Evaluate Impact of Spray Drying Process Parameters and Equipment Type on the Granule Characteristic of the Immediate Release Tablets of a BCS (Biopharmaceutical Classification System) Class –IV Drug

Saurabh Shah, Lalji Kathiria, Milan Babu

saurabh.shah@thermofisher.com | lalji.kathiria@thermofisher.com | milan.babu@thermofisher.com

Thermo Fisher Scientific

aaps PharmSci 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

To study the impact of spray drying process parameters and equipment type on the granule characteristics of immediate release (IR) tablets containing a high drug load (40%).

METHOD(S)

Spray drying process for IR product was developed using a Niro Aeromatic S2 fluid bed granulator (FBG) (campaign 1). The process was linearly scaled up from Aeromatic S2 to S4 FBG (campaign 2). Variation in content uniformity (CU), as evidenced by high Acceptance value (AV), was observed as a result of increased granule particle size. Particle size reduction through milling study shown lower AV warranted further development on granule properties. In order to identify the processing conditions that resulted in unexpected increase in granule particle size, two granulations study (campaign 3) were evaluated. Several changes such as bowl fill volume, binder spray rate, airflow were made in campaign 3 to identify the process parameters that could influence the granule particle size. The bowl fill for both batches was reduced from 74% to 37% and as a result, the binder spray rate was reduced to accommodate the smaller bowl size. In addition, the airflow for both batches was reduced to 650 cfm in order to align the superficial velocity which was used for previous small-scale batches produced on S2 FBG. Based on results from campaign 3, changes were implemented in campaign 4 including the increased spray-shake cycle interval. Three registration stability batches (campaign 5) were manufactured using parameters identified during campaign 4.

The process was then transferred from S4 FBG to MP4 FBG. A development batch (campaign 6) was manufactured to demonstrate comparability between the S4 and MP4 FBG. Given that the S4 and MP4 FBG were of the same design and operating principles, manufacturing was anticipated to proceed similarly regardless of which granulator was used. In addition, MP4 granulator had several merits including recipe driven process equipped with a PID feedback system to maintain parameter targets versus operator-controlled process and a dual-chamber filter system that allowed uninterrupted processing during the filter shake-cycle. The target spray rate for the binder solution was 300 g/min in campaign 5 and 6. The inlet air volume, which is the input parameter on both the S4 and MP4 granulators, was further reduced from 650 to 450 cfm in order to maintain a constant superficial velocity (CSV) of approximately 125 m/s. Maintaining a CSV when transferring processes between FBGs is a common practice that is used to accommodate for differences in equipment geometry. The inlet temperature was reduced from 85 to 75 °C in order to operate within the temperature range that was qualified for the MP4. The atomization air was selected as 3.5 bar based on the results of the process optimization batches.

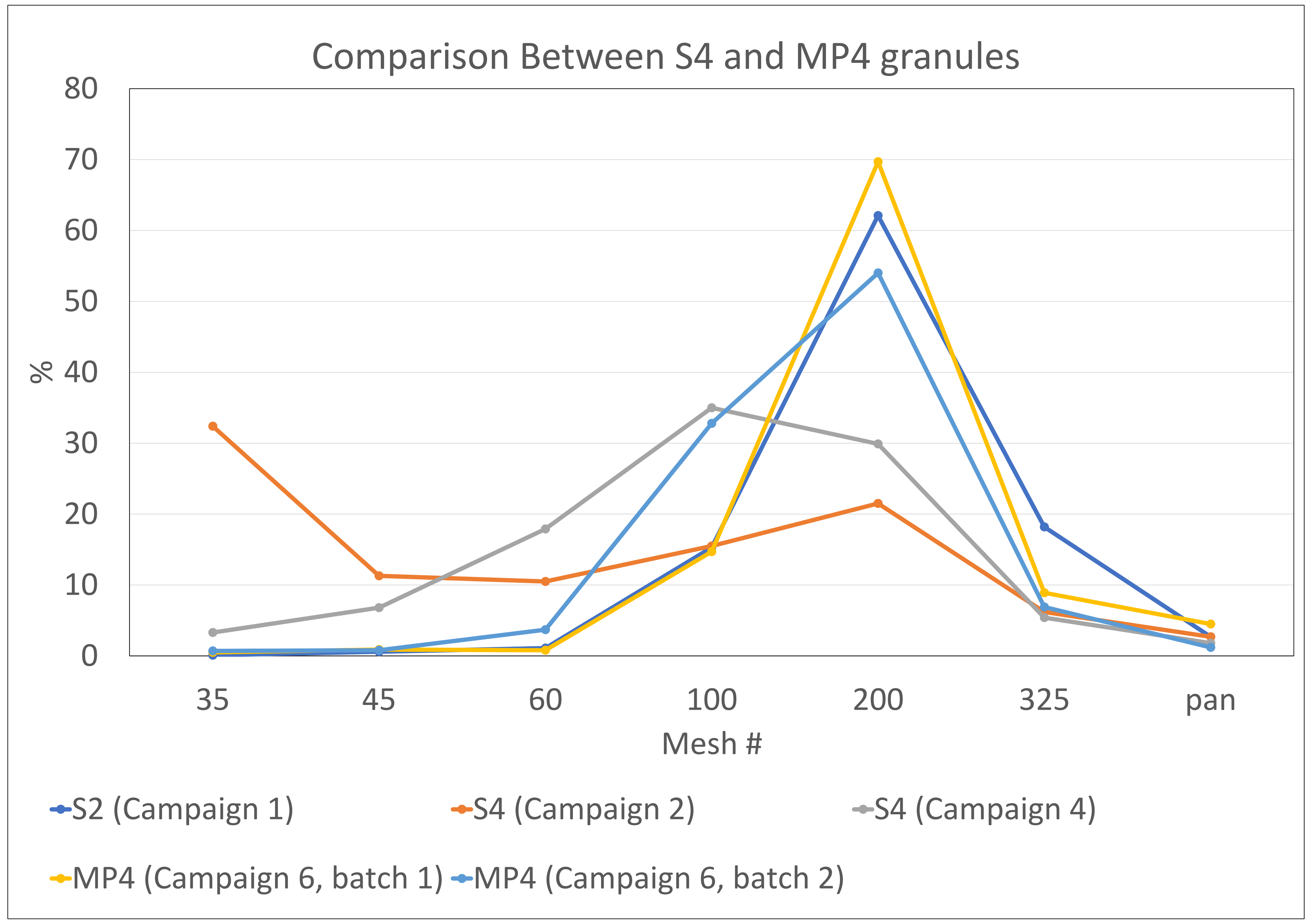
RESULT(S)

The geometric mean particle size (GMS) and % particles retained on the 500 µm sieve in campaign 3 were similar to campaign 2 despite the changes in blow fill, spray rate and inlet air volume. Hence, two additional changes were made in campaign 4 including increase in the filter shake interval from 90 to 300 sec and an adjustment in spray nozzle tip position from 1 mm to 3 mm from the air cap. The GMS and % particles retained on the 500 µm sieve in campaign 4 dropped to 204 µm and 4%, respectively. Though all these changes did not facilitate the reduction in the GMS and %particles retained on the 500 µm sieve in campaign 4 and remain inclusive, the increase in filter bag shake interval was thought to be an important factor. The GMS in campaign 5 was also observed below 175 µm and % particles retained on the 500 µm sieve was less than 8%. The AV values in campaign 5 were below 4.5 for all three registration batches compared to 6.1 and 13.1 from campaign 3. Following transfer of product from S4 to MP4 FBG, the material properties were observed to similar while comparing campaign 5 and 6. Small reductions in the GMS, quantity of particles ≥ 500 mm and quantity of particles ≤ 44 mm were noted in campaign 6 suggested a narrowing of the distribution, where greater than 60% of the particles were retained on the 75 µm sieve for this batch.

Process parameters	Campaign #1	Campaign #2	Campaign #4	Campaign #6, Batch #1	Campaign #6, Batch #2
Equipment	S2	S4	S4	MP4	MP4
Batch Size (kg)	10 kg	65 kg	32.5 kg	32.5 kg	32.5 kg
Spray rate (g/min)	100 ± 10	650 ± 100	300 ± 60	300± 30	300± 30
Atomizing Air pressure (bar)	1.5	5	5	5	3.5
Shake time (Sec)	15	15	10	15	15
Shake interval (sec)	90	90	300	120	120
Inlet temperature (ºC)	85	85	85	75	75
Air Flow (cfm)	100 - 200	900 - 920	640 – 660	450	450

CONCLUSION(S)

The S4 FBG has a single filter chamber, as a result the granulation process is interrupted during the shake cycle. This interruption includes a shut-off of not only the airflow but also the binder-spray rate. The interruption of the process was thought to be an important factor in the increased granule particle size in campaign 3. As a result, MP4 was determined to be suitable for commercial production. The particle size distribution was noticeably improved from S4 to MP4 granulation FBG. The data from particle size distribution suggested narrow distribution, which eventually reduced content uniformity variation, as evident by low AV.



patheon by Thermo Fisher Scientific