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Review Article

Model-based analysis of high shear wet granulation from batch to continuous processes in pharmaceutical production – A critical review

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ABSTRACT

The manufacturing of pharmaceutical dosage forms, which has traditionally been a batch-wise process, is now also transformed into a series of continuous operations. Some operations such as tabletting and milling are already performed in continuous mode, while the adaptation towards a complete continuous production line is still hampered by complex steps such as granulation and drying which are considered to be too inflexible to handle potential product change-overs. Granulation is necessary in order to achieve good flowability properties and better control of drug content uniformity. This paper reviews modelling and supporting measurement tools for the high shear wet granulation (HSWG) process, which is an important granulation technique due to the inherent benefits and the suitability of this unit operation for the desired switch to continuous mode. For gaining improved insight into the complete system, particle-level mechanisms are required to be better understood, and linked with an appropriate meso- or macro-scale model. A brief review has been provided to understand the mechanisms of the granulation process at micro- or particle-level such as those involving wetting and nucleation, aggregation, breakage and consolidation. Further, population balance modelling (PBM) and the discrete element method (DEM), which are the current state-of-the-art methods for granulation modelling at micro- to meso-scale, are discussed. The DEM approach has a major role to play in future research as it bridges the gap between micro- and meso-scales. Furthermore, interesting developments in the measurement technologies are discussed with a focus towards inline measurements of the granulation process to obtain experimental data which are required for developing good models. Based on the current state of the developments, the review focuses on the twin-screw granulator as a device for continuous HSWG and attempts to critically evaluate the current process. As a result, a set of open research questions are identified. These questions need to be answered in the future in order to fill the knowledge gap that currently exists both at micro- and macro-scale, and which is currently limiting the further development of the process to its full potential in pharmaceutical applications.

1. Introduction

Granulation is a size enlargement process to form granules with controlled properties, starting from a particulate feed and a liquid as raw materials. It is a key process adopted in a range of industries for production of pharmaceuticals, detergents, agricultural and food products, agro-chemicals, enzymes, etc. Granulation is mainly performed to improve the flowability of powders, to reduce dustiness and co-mixing of materials which will otherwise segregate or form a cake [1,2]. The major granule properties such as granule size distribution (GSD) and porosity, are driven by the rate of various macroscopic mechanisms during the granulation process, e.g. nucleation, aggregation, layering, breakage, consolidation [1–3].

Despite the challenges involved, continuous processing has become preferable for all major industries in the past decades due to the fact that continuous operation usually comes with several benefits for the process (Table 1). However, the pharmaceutical industry is a clear exception, and has for many years mainly relied on conventional batch manufacturing, largely due to a rigid regulatory framework and due to uncertainty in industry about the attitude of the regulators towards more continuous production processes. Moreover, the conventional pharmaceutical quality

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List of Abbreviations

(s,l,g)	vector representing solid, liquid, and gas volumes of a granule
$\beta(x,y)$	aggregation kernel
δ	delta-dirac function
$\dot{Z}$	spatial velocity in the external coordinate
μ	liquid viscosity
θ	solid–liquid contact angle
ε	porosity
$F(s,l,g,t)$	population density of a granule at time, t
l	size of particles
m	total mass of the granule particle
$M(v,t)$	mass of granulation liquid in the size range
$n(x,t)$	number distribution of particles
w	fractional granulation liquid content
x	scalar-state variable that represents particle size
γ_{LV}	surface tension of the liquid
$\tau_{wetting}$	theoretical liquid penetration time
ε_S	surface porosity
$\zeta_{break}(x,y)$	the probability distribution function
B^0	nucleation rate
$B_{agg}(x)$	birth rate of particles of size x
$D_{agg}(x)$	death rate of particles of size x
$K_{break}(x)$	breakage kernel
l_0	size of the nuclei
r_d	radius of footprint of drop on powder surface
R_{pore}	effective pore radius based on cylindrical pores
V_0	total volume of drop
AE	acoustic emission sensor
CFD	computational fluid dynamics
CM	compartmental model
DEM	discrete element method
FBRM	Focused beam reflectance measurement
FVM	finite volume method
GSD	granule size distribution
HSWG	high shear wet granulation
ICH	International Conference on Harmonization
MTR	Mixer Torque Rheometer
NIR	near-infra red spectroscopy
PAT	process analytical technology
PBE	population balance equation
PBM	population balance modelling
PEPT	Positron Emission Particle Tracking
PIV	Particle Image Velocimetry
QbD	Quality by Design
RTD	residence time distribution
RTRT	Release Testing
TSG	twin-screw granulators
US FDA	United States Food and Drug Administration
VoF	Volume of Fluid

Table 1
Benefits and challenges of continuous processing.

Benefits	Challenges
Improved and more consistent quality	More precise measurement and control required
Increased throughput	Continuous flow and level measurement
Reduced inventory and associated storage	Modulating flow and level control
Reduced raw material usage	Real-time in-process quality measurement
Reduced waste products	Real-time quality control
Improved process safety	Integration of several unit operations, also w.r.t. control
Reduced air, water and power utility usage	Extensive personnel training, particularly for operators
Reduced process footprint	Redundant controls and instrumentation
Reduced clean-up time	Rapid corrections to all process variations
Reduced operator involvement	Advanced process control

control systems are based on off-line analysis in analytical laboratories, which is in sharp contrast to the real-time in-process analysis methods that are needed for continuous processing. Continuous real-time quality monitoring and control is indeed indispensable for efficient continuous production.

The introduction of the process analytical technology (PAT) process analytical technology guidance [4] was an important milestone for the pharmaceutical industry, since it is one of the first documents published by regulatory authorities promoting a new pharmaceutical production model based on the *Quality by Design* Quality by Design (QbD) concept. The concept relies on a science- and risk-based holistic development of processes and products such that, *quality cannot be tested into products; it should be built-in or should be by design*. In addition to the new concepts considered by the United States Food and Drug Administration (US FDA), the use of quality risk management principles and the application of an appropriate pharmaceutical quality system, as defined within the International Conference on Harmonization (ICH) documents Q8, Q9 and Q10 [5–7] provided the platform for establishing a new release decision-making strategy for marketed products, i.e. the Real-Time Release Testing (RTRT) strategy [8]. Furthermore, ICH published a more recent and extensive guidance for harmonising the scientific and technical principles related to the description and justification of the drug development and complete manufacturing process [9]. All these developments and publications have reduced the regulatory uncertainty, and opened new and exciting possibilities for innovation in pharmaceutical manufacturing, resulting in significant efforts for designing new and more efficient production strategies. Continuous manufacturing of solid dosage pharmaceutical products is in line with the efforts aiming at improving product quality, reducing manufacturing cost, and essentially providing safer products to the patients. The *one-in-one-out* principle for the raw materials in this production scheme leads to reduced cycle times and improved process throughput. Schaber et al. [11] showed that continuous processing has a clear economic advantage over batch processing. Cervera-Padrell et al. [12] demonstrated that the switch from batch to continuous processing for organic synthesis of small molecules resulted in a reduction in the process mass intensity by about 50%, thus resulting in a considerably greener continuous production process. The desired paradigm shift from batch to continuous mode at production scale in the pharmaceutical sector requires a reliable continuous granulation process. An example of a production line used for the continuous manufacturing of tablets is shown in Fig. 1 [10]. Some of the process steps in the pharmaceutical production process are in fact continuous as such (e.g. milling, tabletting), but the production of granules is typically performed using inherent batch unit operations. Various granulation techniques that are widely used in the pharmaceutical industry are summarised in Table 2.

Wet granulation is a commonly used unit operation for solid dosage form manufacturing which is attributed to the more