A Quality by Design Approach to Optimize and Accelerate Formulation and Process Development Leading towards Registration Batches Manufacturing

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PURPOSE

- Roller compaction is a commonly used size enlargement unit operation in the pharmaceutical industry. It is often preferred to overcome unfavorable physical properties of powders and active pharmaceutical ingredients (APIs) that include poor flow, low bulk density, blend uniformity, and segregation of powder blends by optimizing Critical Process Parameters (CPPs) and excipients
- Roller compaction processes are shown to have notable effects on particles size distribution, flowability, homogeneity, compressibility, compactability of APIs, and excipients which can consequently affect dissolution profiles, disintegration times, hardness and other post compression parameters of tablets

OBJECTIVE

- To improve the existing formulation composition and manufacturing process of compound X which was designed for early phase development
- Process optimization activities focused on improving the flow characteristics of the granules, minimizing or eliminating segregation and increasing the manufacturing yield with the aim of achieving a robust process prior to the product registration campaign

METHODS

- Blending was done using the Bohle Bin Blender
  - Pre-blend was prepared in 300 L at 70% fill volume with 480 revolution
  - Final-blend was prepared in 300 L at 55% fill volume with 60 revolutions
- Roller compaction using Gerteis Minipactor
  - Critical material attributes, formulation variables and Critical Process Parameters (CPPs) of the roller compaction process were identified
  - Process parameters such as roll force, roll speed, roll gap, and granulator speed on the Critical Quality Attributes (CQAs) of the drug product were studied in sub-batches (Batch size:1 kg) to evaluate powder flow, solid fraction of compacted granules, content uniformity and dissolution
- Design of experiment (DoE, JMP software) with 4 factors and 2 levels was utilized to evaluate the parameters of significance in the manufacturing process
- Effect of granulator screens (0.8 mm and 1.25 mm vs target 1.0 mm) was studied in separate experiments
- Point optimization analysis was performed based on the input of ideal target response variables to identify and establish target process parameters
- Impact of Filler 1 to Filler 2 ratio (1:3 to 3:1), disintegrant levels (2 to 8%) and lubricant levels (0.2 -0.8%) were also studied for their impact on drug product CQAs

FORMULATION COMPOSITION

Description	Function
Intra-Granular	
Compound X (API)	Active Pharmaceutical Ingredient
Microcrystalline Cellulose (Avicel PH 102)	Diluent
Mannitol (Pearlitol 100SD)	Diluent
Croscarmellose Sodium (Ac-Di-Sol)	Disintegrant
Colloidal Silicon Dioxide (Cab-O-Sil)	Glidant
Magnesium Stearate	Lubricant
Extra-Granular	
Magnesium Stearate	Lubricant

Proportional weights were used to fill the capsules of different strengths (10/20/40/60 mg)

PRE- BLENDING & ROLLER COMPACTION

Drug Product CQA	Screen size	Blend Time	Roll Type	Roll Speed	Roll Force	Screw Speed	Granulator Screen	Granulator Speed
Compaction			Medium	Medium	High	Medium		
Dissolution	Low	Medium	Medium	Medium	High	Medium	Medium	Medium
Granule Density				Medium	High	Medium	Medium	Medium
Flow				Medium	High	Medium	Medium	Medium
Content Uniformity AQL Defect	Low	High						
		High						

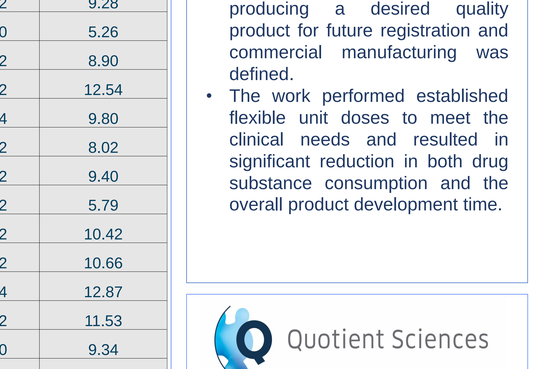
FINAL BLENDING, ENCAPSULATION, POLISHING & WEIGHT SORTING

Drug Product CQA	Blend Time	Capsule weight	Capsule Closure	Encapsulator speed	Tamping	Brush Speed
Assay		Medium			Medium	High
Dissolution	Medium				Medium	
Appearance			Medium	High		Low
AQL defect	High		Medium			
Content Uniformity	Medium			Low		High

CRITICAL QUALITY ATTRIBUTES OF DRUG SUBSTANCE

Drug Product CQA	Purity	Solid State Form	Particle Size Distribution	Solubility	Particle Morphology	Powder Flow Characteristics	Hygroscopicity
Assay/ Degradants	Low						
Dissolution		Medium	High	Low	Low		
Related Substances		Low					
Water Content/ Stability		Medium					Medium
Content Uniformity			High		Low	Low	

MANUFACTURING PROCESS

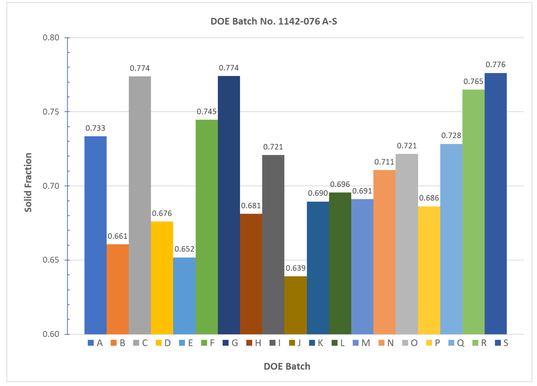


RESULT(S)

- Solid fractions of compacted ribbons studied at various roller compaction conditions were within the range of 0.63-0.78 with optimum solid fraction values of 0.70
- Optimum ranges for roll speed, roll gap, roll force and granulator speed were established
- The order of impact of process parameters in influencing granule properties was roll force > roll gap > granulator speed > roll speed
- Uniformity sample analysis demonstrated that risk to uniformity reduced by adjusting the number of blender revolutions and maintaining the ideal blender fill volume throughout the scale up
- The process was scaled up from 11 kg to 85 kg by maintaining the number of revolutions constant from 40L bin to 300L bin with RSD values less than 2%
- Blends consisting of varying amounts of filler, disintegration and lubricant levels processed at optimized conditions resulted in acceptable dissolution profiles confirming robustness of the formulation developed
- Selection of appropriate capsule size and dosing disc allowed manufacturing of a range of doses for clinical supply to support ongoing clinical trials and to finalize suitable doses for registration batches
- Parallel formulation and manufacturing process parameters optimization allowed the program to accelerate towards registration batch manufacturing phase once the final capsules strengths are confirmed

ROLLER COMPACTION PROCESS PARAMETERS

Parameter	Low	Target	High
Compaction force (kN)	5 (-1)	7 (0)	9 (+1)
Roller speed (rpm)	2 (-1)	4 (0)	6 (+1)
Gap width (mm)	1 (-1)	2 (0)	3 (+1)
Granulating speed (rpm)	45 (-1)	65 (0)	85 (+1)
Screen size (mm)[A]	0.8 mm	1.0 mm	1.25 mm



ROLLER COMPACTION PROCESS PARAMETERS (19 batches)

Run #	Factor 1 Compaction Force (kN)	Factor 2 Roll Speed (rpm)	Factor 3 Gap Width (mm)	Factor 4 Granulator Speed (rpm)
1	0 (7KN)	0 (4rpm)	0 (2mm)	0 (65rpm)
2	-1(5KN)	-1(2rpm)	1(3mm)	-1(45rpm)
3	1(9KN)	-1(2rpm)	-1(1mm)	-1(45rpm)
4	-1(5KN)	1(6rpm)	1(3mm)	-1(45rpm)
5	-1(5KN)	-1(2rpm)	1(3mm)	1(85rpm)
6	1(9KN)	-1(2rpm)	1(3mm)	1(85rpm)
7	1(9KN)	-1(2rpm)	-1(1mm)	1(85rpm)
8	-1(5KN)	1(6rpm)	-1(1mm)	-1(45rpm)
9	1(9KN)	1(6rpm)	1(3mm)	-1(45rpm)
10	-1(5KN)	1(6rpm)	1(3mm)	1(85rpm)
11	0 (7KN)	0 (4rpm)	0 (2mm)	0 (65rpm)
12	-1(5KN)	-1(2rpm)	-1(1mm)	1(85rpm)
13	-1(5KN)	-1(2rpm)	-1(1mm)	-1(45rpm)
14	0 (7KN)	0 (4rpm)	0 (2mm)	0 (65rpm)
15	1(9KN)	-1(2rpm)	1(3mm)	-1(45rpm)
16	-1(5KN)	1(6rpm)	-1(1mm)	1(85rpm)
17	1(9KN)	1(6rpm)	1(3mm)	1(85rpm)
18	1(9KN)	1(6rpm)	-1(1mm)	-1(45rpm)
19	1(9KN)	1(6rpm)	-1(1mm)	1(85rpm)

BLEND UNIFORMITY DATA

Final Pre-Blend IBC

Location	Value (%)
A1	98.4
B1	97.9
C1	98.9
D1	98.7
E1	98.3
F1	100.4
G1	99.1
H1	99.6
I1	99.8
J1	99.0
K1	99.4
L1	96.6
Mean	98.8
SD	1.0
%RSD	1.0

Final Blend IBC

Location	Value (%)
A1	98.2
B1	98.0
C1	98.6
D1	97.9
E1	97.3
F1	97.9
G1	97.0
H1	97.6
I1	98.9
J1	97.4
K1	97.8
L1	96.9
Mean	97.8
SD	0.6
%RSD	0.6

CONTENT UNIFORMITY DATA

Run #	Mean	AV	RSD
1	98.44	4.2	0.017
2	96.33	6.8	0.020
3	99.46	6.6	0.028
4	95.94	5.3	0.012
5	95.45	7.4	0.019
6	96.64	9.4	0.033
7	96.15	7.7	0.023
8	92.72	12.7	0.031
9	91.79	17.2	0.048
10	92.88	12.8	0.032
11	95.56	9.0	0.026
12	94.00	13.0	0.038
13	93.48	13.2	0.036
14	90.00	17.3	0.041
15	91.65	16.9	0.046
16	97.51	7.1	0.026
17	94.39	12.9	0.039
18	97.32	10.5	0.040
19	96.86	8.7	0.031

FLOWABILITY MEASUREMENTS

Flodex	% Retention on Pan
12	8.68
14	14.29
10	1.56
14	16.47
14	15.74
12	9.28
10	5.26
12	8.90
12	12.54
14	9.80
12	8.02
12	9.40
12	5.79
12	10.42
12	10.66
14	12.87
12	11.53
10	9.34
10	7.73

CONCLUSION

- The adoption of parallel formulation development and QbD approach towards process optimization resulted in the identification of CPPs.
- Risks were successfully reduced to acceptable levels within the studied design space, and a robust manufacturing process producing a desired quality product for future registration and commercial manufacturing was defined.
- The work performed established flexible unit doses to meet the clinical needs and resulted in significant reduction in both drug substance consumption and the overall product development time.

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