	5	90.12	8.49
B2	0	-1	15	5	94.53	5.86
B3	1	-1	25	5	95.07	5.28
B4	-1	0	5	10	96.32	2.20
B5	0	0	15	10	99.13	0.93
B6	1	0	25	10	97.33	2.99
B7	-1	1	5	15	97.77	3.50
B8	0	1	15	15	98.56	2.44
B9	1	1	25	15	98.05	3.86
B10	0	0	15	10	98.68	1.03
B11	0	0	15	10	98.72	1.48
B12	0	0	15	10	99.27	1.00
B13	0	0	15	10	98.89	0.85

4. Results and Discussion

5.1 Qualitative risk assessment

The Ishikawa diagram providing the cause-effect relationship among the factors affecting the drug product CQAs is depicted in Figure 2.

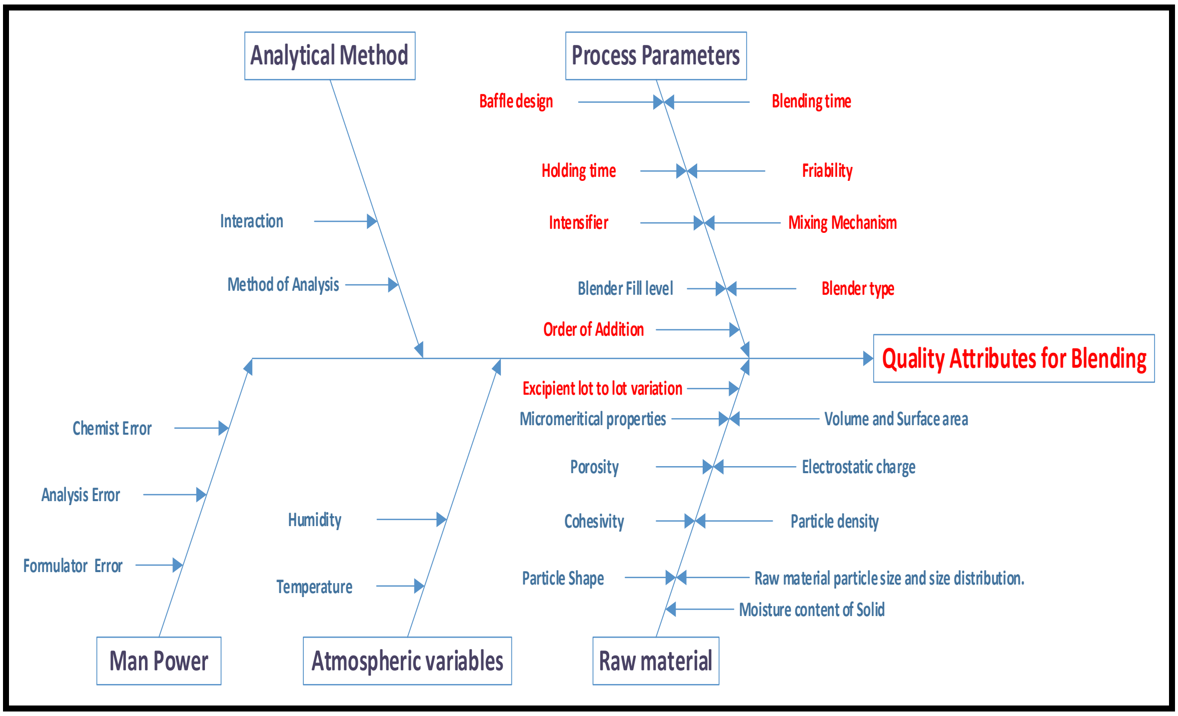

Figure.2. Ishikawa diagram establishing cause-effect relationship for quality attributes for blending.

5.2 Quantitative risk assessment

For quantitative risk assessment RPN score was calculated for all the factors considering following scenarios. Occurrence is the probability or the likelihood of an event to occur it was ranked as 5, frequent; 4, probable;3, occasional;2, remote and 1, improbable to occur. Severity is a measure of how severe of an effect a given failure mode would cause. This was ranked as 5, catastrophic; 4, critical; 3, serious; 2, minor and 1, negligible or no effect. The final parameter is detectability which means the ease that the failure mode can be detected. The more detectable a failure mode is, the less risky it presents to product quality. For D the rank was given as 1, absolutely certain or easily detectable;2, high detectable;3, moderately detectable;4, low or remote detectable and 5 as hard to detect or absolute uncertain.

Table 5. Summary of FMEA analysis illustrating RPN scores for various formulation and process variables.

Sl. No.	Quality Attributes	O	S	D	Total
1	Blend Particle size distribution	3	3	3	27
2	Particle shape	3	2	2	12
3	Particle density	3	2	3	18
4	Humidity and Temperature	3	3	3	27
5	Blender Speed	3	4	4	48
6	Porosity	2	2	2	8
7	Volume	3	3	3	27
8	Electrostatic charge	2	3	2	12
9	Surface area	2	2	2	8
10	Flow properties of material	4	3	3	36
11	Moisture content of solid	3	4	3	36
12	Blender fill level	2	2	2	8

13	Weight ratio of API/Excipients	4	3	3	36
14	Blending time	3	4	4	48

Out of the all the mentioned variables, eight variables were selected having the RPN score more than 20 and they were taken further for screening study.

5.3 Factor screening using Plackett Burman Design

The results of placket burman design are shown in Table 4. The Pareto charts plotted for each response are mentioned in Figure 3. As shown in figure 3 the blender speed (H) and Blending time (D) were found to be significant as confirmed by factorial regression analysis for blend uniformity, while the blending time has significant effect on %RSD. Based on the above-mentioned responses, blending time and blender speed were selected for further optimization whilst other parameters were kept on low levels.

Table 6 Plackett Burman experimental design matrix (in coded level) and experimental results

No.	A	B	C	D	E	F	G	H	BU (%)	RSD (%)
1	1	-1	1	-1	-1	-1	1	1	95.74	6.08
2	1	1	-1	1	-1	-1	-1	1	97.44	4.06
3	-1	1	1	-1	1	-1	-1	-1	98.7	2.5
4	1	-1	1	1	-1	1	-1	-1	99.25	1.16
5	1	1	-1	1	1	-1	1	-1	99.03	1.34
6	1	1	1	-1	1	1	-1	1	90.62	6.25
7	-1	1	1	1	-1	1	1	-1	99.04	1.27
8	-1	-1	1	1	1	-1	1	1	98.23	1.66
9	-1	-1	-1	1	1	1	-1	1	98.33	2.85
10	1	-1	-1	-1	1	1	1	-1	99.09	1.3
11	-1	1	-1	-1	-1	1	1	1	93.52	7.31
12	-1	-1	-1	-1	-1	-1	-1	-1	98.84	0.82

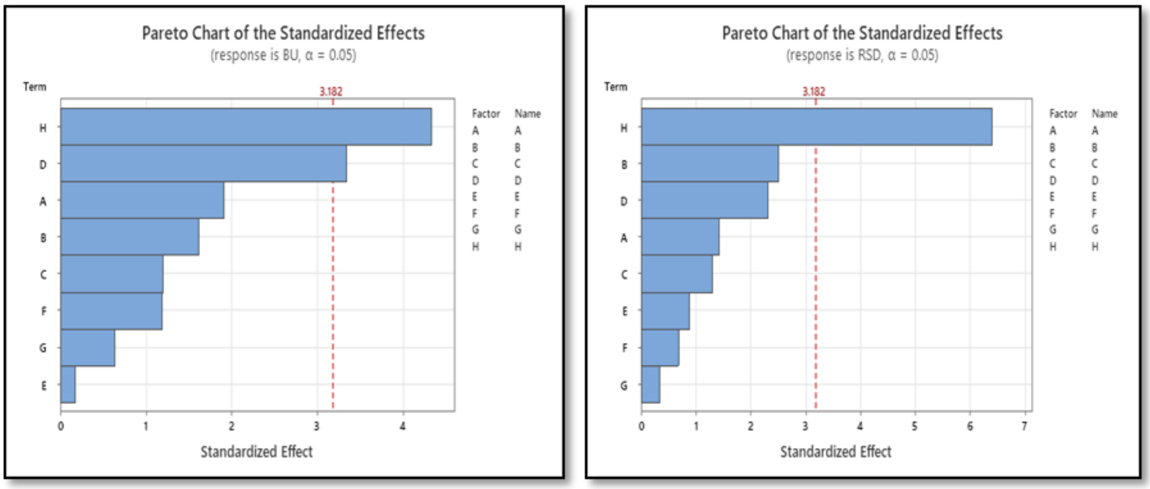

Figure 3. Pareto charts for blend uniformity and %RSD

5.4 Derivation of design space using 3^2 full factorial design

A 3^2 full factorial design was used for further optimization of selected parameters suggested by placketburman design. The polynomial equations for blend uniformity and %RSD are shown in the given equation below.

$Y1\ (BU) = +98.82 + 1.04*X_1 + 2.44*X_2 - 1.1*X_1X_2 - 1.72*X_1^2 - 2.00*X_2^2$ ………………. (2)

$Y2\ (RSD) = +1.11 - 0.34*X_1 - 1.64*X_2 + 0.89*X_1X_2 + 1.34*X_1^2 + 2.90*X_2^2$ ………………. (3)

As observed from the polynomial equation the blend uniformity are positively affected by blending time and blender speed while the %RSD is negatively impacted by blending time and blender peed. Both the responses followed quadratic model as it can be observed by contour plots and confirmed by the ANOVA tables for blend uniformity and %RSD (Table 7 and 8), it explains the importance of interaction terms on the dependent variable.

Table 7 ANOVA table for Y1 (BU)

Source	Sum of Squares	df	Mean Square	F value	p value	
Model	78.61	5	15.72	51.50	<0.0001	Significant
X1	6.49	1	6.49	21.26	0.0025	
X2	35.82	1	35.82	117.34	<0.0001	
X1X2	5.45	1	5.45	17.86	0.0039	
X_1^2	8.14	1	8.14	26.67	0.0013	
X_2^2	11.01	1	11.01	36.08	0.0005	
Residual	2.14	7	0.31			
Lack of Fit	1.87	3	0.62	9.48	0.0273	
Pure error	0.26	4	0.066			
Cor Total	80.74	12				

Table 8 ANOVA table for Y2 (RSD)

Source	Sum of Squares	DF	Mean Sqaure	F value	P value	
Model	62.49	5	12.50	43.62	<0.0001	significant
X1	0.71	1	0.71	2.47	*0.1601*	
X2	16.10	1	16.10	56.21	0.0001	
X1X2	3.19	1	3.19	11.12	0.0125	
X_1^2	4.97	1	4.97	17.35	0.0042	
X_2^2	23.18	1	23.18	80.89	<0.0001	
Residual	2.01	7	0.29			
Lack of Fit	1.76	3	0.59	9.72	0.0262	
Pure error	0.24	4	0.060			
Cor Total	64.50	12				

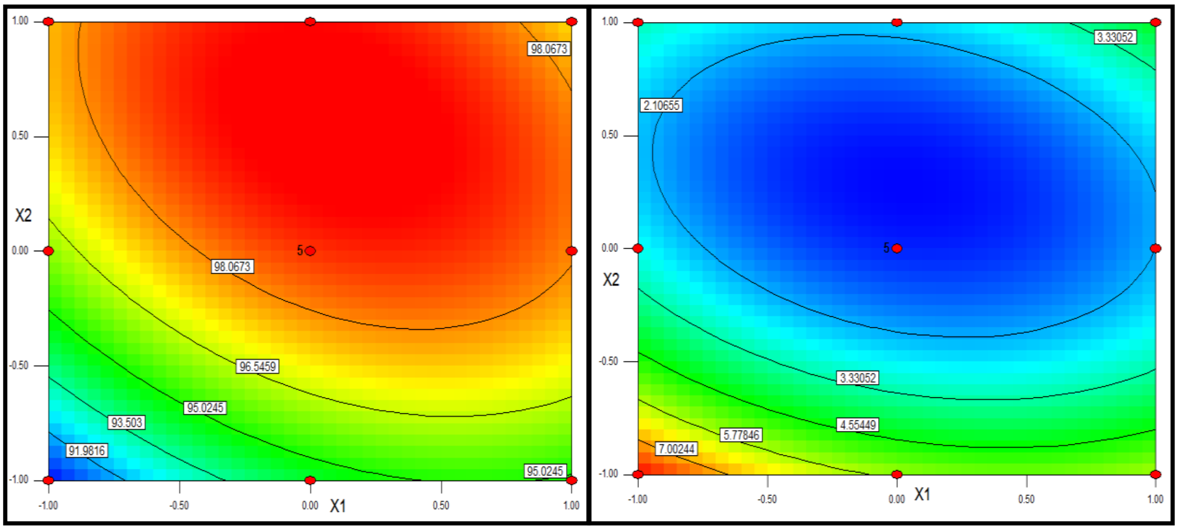

Figure 4. Contour plots for (A)blend uniformity and (B)%RSD for blending

Based on the results obtained a cut off values of 99-100% for blend uniformity and 0-2% for %RSD values and an overlay plot was obtained (Figure 5)

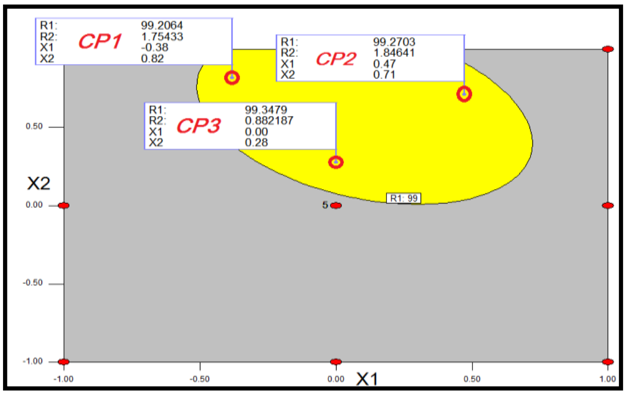

Figure 5. Overlay plot

Based on the given design space three check point batches were prepared, their composition is shown in the Table. %Prediction error was found to be less than 5% in all prepared checkpoint batches which confirms the prediction power of the model suggested by software.

Table 9. Check point batches composition

Batch	X1	X2	X1	X2
CP1	-0.38	0.82	11.2	14.1
CP2	0.47	0.71	19.7	13.55
CP3	0.00	0.28	15	11.4

Table 10. % PE between Experimental value Vs Predicted values

Batch	Y1 (BU)			Y2 (RSD)		
	Predicted	Experimental	%PE	Predicted	Experimental	%PE
CP1	99.21	98.67	0.544	1.75	1.85	5.714
CP2	99.27	98.75	0.523	1.85	1.93	4.324
CP3	99.34	99.05	0.292	0.88	0.92	4.545

5.5 Derivation of control space

For setting a risk-free blending operation, it is necessary to outline control space where the operation can be performed without any error and 100% quality can be assured. So, in following figure (figure 7) control space is marked (Green Square). The ranges of knowledge space, design space and control space are shown in Table 11.

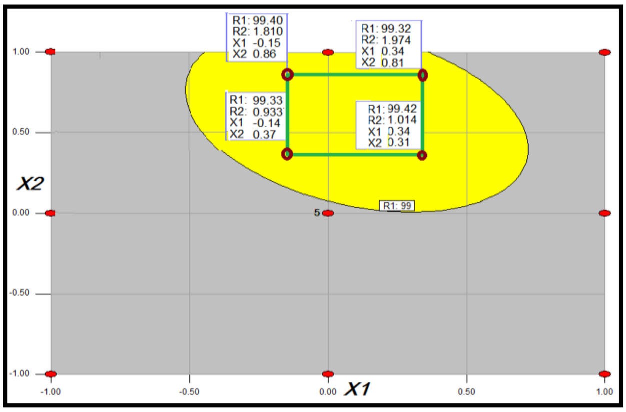

Figure 7 Derivation of control space

Table 11 Range of processing parameters

DoE region	Coded value		Actual value	
	Blending Speed (RPM)	Blending Time (Min.)	Blending Speed (RPM)	Blending Time (Min.)
Knowledge space	-1 to +1	-1 to +1	5-25	5-15
Design space	-0.5 to +0.72	0.0-1.0	10-22	10-15
Control space	-0.2 to 0.3	0.4-0.8	13-18	12-14

5. Conclusion

From the results of the presented study, it can be concluded that blending step is important step for QC Analysis testing (Assay and Content Uniformity) of final products. Applied QbD tools have assisted scientifically in outlining of control space. For the proposed material bed, if blending is performed in the optimized conditions (i.e., blending speed: 13-18 RPM and Blending Time: 12-14 Minutes), and Mixing Uniformity of blend can be assured with no risk of demixing.

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