Scale-up challenge of a Low-Dose Tablet Formulation through blending and roller compaction optimization

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PURPOSE

- Drug X, an aldosterone synthase inhibitor, is a high solubility, low permeability small molecule drug.
- The purpose of this investigation was to address the content uniformity challenge faced during the scale up for a low dose tablet formulation of Drug X on an accelerated development program. Experiments were performed to demonstrate optimized processing prior to clinical trial manufacturing (CTM).

OBJECTIVE

The following approach were investigated to improve content uniformity (CU) of the formulation:

- Addition of milling and blending steps with careful selection of order of addition and proportions of ingredients.
- Different parameters of roller compactor was studied to improve CU of granules.

METHODS

Roller compacted low dose tablets were scaled up from a 1 kg to 4 kg batch size using a V-blender with an identical fill volume maintained during the study. A pre-blend was roller compacted using a Gerteis Minipactor followed by final blending in the V-blender. Tablets were compressed using Korsch XL 100 equipment. A modified blending process was attempted with additional milling and mixing steps, and careful selection of order of ingredients of the current formulation and their proportion at each mixing step. API uniformity across roller compacted granules was then tested to understand the segregation potential of the final blend. In separate experiments, roller compaction parameters were studied in the range of 6-8 kN/cm roll force, 1.5-2.0 mm gap width at 0.8- and 1.0-mm screens. Finally, a CTM scale up batch at 4 kg batch size was manufactured using the optimized process parameters identified at each processing step.

Major modifications to the manufacturing process consisted of passing Drug X through a #60 mesh screen, geometric dilution, and introduction of Turbula mixture during Pre Blending. Drug X was blended with excipients in equal proportions until all excipients had been thoroughly mixed. All Microcrystalline Cellulose (MCC) was moved to intra-granular section to assist the geometric dilution method.

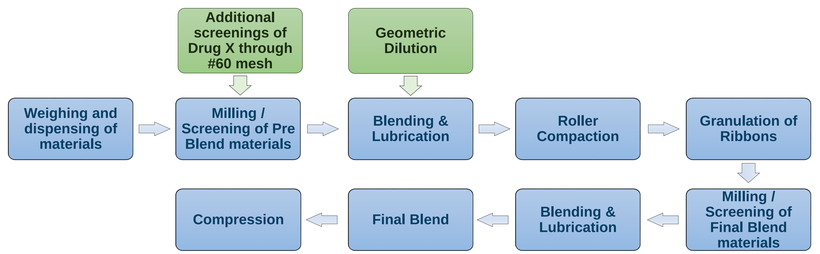

Figure 1: *Manufacturing flow chart of original and modified processes*

RESULT(S)

Initial Process Results

- Formulations for the initial process are documented in **Table 1**.
- Initial development batches were manufactured at 4 kg scale based on the 1 kg CTM batch process exhibited CU issues with extremely high Acceptance Value (AV) (**Tables 3-4, Figure 4**).
- Further evaluation of pre-blend and final blend Blend Uniformity (BU) data shows high variability of the drug content at various steps of the manufacturing process. (**Figure 2**).
- Stratified uniformity samples collected during 2 mg batch run using gravity feeder shows more variability and values were out of acceptable range (95.0 – 105.0%) (**Figure 5**).
- In addition, evaluation of the sieve cut analysis of the roller compacted granules results in the occurrence of segregation the during compression process, and suggests the need for redesign of both the blending and roller compaction activities (**Figure 3**).

Component	%w/w	
	1 mg	2 mg
Drug X	1.250[A]	2.500[A]
Lactose Anhydrous	38.375[B]	37.125[B]
Microcrystalline Cellulose	38.375	38.375
Croscarmellose Sodium	2.500	2.500
Colloidal Silicon Dioxide	0.750	0.750
Magnesium Stearate	0.250	0.250
Total Intra-granular	**81.500**	**81.500**
Microcrystalline Cellulose	15.000	15.000
Croscarmellose Sodium	2.500	2.500
Colloidal Silicon Dioxide	0.250	0.250
Magnesium Stearate	0.750	0.750
Total Extra-Granular	**18.500**	**18.500**
TOTAL	**100.000**	**100.000**

[A] Adjusted based on Use-as-Value of the API
[B] Adjusted based on Lactose Adjustment Calculation

Table 1: *Formulation of two dosages with initial process*

Component	%w/w	
	1 mg	2 mg
Drug X	1.250[A]	2.500[A]
Lactose Anhydrous	38.375[B]	37.125[B]
Microcrystalline Cellulose	53.375	53.375
Croscarmellose Sodium	2.500	2.500
Colloidal Silicon Dioxide	0.750	0.750
Magnesium Stearate	0.250	0.250
Total Intra-granular	**96.500**	**96.500**
Croscarmellose Sodium	2.500	2.500
Colloidal Silicon Dioxide	0.250	0.250
Magnesium Stearate	0.750	0.750
Total Extra-Granular	**3.500**	**3.500**
TOTAL	**100.000**	**100.000**

[A] Adjusted based on Use-as-Value of the API
[B] Adjusted based on Lactose Adjustment Calculation

Table 2: *Formulation of two dosages with modified process*

Batch size	1 kg Scale (CTM)		4 kg Scale (Development)			4 kg Scale (CTM)	
Manufacturing Process	Original Blending/Roller Compaction		Original Blending/ Roller Compaction			Modified Blending/ Optimized Roller Compaction	
Dose	2.5 mg	5 mg	0.5 mg	1 mg	2 mg	1 mg	2 mg
Drug Load	0.625%	2.500%	0.625%	1.250%	2.500%	1.250%	2.500%
Assay	97.0	97.6	95.0	97.8	90.5	98.0	99.0
SD	3.9	2.9	6.2	7.9	7.2	2.2	1.6
AV	**10.7**	**8.9**	**18.5**	**19.8**	**25.3**	**7.2**	**4.2**

Table 3: *Assay and Acceptance Value of original and modified process batches*

Tablet No.	0.5 mg	1 mg	1 mg (additional blending)	2 mg
1	92.5	102.5	97.9	82.7
2	85.9	91.2	100.6	80.9
3	85.8	89.9	97.4	97.8
4	98.9	91.9	96.1	101.9
5	103.1	100.6	130.4	94.2
6	99.5	115.4	97.2	93.2
7	96.0	91.2	95.0	81.8
8	99.9	103.3	92.7	86.5
9	89.2	96.6	92.0	91.5
10	99.0	94.9	95.5	94.5
Avg	**95.0**	**97.8**	**99.5**	**90.5**
SD	**6.2**	**7.9**	**11.1**	**7.2**
%RSD	**6.6**	**8.1**	**11.2**	**8.0**
AV	**18.5**	**19.8**	**26.8**	**25.3**

Table 4: *Initial Process Content Uniformity*

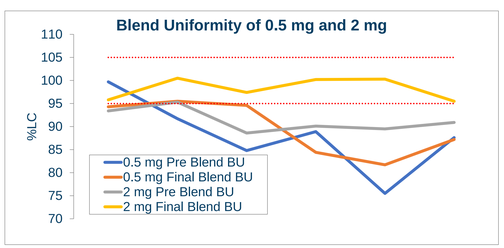

Figure 2: *Blend Uniformity of 0.5 mg and 2 mg development batches using original process*

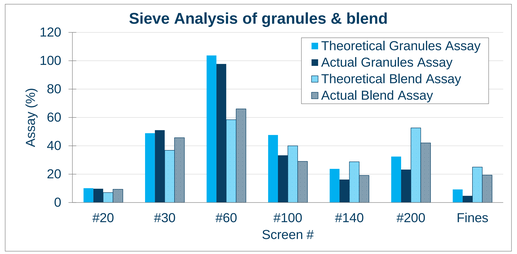

Figure 3: *Sieve Analysis of Roller Compacted Granules and Final Blend of Original Process Batch*

Modified Process Results

- Formulation for the modified process is documented in **Table 2**.
- Development trials with modified process utilize 2 different screen sizes for the granulator of the Roller Compactor, 0.8 and 1.0 mm, each screen size corresponded with different compression forces and gap sizes (**Figures 6-7**). Compaction force of 8 kN/cm, roll speed of 2 rpm, gap width of 2.0 mm with 0.8 mm screen size resulted in a more uniform distribution of granules (**Table 3**).
- Clinical batches manufactured at 4 kg with modified blending and roller compaction process resulted in mean assay of 98.0% (SD: 2.2 and AV= 7.0) and 99.0% (SD:1.6 and AV= 4.2) for 1 mg and 2 mg, respectively suggesting the success of the redesigned process towards achieving a robust process to meet the future clinical needs (**Figure 4**).

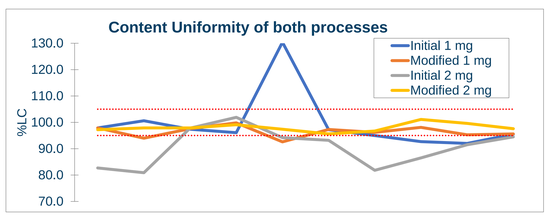

Figure 4: *Content Uniformity of initial and modified process of two dosages, 1 and 2 mg*

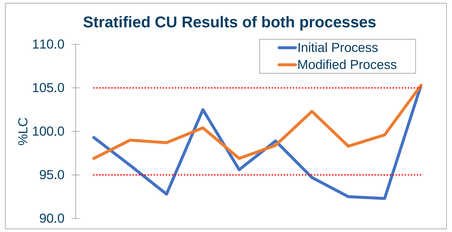

Figure 5: *Content Uniformity of Stratified samples from initial and modified process*

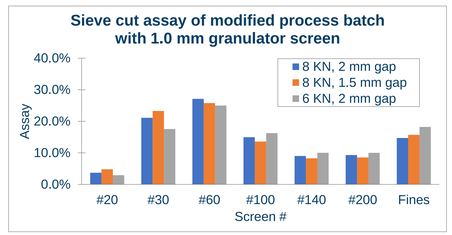

Figure 6: *Sieve cut assay of modified process batch utilizing 1.0 mm granulator screen during roller compaction*

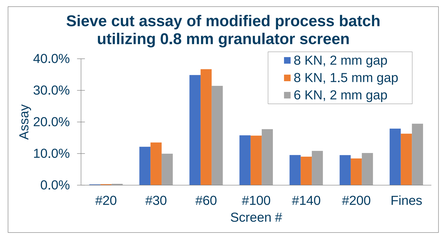

Figure 7: *Sieve cut assay of modified process batch utilizing 0.8 mm granulator screen during roller compaction*

CONCLUSION

Development of a pre-blending process with careful selection of order of ingredients and initial mixing steps, followed by optimization of roller compaction process parameters and usage of gravity feeder over force feeder, assisted in minimizing segregation potential and overcoming content uniformity issues during scale up of a low dose tablet formulation. Implementation of optimized mixing techniques combined with good process controls at early stages are key to the successful scale up of low dose products during accelerated drug development.

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