Experimental investigation of residence time, granulation liquid and granule size distributions in twin-screw granulation

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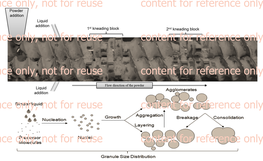
Introduction

- **Continuous wet granulation** performed using a twin-screw granulator (TSG) is an important part of future continuous manufacturing of pharmaceutical solid dosage forms.
- The extent of different **rate processes such as growth and breakage** involved in granulation is greatly **governed by the residence time, axial mixing and solid-liquid mixing** of the granulation material.
- However, due to a lack of suitable techniques, **a detailed investigation of flow characterisation and solid-liquid mixing in a TSG is missing**.
- **Objective:** Study the impact of process and equipment parameters on the residence time, the granulation liquid-powder mixing and the resulting granule size distributions during twin-screw granulation.

Twin-Screw Granulator applies High Shear Wet Granulation

- Granulation time is short (in the order of seconds).
- At appropriate time scales and conditions, granulation is in steady state.
- Both screw configuration and process conditions dictate granulation time and mixing during twin-screw granulation.



Factors and responses investigated in this study

Granulation Process

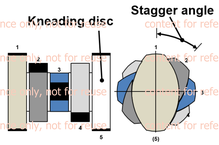
Continuous twin-screw granulator (25 mm diameter), the ConsiGma™-25 system by GEA Pharma Systems nv., Belgium.

Formulation of granules

Lactose monohydrate was granulated with distilled water. After granulation, wet granules were collected and tray dried.

Screw Configuration

- Number of kneading discs (4, 6, 2×6)
- Stagger angle (30, 60, 120°)



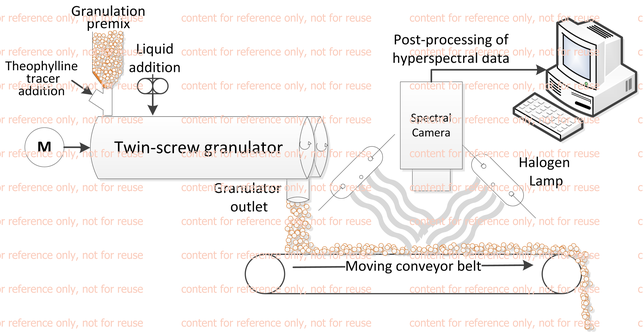
Process parameters

- Material throughput (10-25 kg/h)
- Screw speed (500-900 rpm)
- Granulation liquid-to-solid ratio (6-8 %)

Responses

- Sieving method to quantify granule size distribution as fines (<150 μm), yield (150-1400 μm) and oversized (>1400 μm) fractions.
- NIR-Chemical imaging for measurement of granulation time and mixing.

NIR- Chemical imaging for fast and accurate measurement.



The hyperspectral data was post-processed, using a spectral-match filter to estimate the spatio-temporal variation in the theophylline level for residence time distribution measurement, and using the band ratio method to estimate the moisture distribution for solid-liquid mixing study.

- Process variations lead to change in delay in the onset of tracer and width of the distribution leading to different RTDs e(t), quantified as mean residence time

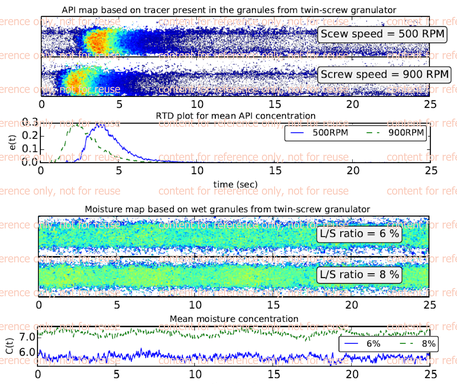
$$t_m = \frac{\int_0^\infty t.e(t)dt}{\int_0^\infty e(t)dt}$$

and Péclet number

$$\frac{\sigma_{t_m}^2}{t_m^2} \approx \frac{2Pe - 2 + 2 \cdot e^{-Pe}}{Pe^2}$$

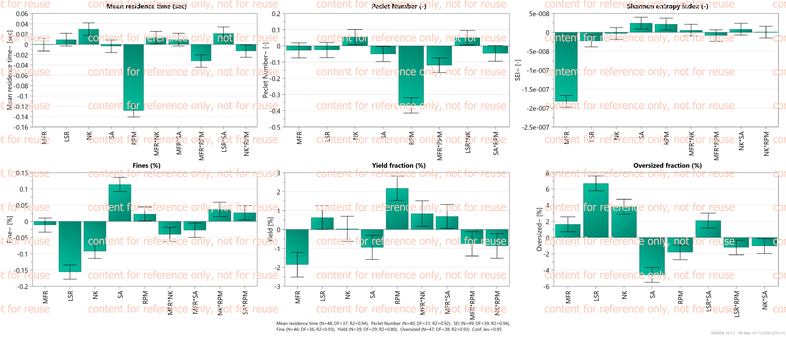
- Process variations also lead to different moisture distribution and mean moisture content C(t), indicating changes in the solid-liquid mixing achieved, quantified as Shannon entropy index

$$H(X) = -\frac{1}{log(n_c)} \sum_{j=1}^{n_c} P(X_j) \log_2 P(X_j)$$



Results

- The obtained data were all evaluated using the partial least square (PLS) algorithm (Modde 9.0 software, Umetrics, Umeå, Sweden) to estimate the effects of the factors on the responses (fines, yield and oversized).



- Screw speed most dominantly influenced the mean residence time and axial mixing inside the granulator.
- At a high material throughput, the solid-liquid mixing inside the granulator is inferior.
- In lack of good mixing, change in the L/S ratio resulted in change in fine and oversized fractions without significant influence on the yield fraction.

Take home message

A **balance between material throughput and screw speed is required** to achieve the required granulation time and solid-liquid mixing **for achieving high granulation yield**.

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