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Empirical to mechanistic modelling in high shear granulation

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Abstract

This paper gives an overview of the different models available for granulation in high shear mixers with a focus on applicability in the pharmaceutical industry. Three examples of applications are given. The examples indicate the potential of mechanistically based models for scale-up and the importance of understanding the dynamics of the granulation process. The first two examples show how the impeller torque can be modelled and predicted in the dry and wet mixing phases of the high shear granulation process, using a solid mechanics and a hierarchical multivariate model, respectively. In the third application the particle size distribution is modelled using population balances and it is shown how different operating conditions can be included in the coalescence kernel to describe the granule growth.

Keywords: Agglomeration; Granulation; Population balance; Multivariate modelling; Scale-up; Solid mechanics

1. Introduction

Wet granulation in high shear mixers is an important unit operation step often used in the development and manufacturing of pharmaceutical oral solid dosage forms. It is a complex process that comprises a dry high shear mixing step and a step of high shear mixing with agglomeration. In the pharmaceutical industry it is important to find and develop different generic ways to model and monitor the granulation process to enable predictive scale-up and control of the process. There are a range of different granulation models ranging from purely empirical to more or less mechanistical ones. However, there is still a lack of understanding of the coalescence and breakage mechanisms on a particle–particle level, which limits the use of the models. In order to find mechanisms based on first principles, it is of greatest importance to be able to predict the flow pattern in the bowl. A lot of research has been conducted in understanding the underlying mechanisms of agglomeration (e.g. Biggs et al., 2003; Iveson et al., 2001; Knight et al., 1999; Litster, 2003; Liu et al., 2000), but it is still difficult to quantitatively explain the process. Faure et al. (2001) have stated that “A good understanding of the granulation process on a micro-scale and a working model of the population balance in a small-scale granulator should one day be extremely valuable for scale-up in larger machines.” From an industrial perspective there is an economic issue for understanding the mechanisms, as this would make transfer and scale-up to manufacturing sites much easier and faster.

There is no easy way to control and adjust the granulation process in high shear mixers. The best possible industrial tools today are based on using the granulator power consumption as an indicator of the status of the process. However Bardin et al. (2004) have made a critical review of the use of mixer power/torque and mixer work for process control and suggest a method where the work done by the mixer, i.e., the integrated power over time, is used as a measure of when to stop the process. Michaels (2003) points out that design and analysis of industrial particulate processes remain rooted in empirism, scale-up are based on heuristics and quantitative design methods are non-existent. The aim

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Table 1
An overview of different granulation models ranging from pure empirical to more or less mechanistic ones

	Method	Characteristics	+/−	Reference
Empirical	Multivariate process modelling	Statistical models	+ Good results within experimental space − Totally empirical	Miyamoto et al. (1997) Wehrlé et al. (1993)
	Relative swept volume	Relative swept volume held constant during scale-up	+ Simple to use − Weak physical relevance	Schaefer (1988)
	Tip speed	Tip speed held constant during scale-up	+ Simple to use − Weak physical relevance	Ameye et al. (2002)
	Dimensionless numbers	Different dimensionless numbers held constant during scale-up	+ Simple to use − Weak physical relevance	Faure et al. (1999)
	Normalized impeller work	Energy/mass = const	+ Theoretical relevance − Calibration required	Sirois and Craig (2000)
	Power consumption and/or temperature	Power consumption as end point	+ New, promising − Macroscopic	Betz et al. (2004), Landin et al. (1999)
	Integrated power over time	Mixer work as endpoint	+ New, promising − Macroscopic	Bardin et al. (2004)
	Solid mechanics models	Friction models	+ Mechanistically derived − Dry powders only	Knight et al. (2001)
	Population balances	Coalescence probability Coalescence factors functions of process variables	+ Mechanistically derived − Some empirical fitting required	Iveson (2002), Jansson et al. (2004), Sanders et al. (2003), Verkoeijen et al. (2002)
Mechanistic	DEM models	Flow patterns	+ Mechanistically derived − Few particles in models	Kuo et al. (2002)

of this paper is to give an overview of the different types of industrial process models available that are applicable to high shear granulation. Focus will be on models used for scale-up, as this is the most important feature from an industrial perspective. However, other models will be discussed briefly, too. In this paper, examples of three process models will be given. The first is based on the theory of solid mechanics, the second on multivariate data analysis and the third on population balance modelling. In the future it would be desirable to combine these models to one generic process model.

2. Overview of empirical to mechanistic process models

In the literature, the different process models range from purely empirical ones to more or less mechanistic models with some fitting included. Empirical models are based on historical data and as such they are of limited use in new applications outside the experimental space studied. There is a strong need to move from empirical to more mechanistic models in order to enable simplified scale-up and process control. The desired future state of process models should be predictive, mechanistic in-silico type of models where different geometrical layouts, operating conditions, powder and granule properties could be handled and explained. Table 1 gives a comprehensive overview of models used mainly for wet granulation but also for dry powder mixing. The characteristics, advantages and disadvantages are also listed. Table 1 requires some comments. A multivariate model can be considered as semiempirical if there is physical relevance behind the different parameters used. However, the model cannot be extrapolated to be valid outside the boundaries on which it is based. Therefore experiments have to be performed on both scales if used for scale-up. The friction model derived by Knight et al. (2001) is only applicable for predicting the torque during dry powder mixing.

The mean particle size and particle size distribution are two very important parameters to control in the total tablet manufacturing process (Bardin et al., 2004). The use of population balances is one way that enables modelling and prediction of the outcome of a granulation process. If the mechanisms behind coalescence and flow pattern were completely known, the model could be used independent of granulator size. However, quite a high degree of empirical or semiempirical fitting has to be performed, which makes the model weaker for predicting the outcome on another scale. The discrete element modelling (DEM) models have shown promising results for the future, but population balances have to be included in the models to handle agglomeration. The DEM