Development of a High Shear Wet Granulation Process Through the Use of Design of Experiments

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PURPOSE

Compound X is a micronized BCS class 2 drug substance with a very low bulk density (less than 0.2 g/mL), formulated at 75% drug load as an immediate release capsule. High shear wet granulation was selected as the method of manufacture to achieve sufficient densification to fit the required dose into a capsule shell. Water was used as the granulation medium and the process was successfully scaled up from prototype batch size (approximately 1.1 kg in a PMA-10 granulator) to Phase 3 clinical batch size (approximately 7 kg in a PMA-65) by keeping granulator fill volume, water quantity, and mixing times constant. Impeller speed for scale-up was determined via constant Froude number.

To meet estimated commercial projections it was necessary to increase granulator fill volume by approximately 50%. Since a change in fill volume often leads to changes in mixing efficiency within a granulator, it was necessary to completely re-evaluate wet granulation parameters. A DoE study was conducted at the increased fill volume to examine the effects of water quantity, impeller speed, and wet massing time on capsule dissolution (to target the Phase 3 clinical batch dissolution profile) and granulation flowability via Hanson Flodex for information purposes to provide an indication of potential weight variation during encapsulation.

From the DoE, it was determined that dissolution was impacted by wet massing time > impeller speed > water quantity. Granulation flowability was impacted by wet massing time > water quantity > impeller speed.

METHOD(S)

The DoE trials were manufactured in a 3 L high shear granulator (KG-3). The Phase 3 clinical batch served as a reference for the DoE study, where water quantity (Phase 3 ± 10%), wet massing time (Phase 3 ± 2 minutes), and impeller speed were examined for their impact on dissolution profile and granulation flowability. The fractional factorial study consisted of 4 trials (2^{3-1}) where high and low settings for each parameter were used in combination, plus one center point trial for a total of 5 trials.

It was determined that commercial scale batches would be manufactured in either a PMA-600 or PMA-1200, so the Froude number equivalents of the maximum and minimum achievable impeller speeds on the PMA-600 served as the high (530 rpm) and low (280 rpm) settings for the study, respectively. Since the impeller speed used for the Phase 3 clinical batch was already very close to the high setting for the study, it was not used as the center point for the study. Instead, the Froude number equivalent of maximum achievable impeller speed on the PMA-1200 (360 rpm) was selected as a more appropriate center point, though not perfectly in the middle of the high and low settings. Kneading times, drying endpoint, and milling parameters remained consistent across the study. A summary of the DoE trial settings is presented in Table 1.

Table 1: High, Center, and Low Settings used for Compound X Wet Granulation DoE trials.

Setting	Relative Water Quantity	Relative Impeller Speed	Relative Wet Massing Time
High	+1	+1	+1
Center	0	0	0
Low	-1	-0.7	-1

Phase 3 clinical capsules exhibited rapid dissolution and served as the target dissolution profile. Flowability was assessed via Hanson Flodex (critical orifice diameter) for information purposes to provide an indication of encapsulation performance. Each DoE trial was ranked for how closely their dissolution profile matched the Phase 3 clinical capsules and for their granulation flowability. Based on the dissolution and flowability rankings, each wet granulation parameter was weighted for their impact.

RESULT(S)

A summary of the DoE trial settings and their corresponding response factors is presented in Table 2 below.

Table 2: Dissolution and Flowability Rankings (lower number is better) from Wet Granulation DoE Trials at Increased Granulator Fill Volume.

		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Input Variable	Water Quantity	Center	High	High	Low	Low
	Impeller Speed	Center	Low	High	Low	High
	Wet Massing Time	Center	High	Low	Low	High
Response Factor	Dissolution Rank	4	3	2	1*	5
	Flowability Rank	3	1	4	5	2

**Matched the dissolution profile of Phase 3 clinical capsules*

Dissolution rate is typically inversely related to water quantity, impeller speed, and wet massing time. Higher values for these input variables typically give rise to larger, less porous particles. Trial 4, which used all low settings, had the fastest dissolution and was the only trial that had a dissolution profile that resembled Phase 3 clinical capsules.

Wet massing time appeared to have the strongest influence on dissolution, as Trial 3 (high water quantity, high impeller speed, and low wet massing time) had the second fastest dissolution despite the use of high water quantity and impeller speed.

Impeller speed appeared to be the next most influential parameter as Trial 2 (high water quantity, low impeller speed, high wet massing time) had the next highest dissolution rank.

Water quantity appeared to have the weakest influence on dissolution, where Trial 5 (low water quantity, high impeller speed, high wet massing time) had the slowest dissolution.

Wet massing time appeared to also have the greatest influence of flowability, followed by water quantity, and then finally by impeller speed. Although Trial 4 (all low settings) had the poorest flowability of all the trials, priority was given to matching the dissolution profile of Phase 3 clinical capsules, and Trial 4 was the only trial to achieve this benchmark. In addition, the poor flowability of Trial 4 was still deemed to be sufficient to attain acceptable weight variation during encapsulation on an automatic encapsulator.

The dissolution and flowability rankings of the center point batch may have changed if impeller speed was the midpoint of the high and low settings; however, the rankings of the other DoE trials would remain the same relative to one another other.

A summary of the wet granulation input variables and their relative effect on dissolution and flowability is presented in Table 3.

Table 3: Effect of Water Quantity, Impeller Speed, and Wet Massing Time on Dissolution and Flowability for Compound X (*lower number means greater magnitude of effect*).

Input Variable	Relative Effect on Dissolution	Relative Effect on Flowability
Water Quantity	3	2
Impeller Speed	2	3
Wet Massing Time	1	1

CONCLUSION(S)

DoE was used to evaluate the effects of wet granulation parameters of water quantity, impeller speed, and wet massing time for their effect on response factors of capsule dissolution and granulation flowability for Compound X. From the study it was determined that dissolution was affected by wet massing time > impeller speed > water quantity. Granulation flowability was affected by wet massing time > water quantity > impeller speed.

Learnings from the wet granulation DoE study (low water quantity, impeller speed, and wet massing time) were applied to further development batches for Compound X. Granulations were ultimately scaled up in a PMA-600 granulator and used in the successful manufacture of capsules for Registration.

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