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QbD Based Approach to Design Controlled Strategy for Wet Granulation Method Using Plackett Burman Design-Case Study

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Abstract

Objective: The objective of present work describes developing controlled strategy for wet granulation process by identifying critical process parameters and study was done using DoE in support of Quality by Design (QbD).

Material and Method: The manufacturing process involves wet granulation process, fluid bed drying, milling, blending, Lubrication, compression and coating. For wet granulation process identified critical process parameters were studies using, the Plackett-Burman factorial design to study four factors at two levels. The DOE was generated and analyzed using Design expert 8 software.

Results and Discussion: Total 12 trails and were conducted from RUN 1-12. All trials physical properties (bulk and tapped densities), tablet parameters and dissolution profile of the tablets were evaluated. Based on the results, it can be concluded that none of the CPP's have very significant effect on dissolution but impeller speed and wet massing time showed significant effect on disintegration time. At lower level of impeller speed and binder addition rate, higher level of wet massing time model demonstrated higher release profile.

Conclusion: Understanding of manufacturing process is of key importance to successful implementation of QbD approach. Using a Design of Experiments approach (Plackett Burman design), the range of operation for the critical process parameters, including the impeller RPM, the rate of water addition, mixing time and the kneading time range were proposed and established control strategy. Operational ranges of critical parameters should be optimized in order to produce quality product in a repeatable manner. Process outcomes within the spec limits indicate a lack of CPPs. Further these categorical variables were identified for use in registration and validation batch manufacture.

Keywords: CPP; Plackett-Burman; DoE, High shear granulation; CQA; DoE; QbD; Control strategy

Introduction

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. In addition, we can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters [1].

The manufacturing process development programme or process improvement programme should identify any critical process parameters that should be monitored or controlled to ensure that the product is of the desired quality.

Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. Once the significant parameters are identified, they can be further studied to achieve a higher level of process understanding.

Drug product Critical Quality Attributes (CQA) should be listed out and quantitatively described by target values and acceptance criteria. Excipients and packaging systems should be carefully selected taking into consideration drug product destination, patient's compliance, API stability and pharmacokinetics as well as manufacturing process suitability [2].

The manufacturing process is well understood when target product profile is defined, product composition and production route are established, critical process parameters (CPP) are selected, control methods developed, proven acceptable ranges (PARs) and design space are established [1].

Level of the process understanding seems to be in an inverse relationship with risk of producing poor quality products. Therefore, scientific understanding of processes would substantially facilitate implementation of changes.

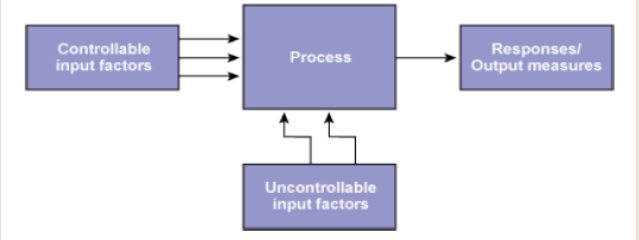

Figure 1: Relationship between the factors and responses [4].

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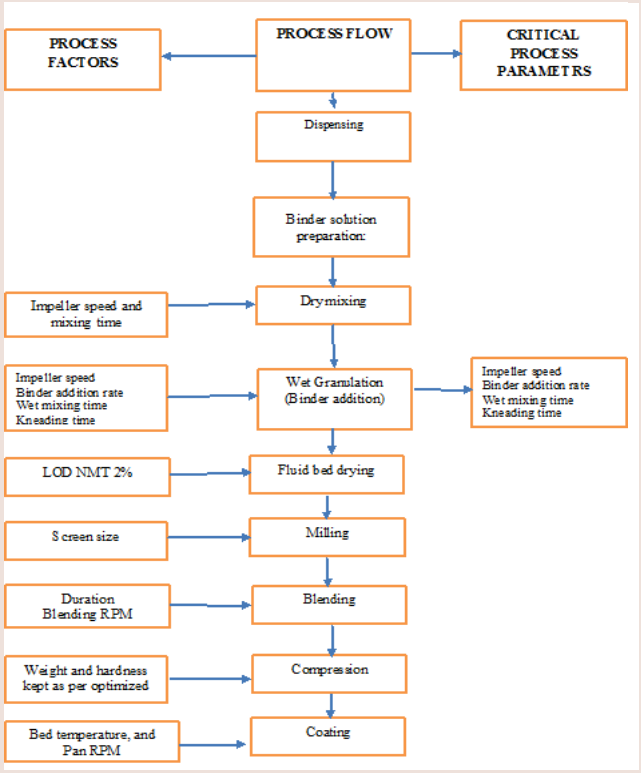

Figure 2: Process flow chart.

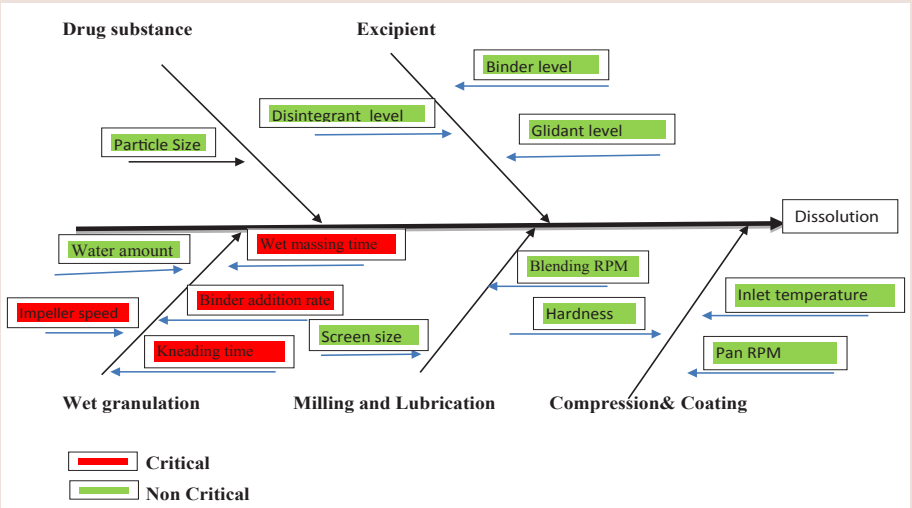

Figure 3: Effect of material attribute and process parameters (Wet granulation).

Design of experiments (DOE) is a systematic method to determine the relationship between factors affecting a process and the output of that process. In other words, it is used to find cause-and-effect relationships. This information is needed to manage process inputs in order to optimize the output [3].

The most commonly used terms in the DOE methodology include: controllable and uncontrollable input factors, responses, hypothesis testing, blocking, replication and interaction.

The controllable input factors can be modified to optimize the output. The relationship between the factors and responses is shown in Figure 1.

Generally, for test of k factors each at 2 levels, the factorial design requires 2k runs of experimentation. As the number of factors or levels increases, the number of runs increases rapidly: 4 factors at two levels need to be tested within 16 runs but 6 factors at two levels require 64 runs [2].

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Table 1: Critical parameters investigation of granulate containing PM01 substance manufacturing: Plackett-Burman Design (n = 12, k = 11). The main effects of the processes are presented. Only four factors were studied remaining were kept as dummy.

	Factors [k] screened for criticality				
RUN	**Impeller RPM (200 - 400)**	**Binder addition rate (100 - 150) gms /min**	**Actual time taken in seconds (80" - 54")**	**Wet mixing time (2 - 3 Min)**	**Kneading time (Sec) (30" - 60")**
1*	400	150	57	2	60
2	400	100	90	3	60
3*	200	100	82	2	30
4	200	100	81	3	30
5*	200	100	80	2	60
6*	400	150	52	2	30
7	400	150	62	3	30
8*	200	150	60	2	60
9*	400	100	83	2	30
10*	200	150	58	3	60
11*	400	100	84	3	60
12	200	150	84	3	30

*To these trails additional water was added. Additional water has no critical impact on CQA.

Table 2: Granulometry of lubricated granules.

Granules parameter	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10	Run 11	Run 12
Bulk density (g/ml)	0.44	0.4	0.43	0.42	0.44	0.43	0.39	0.43	0.43	0.44	0.45	0.42
Tapped density (g/ml)	0.52	0.5	0.52	0.52	0.53	0.52	0.49	0.52	0.51	0.54	0.53	0.52
Compressibility Index (%)	15.38	20.00	17.31	19.23	16.98	17.31	20.41	17.31	15.69	18.52	15.09	19.23
Hausner Ratio	1.18	1.25	1.21	1.24	1.20	1.21	1.26	1.21	1.19	1.23	1.18	1.24
Particle size Distribution												
Sieve # 20 ASTM	0.42	0.47	2.60	0.25	2.90	3.30	2.15	5.75	3.80	3.20	4.24	1.85
Sieve # 30 ASTM	30.32	24.03	43.28	34.47	47.34	41.58	34.11	39.85	40.73	35.71	46.38	29.58
Sieve # 40 ASTM	3.28	4.88	3.10	3.57	4.52	2.87	2.95	3.72	3.92	3.80	1.97	1.95
Sieve # 60 ASTM	11.23	9.04	9.12	9.14	7.42	8.90	8.89	8.72	10.14	8.72	7.56	7.53
Sieve # 80 ASTM	11.28	13.53	10.24	11.96	9.24	7.60	8.69	9.22	9.77	11.19	6.53	12.17
Sieve # 100 ASTM	12.76	11.47	9.77	10.06	8.91	7.87	6.49	8.77	8.20	9.52	6.41	9.95
Sieve # 200 ASTM	19.90	21.70	15.93	18.52	13.08	18.14	21.52	16.91	15.67	18.31	14.74	23.99
Pan	10.00	13.75	6.72	9.96	4.29	9.85	15.83	7.22	7.80	7.94	9.75	10.07
Sieve #60ASTM (Retain)	45.25	38.43	58.09	47.43	62.17	56.65	48.09	58.03	58.60	51.42	60.15	40.90
Sieve #60ASTM (passed)	53.94	60.46	42.66	50.50	35.53	43.45	52.53	42.12	41.43	46.95	37.43	56.18

Plackett-Burman (PB) designs are a class of fractional factorial designs first developed by two mathematicians/statisticians: R.L. Plackett and J.P. Burman, at the University of Newcastle in Northeast England in 1946 [3,6]. Plackett-Burman design is helpful or in the case of screening with a higher number of factors or if complete knowledge about the system is unavailable [7]. The design attributed to Plackett and Burman is a two level fractional factorial design. It enables to study k = N-1 variables in N runs, when N is a multiple of 4. In this way 7 factors can be tested within 8 runs, so number of trials may be reduced down to absolute minimum. The plan is dedicated for screening out numerous factors in order to choose the ones that mostly impact the process outcomes [2]. It is also reasonable to use PB designs when one wants to demonstrate ruggedness or robustness of equipment or processes [3].

In present system, product quality is ensured by fixing the process to produce the active ingredient, raw material testing, performing the drug product manufacturing process as described in a fixed batch record, in-process material testing, and end product testing [8].

Thus in present study Process risk analysis was performed to identify CPP effecting CQA's and develop a design space using placket Burman design and propose a controlled strategy for manufacturing process.

Experimental

Material and Methods

Materials: Active pharmaceutical agent coded as PM1, Pre-

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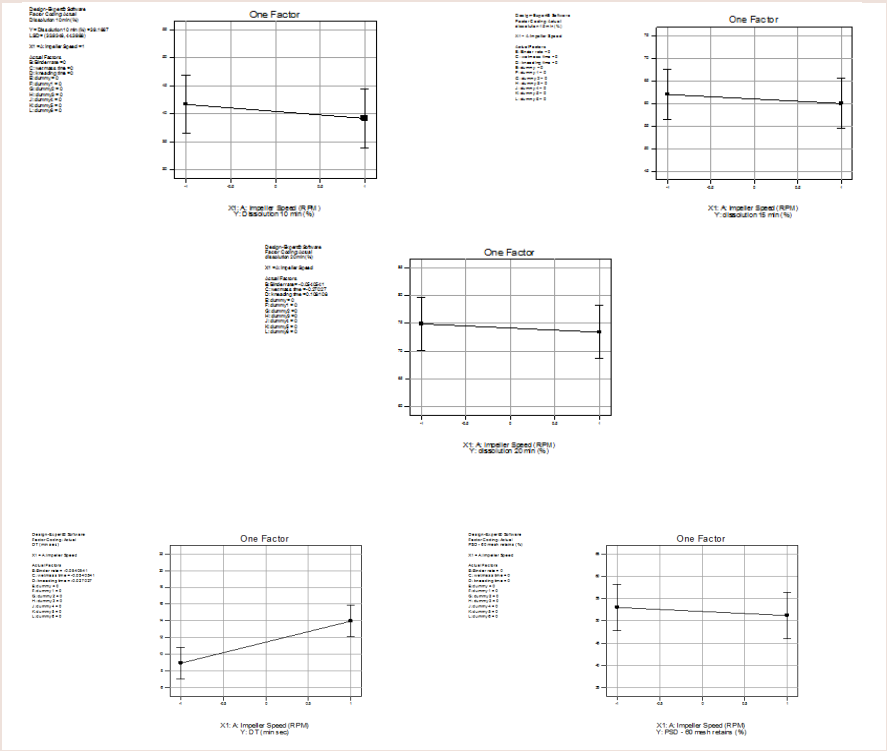

Figure 4: Individual factor effect on response.

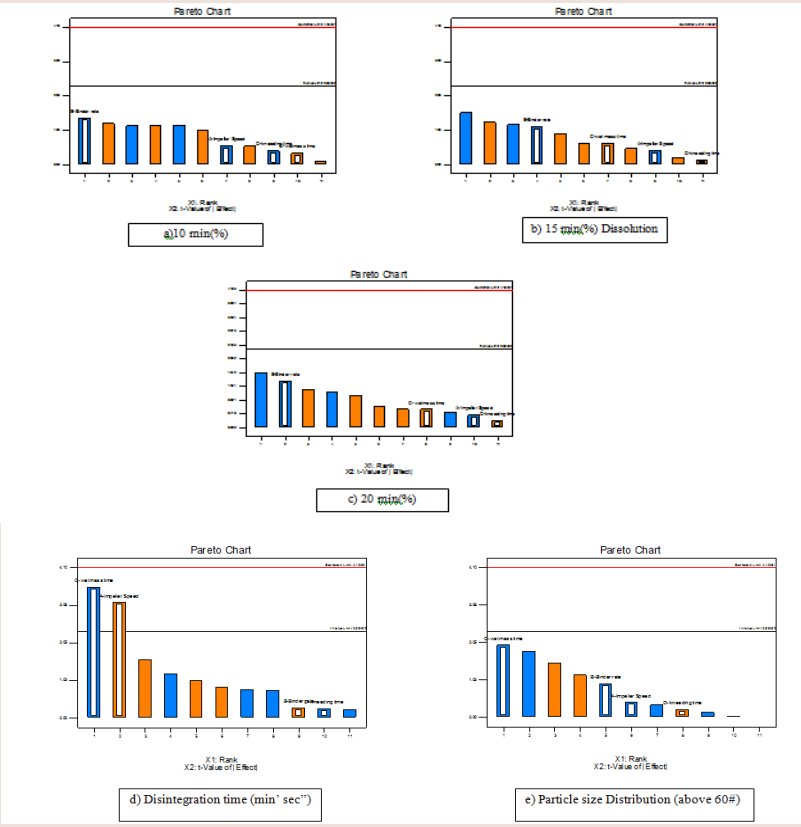

Figure 5: Pareto plot for all response.

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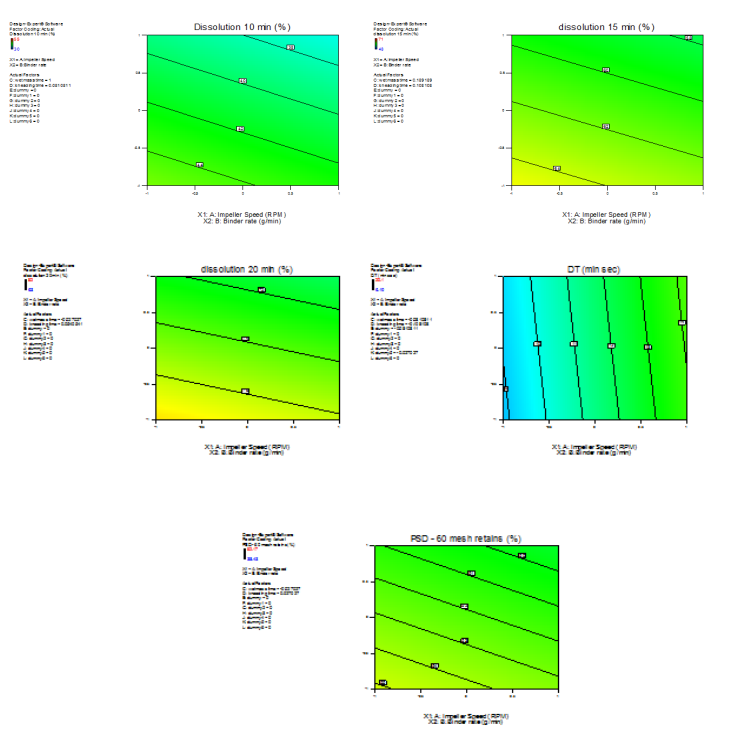

Figure 6: Counter plot for all response.

Table 3: Core Tablet parameters.

Parameters	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10	Run 11	Run 12
Average wt (gms)	8.16	8.2	8.2	8.1	8.27	8.25	8.13	8.24	8.25	8.13	8.16	8.2
Individual weight(mg)	795 - 827	816 - 827	804 - 831	808 - 820	792 - 854	807 - 837	806 - 821	801 - 842	813 - 837	804 - 819	795 - 827	816 - 827
Thickness(mm)	6.33 - 6.47	6.42 - 6.49	6.37 - 6.50	6.41 - 6.48	6.30 - 6.43	6.28 - 6.34	6.36 - 6.44	6.29 - 6.44	6.45 - 6.52	6.44 - 6.48	6.33 - 6.47	6.42 - 6.49
Hardness(N)	143 - 219	195 - 201	191 - 224	174 - 190	169 - 240	180 - 235	177 - 205	160 - 211	148 - 198	166 - 189	143 - 219	195 - 201
DT (min'' sec')	12'22" - 16'29"	9'26" - 12'21"	6'55" - 12'10"	4'55" - 5'50"	5'30" - 14'10"	12'10" - 16'21"	5'33" - 10'54"	7'14" - 9'20"	10'40" - 17'01"	7'16" - 9'10"	7'41" - 12'32"	7'42" - 11'24"
Friability (%)	0.08	0.09	0.07	0.09	0.05	0.08	0.06	0.07	0.05	0.08	0.07	0.02

Note: Tablet hardness had no much critical impact on disintegration time.

gelatinized Starch (STARCH 1500, colorcon), Sodium Lauryl Sulfate (BASF), Povidone K29/32(ISP TECHNOLOGIES), Colloidal Silicon Dioxide (Evonik), Sodium Starch glycolate (JRS), Stearic Acid (BASF), Magnesium Stearate (Perter-Geven). Purified water (USP) was used as granulating fluid. All material used were tested and released as per USP.

Equipment used: HMG 6 L granulator, GPCG fluid bed processor, CO-mill (Glatt) and halogen Moisture analyzer, KORSCH Tablet Compression Machine.

Instrument used: Disintegration Tester, Hardness tester, Friability tester.

Methods: API and Pregelatinized Starch is dry mixed in HMG followed by addition of binder solution containing Povidone and SLS to the dry mix blend. During granulation stage impeller RPM, the binder addition, wet massing time, kneading time were changed as per the Design trials. After granulation drying material was transferred tofluid bed processer and set the inlet air to achieve the satisfied material fluidization, set the inlet air temperature at 60 °C ± 10 °C. Granules dried till target LOD NLT 2% is achieved. The dry granules were milled through comil. Setup the bin blender. Put quantity of Sodium starch glycolate into Silica Colloidal anhydrous and mix manually and then put mixture into the bin Blender and mix the materials for 10 min and followed by lubrication using stearic acid and magnesium stearate for 5 minutes. The compression was performed in KORSCH machine. The coating was carried in Glatt coating machine with a tablet percentage buildup of 2% using Opadry coating suspension 750 mg. The details process flow is given in Figure 2.

In-process control

Bulk and tapped density: The bulk and tapped density were measured in accordance with USP.

Particle size distribution (PSD): The PSD of granulate was

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Table 4: Coated Tablet parameters.

Parameters	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10	Run 11	Run 12
Average wt	8.24	8.35	8.36	8.29	8.45	8.37	8.26	8.32	8.38	8.24	8.39	8.41
Individual weight(mg)	806 - 839	834 - 841	816 - 857	827 - 835	811 - 856	818 - 849	814 - 836	810 - 844	825 - 851	817 - 835	824 - 862	834 - 852
Thickness(mm	6.47 - 6.54	6.46 - 6.54	6.43 - 6.53	6.51 - 6.58	6.33 - 6.51	6.41 - 6.52	6.39 - 6.45	6.40 - 6.58	6.40 - 6.56	6.41 - 6.49	6.43 - 6.53	6.43 - 6.53
Hardness(N)	206 - 263	210 - 235	226 - 308	196 - 216	199 - 311	225 - 282	192 - 236	141 - 232	168 - 237	174 - 202	176 - 225	206 - 245
DT	9'58" - 20'10"	7'16" - 9'22"	6'01" - 11'24"	6'05" - 6'19"	7'15" - 13'22"	13'28" - 17'41"	7'05" - 9'51"	6'22" - 6'53"	12'57" - 16'42"	6'10" - 7'29"	8'57" - 10'26"	5'40" - 8'30"

Table 5: The main response are presented.

	Factors [k] screened for criticality					Response				
RUN	**Impeller RPM(A) (200 - 400)**	**Binder addition rate (B)(100 - 150) gms /min**	**Actual time taken in seconds (80" - 54")**	**Wet mixing time (C) (2 - 3 Min)**	**Kneading time (D) (30" - 60" Sec)**	**Dissolution %**			**DT (min' sec") NMT 30 Min**	**PSD Above 60#**
						10 Min	**20 Min**	**30 min**		
1*	400	150	57	2	60	35	54	66	9'58" - 20'10"	45.25
2	400	100	90	3	60	40	61	74	7'16" - 9'22"	38.43
3*	200	100	82	2	30	41	61	76	6'01" - 11'24"	58.09
4	200	100	81	3	30	55	71	79	6'05" - 6'19"	47.43
5*	200	100	80	2	60	37	60	77	7'15" - 13'22"	62.17
6*	400	150	52	2	30	30	48	63	13'28" - 17'41"	56.65
7	400	150	62	3	30	42	68	82	7'05" - 9'51"	48.09
8*	200	150	60	2	60	46	67	78	6'22" - 6'53"	58.03
9*	400	100	83	2	30	49	67	79	12'57" - 16'42"	58.60
10*	200	150	58	3	60	40	64	76	6'10" - 7'29"	51.42
11*	400	100	84	3	60	39	62	77	8'57" - 10'26"	60.15
12	200	150	84	3	30	31	49	64	5'40" - 8'30"	40.90

Table 6: DOE Summary: Statistical Analysis.

ANOVA Analysis	Dissolution 10 min		Dissolution 15 min		Dissolution 20min		Disintegration time		PSD #60 mesh Retained	
	p- values	Signal. Response effect	p- values	Signal. Response effect	p- values	Signal. Response effect	p- values	Signal. Response effect	p- values	Signal. Response effect
Impeller speed	0.5898	No	0.6846	No	0.7150	No	0.0160	**Yes**	0.6928	No
Binder addition rate	0.2061	No	0.2960	No	0.2058	No	0.7941	No	0.3837	No
Wet massing time	0.7446	No	0.5455	No	0.5998	No	0.0090	**Yes**	0.0877	No
Kneading Time	0.6911	No	0.8917	No	0.8387	No	0.8050	No	0.8355	No

Table 7: Control strategy for critical process parameters.

Input	Criticality	Control strategy
Process parameters		
Impeller speed	Demonstrated Not Critical	PAR: 200 - 300
Binder addition time	Demonstrated Not Critical	PAR: 50" – 80" sec
Wet massing time	Demonstrated Not Critical	PAR: 2 - 5 min
Kneading time	Demonstrated Not Critical	PAR:30 – 60 sec

PAR: proven acceptable range.

measured by sieve analysis performed in ERWEKA GTB. Test sample of 50 g was treated for 10 min under vibrations of 1.5 cm amplitude. Mass of granulate retained at each sieve was determined and presented as m/m percent.

Loss on drying: Loss on drying was analyzed in Mettler Toledo apparatus. Granulate in quantity of 5 g was dried at 70 °C to constant mass. The loss of mass was presented as percent m/m.

Thickness and Hardness: Thickness and Hardness of the tablets were measured. All the parameters were tested using Erweka apparatus.

Friability: The friability of tablets was checked using CS-2 tester. The analysis was done in accordance with USP method.

Disintegration time: Disintegration of tablets was measured by using Erweka ZT322 tester in line with USP method.

Dissolution: Tablets were tested as per USP monograph recommendation for the API PM01. Media used water, 900 ml using

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USP-II (paddle) at 50 RPM. Time point selected were 10 min, 15 min, 20 min, 30 min, 45 min and 60 min. Samples were Analysed at each time point using Agilent HPLC and detection wavelength at 274 nm.

Critical assessment

Qualitative and quantitative composition of tablets has been defined. Each tablet contained 750mg of PM 01drug substance and the total coated tablet mass was 840 mg. Process flowchart is shown in Figure 2.

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest to the sponsor for each process parameter [8]. Refer Table 1.

The Effect of material and process parameter attribute is described in Figure 2. As mentioned in figure the impeller speed, Binder addition time, wet massing time and kneading time were examined as CPP's. The drug product CQAs Mainly dissolution was studied along with this other CQA like particle size distribution and DT was studied. Acceptance criteria were established for each the CQA, as follows:

Results and Discussion

Feasibility trail were conducted as per the Placket Burman experimental design. Total 12 trails and were conducted from RUN 1-12. During the study RUN 1, 3, 5, 6, 8, 9, 10, 11 used additional water. All trials parameters were tested at core and coated stage. Data are represented in Tables 2 and 3. Three response were selected i.e.; dissolution (10 min, 15 min and 20mim), Particle size distribution of granules and Disintegration time (Table 4 and Figure 3). The effect of factors on response is represented in one factor graph, counter plot and Pareto graph respectively.

Among the selected CPP's, It is demonstrated that active substance dissolution depends on factors like impeller speed and wet massing time (Table 5). The p-value for each CPP's is listed in Table 6 shows the absolute effect values indicate magnitude of each factor impact on active substance dissolution. For one factor response in Figure 4, shows at lower impeller RPM release is more compared at higher RPM and granules formulation had no significant effect by impeller speed.

The One Factor Effects graph shows the linear effect of changing the level of a single factor. It is constructed by predicting the responses for the low (-1) and high (+1) levels of a factor. One factor at a time experimentation - it does not show you the effects of interactions.

It was observed that the low dissolution was determined when high levels impeller speed and lower wet massing time (run 6) contributed together, i.e., granulates were made at high impeller speed and short massing, the Plackett-Burman design due to its messy alias structure does not allow to estimate interactions among screened parameters [2]. Therefore, it was decided to assess criticality of each of the parameters (Table 7).

Based on the results, it can be concluded that none of the CPP's have very significant effect on dissolution but impeller speed and wet massing time showed significant effect on disintegration time. Speed of impeller blade affects collisions between granules. High impeller speed additionally increases temperature of agitated mass which may impact viscosity of binder solution and plasticity of particles. Duration of wet massing time influence on granule growth and showed increase of dissolution at higher level and reduced granular quantity. Binder addition rate at higher level showed reduced dissolution, decreased granular quantity and also increase in disintegration time. Kneading time at higher level showed slightly increase in release, more granular quantity and reduced disintegration time.

The blend PSD, therefore, likely governs the initial onset of the dissolution rate. DOE analysis using the Design Expert® indicates that the CPPs (wet massing time and binder addition rate) their combinations had significant impacts on blend PSD as seen in the Pareto chart in Figure 5. Also disintegration time is direct measure of dissolution; CPP's (wet massing time and impeller speed) had significant effect. But model represents the CPP's effects are below the Bonferroni Limit suggesting almost certainly no significant effect.

The contour plots (Figure 6) describe the relationship between the impeller speed and binder addition rate at lower level the interaction effect showed increased release profile and reduced disintegration.

Conclusion

Understanding of manufacturing process is of key importance to successful implementation of QbD approach. Using a Design of Experiments approach (Plackett Burman design), the range of operation for the critical process parameters, including the impeller RPM, the rate of water addition, mixing time and the kneading time range were proposed and established control strategy. Operational ranges of critical parameters should be optimized in order to produce quality product in a repeatable manner. Process outcomes within the spec limits indicate a lack of CPPs. Further these categorical variables were identified for use in registration and validation batch manufacture. Thus, a control strategy is established to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production.

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