EVALUATION OF FLASHSIZER 3D IMAGING DURING AN EXTRUSION-SPHERONIZATION PROCESS

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INTRODUCTION AND PURPOSE

Extrusion-Spheronization (ES) is a multiple-step agglomeration process:

1. dry blending → 2. granulation → 3. extrusion → 4. spheronization → production of spherical units (i.e. pellets) with a narrow size and shape distribution

- fast process + use of high amounts of water
- Literature: process-induced transformations of API
- Present study: real-time monitoring of size distribution and shape

Materials

Pellet composition:
- 50% (w/w) anhydrous theophylline (TP)
- 50% (w/w) microcrystalline cellulose (MCC, Avicel PH101)
- purified water

Methods

1. Extrusion-Spheronization
   - Nica M6L mixer/granulator
   - Nica E140 radial screen extruder
   - Nica S320 spheroniser
     (Nica System AB, Sweden)

2. Imaging unit - FlashSizer 3D
   - FlashSizer 3D: current process imaging system facts:
     - pixel resolution 10 um
     - image area 1.2x1.6 cm
     - optimal size range 50-2000um
     - 5-20 images/sec
     - calculations ~50ms

3. Experimental setup
   - TP-MCC pellets with 3 levels of granulation liquid:
     - 40% w/w (batch I, a-c)
     - 43% w/w (batch II, a-c)
     - 46% w/w (batch III, a-c)
   - each batch was manufactured in triplicate (total of 9 batches)
   - total spheronization time of 10 min
   - sampling during spheronization:
     - 0 s
     - 20 s
     - 40 s
     - 5 min
     - 6 min
     - 10 min
     - at-line FS3D measurement (1x)
     - off-line FS3D measurement (5x)

Materials AND METHODS

1. Illumination of undispersed powder sample surface by 2 light sources (use of 2 illumination angles):
   - samples are imaged through a glass window
   - 2 light sources, placed 180° from each other in horizontal plane

2. Image capture:
   - image light source 1
   - image light source 2

3. Combination of 2 images for 3D visualization and PSD data extraction:

4. Representation of data:
   - images:
     - PSD as sieve fractions
     - PSD as D10, D50, D90 values
     - relative roughness
RESULTS AND DISCUSSION

1. Comparison of at-line and off-line PSD obtained for batch I, II and III

![Figure 1](image1.png)

Figure 1. At-line and average off-line (with 95% confidence interval) D10, D50 and D90 values of FS3D measurements of batch I (left), batch II (middle) and batch III (right) in function of spheronization time.

Figure 1 displays a good correspondence between at-line and off-line PSD at all 3 water levels. Hence, accurate PSD values were obtained based on a single captured image.

2. Comparison of at-line obtained PSD for each set of replicate batches

![Figure 2](image2.png)

Figure 2. At-line D50 values of batch I (a), batch II (b) and batch III (c) in function of spheronization time.

- Figure 2 displays an increase in average pellet size with increasing water levels (between group variation). At a low water saturation state, the brittle batch I extrudates instantaneously broke up into smaller particles during spheronization, which generated a large amount of fines. This in contrast to batch III, where the increased extrudates’ plasticity initiated the formation of larger spheres.
- Comparing each set of replicate batches (within group variation), an increase in process reproducibility with increasing amount of water was observed. The calculated standard deviation (SD) divided in half by increasing the amount of granulation liquid from 40% to 46%. This decrease in SD was more pronounced for the smallest particles (D10), compared to larger particles (D90) (data not shown).

3. Comparison of at-line obtained images for batch I, II and III

![Figure 3](image3.png)

Figure 3 demonstrates the FS3D images captured after 0, 1, 5 and 10 minutes of spheronization for batch I, II and III.

- Evaluation of FS3D images captured during spheronization demonstrates the slower spheronization rate of batch I compared to the rates of batch II and III.

CONCLUSIONS

The results of this study indicate that based on a single captured FS3D image, representative particle size distributions were calculated. Due to the dual information of size and visual shape, the use of the FS3D technique enhances process information. Combination of these characteristics with the rapidness of the technique, shows the potential of FS3D as a process analytical technology tool during spheronization (and other pharmaceutical production processes).

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