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# An investigation on the evolution of granule formation by in-process sampling of a high shear granulator

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ABSTRACT

Understanding the growth mechanisms in granulation process is an important topic, providing valuable insights and supports control strategies. Typically, observations in high shear granulators are made after stopping the process. In this work, an in-process sampling technique is described and applied to a high shear wet granulation process. Different samples can be collected over the cause of the high shear granulation process. This allowed observation of the evolution of granules during addition of water at a constant flowrate. For a typical pharmaceutical formulation, we observed that granules nucleate in the first 2 min after starting the water addition and then grow to an average size of 200–1200 μm at 12.5 min, corresponding to a sharp increase in torque. Longer water addition times lead to oversized granules and eventually a paste and highly fluctuating torque. Sampling was also continued after stopping water addition which showed with time larger formed granules smoothen, whilst the smaller ones disintegrate. The work shows the in-process sampling can facilitate the identification of the granule growth kinetics and required binder quantity in high shear granulation.



## 1. Introduction

Granulation can be carried out by a wet or dry process, depending on the properties of the primary and final products (Tardos et al., 1997). The wet granulation process is performed by spraying liquid binder onto the particles while agitated in different devices such as tumbling drum, fluidized bed or high shear mixer (Tardos et al., 1997). Wet granulation in a high shear mixer is usually achieved by shorter processing time and more effective liquid binder addition compared to other types of granulations (Augsburger and Vuppala, 1997; Hemati and Benali, 2007). Iveson et al. (2001) states that, wet granulation mechanisms can be described by wetting and nucleation, consolidation during growth and attrition with breakage. These mechanisms control the obtained granule properties. Moreover, they are influenced by a combination of formulation design (e.g. feed powder and binder properties) and process design such as type of granulator and the operating parameters.

Two methods are usually used to characterize the physical properties of the granules. Traditional non-image based methods such as pycnometry, BET analysis as well as X-ray tomography (Klobes et al., 1997; Lowell et al., 2012; Rahmanian et al., 2009; Stanley-Wood and Shubair, 1979) are implemented to characterise the structural properties of the granules. On the other hand, granule size and shape is characterised by the image-based or laser diffraction techniques (Farber et al., 2003; Garboczi, 2002; Hancock and Mullarney, 2005). Although, the image-based techniques are often costly due to operating and capital costs of equipment, it is accurate and give more information (Farber et al., 2003; Garboczi, 2002; Hancock and Mullarney, 2005).

To process most of particles in the granulation system, Tardos et al. (1997) remarked that a number of notes must be considered. A critical minimum amount of liquid binder is an important characteristic of the granulation system to ensure enough stickiness on the particle surface. This note will be studied in further details in this research. Furthermore, process conditions such as impeller tip speed can influence

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the mixing, binder addition and coalescence and/or breakage during granulation process.

A number of researchers investigated the effect of different liquid-binder/solid ratios (Bock and Kraas, 2001; Oulahna et al., 2003; Rahmanian et al., 2009; Realpe and Velázquez, 2008; Saleh et al., 2005) on the granulation process. The role of binder is to form bridges or bonds between the primary particles to form the nuclei and later their coalescence in the granulation process (Mangwandi et al., 2015). It was found that, increasing the liquid/solid ratio leads to an increase in the granule size (Bock and Kraas, 2001; Chitu et al., 2011). In addition, granules produced with high binder viscosity could have a considerably lower strength and wide strength distribution due to poor dispersion of binder on the powder bed (Rahmanian et al., 2011).

Landin et al. (1996) and Betz et al. (2004) have stated that, impeller torque and power consumption values can be used as methods to monitor/follow the granule growth from the initial granule formation phase. Both methods noticeably depend on the cohesive force of the wet mass or the tensile strength of the granules (agglomerates). Furthermore, Sakr et al. (2012) claimed that torque measurement can be used as a reliable control method for monitoring the wetting procedure and scale up, possibly due to the direct relationship of the torque with the mass flow resistance. This information could facilitate selection of a liquid addition range where the granule growth behaviour can be predicted.

The impeller torque profile can be subdivided into three different stages (Leuenberger et al., 2009). In the first stage, a slight increase in torque is usually related to nuclei formation and moisture sorption without the formation of liquid bridges. In the second stage, a rapid/sudden increase in the torque could be due to the attainment of the formation of liquid bridges (pendular). This rapid increase in torque can be correlated with the liquid amount required to achieve the dry binder transition stage. In these conditions, dry binder stickiness promotes a faster granule growth (Cavinato et al., 2010). Finally, a subsequent plateau stage in the torque indicates the transition from the pendular to the funicular state (Leuenberger, 1982). A reliable relationship between power or torque profiles and the saturation degree of the wet mass can be established (Leuenberger, 1982; Leuenberger et al., 1981).

The granulation process in high shear granulators has been investigated at different periods of time, from 2 min (Rahmanian et al., 2011; Realpe and Velázquez, 2008) up to 20 min (Oulahna et al., 2003). The results showed that, increasing the granulation time has a significant effect on granules strength and density, until an optimum time is reached (Rahmanian et al., 2011).

Implementing characterization tools are important for assessing granule qualities and the granulation process. Depending upon whether the assessment is done after or during the process, these tools can be classified as offline and online/inline. In addition, the online tools are more rigorous and accurate and become more critical with the transformation of batch to continuous processing in pharmaceutical applications (Hansuld and Briens, 2014; Suresh et al., 2017).

There are several primary technologies that have been investigated for high-shear wet granulation monitoring. These technologies include power consumption (Hansuld and Briens, 2014; Levin, 2016), near-infrared spectroscopy (Alcalà et al., 2010; Hartung et al., 2011; Liu et al., 2017), Raman spectroscopy (Hansuld and Briens, 2014), capacitance measurements (Hansuld and Briens, 2014), microwave measurements (Hansuld and Briens, 2014; Peters et al., 2017), imaging (Kumar et al., 2015; Soppela et al., 2014), focused beam reflectance measurements (Narang et al., 2017), spatial filter velocimetry (Hansuld and Briens, 2014), stress (Hansuld and Briens, 2014), drag flow force (Narang et al., 2016) and vibration measurements (Hansuld and Briens, 2014), as well as acoustic emissions (Hansuld et al., 2012). In addition, advantages, disadvantages and challenges associated with each method for high-shear wet granulation was summarized by Hansuld and Briens (2014). For example, complexity of implementation and measurements, extensive calibration and data reliability as well as the costs are the main disadvantages and challenges of these methods (Hansuld and Briens, 2014; Suresh et al., 2017).

In this work a simple vacuum base online sampling has been used for granulation as no previous work has been reported in this aspect. It is used to study the effect of different parameters and process conditions during the granulation without stopping the process.

**Table 1 – The properties of the materials.**

| Properties | α-Lactose | Avicel® PH-101 | HPMC |
|---|---|---|---|
| Density (kg/m$^3$) | 1543 | 1555 | 1315 |
| Aspect ratio mean[a] | 0.733 | 0.598 | 0.608 |
| BET surface area, m$^2$/g | 0.3478 | 0.9308 | 0.4913 |
| Solubility in water (%wt)[b] | 21.6 | Insoluble | Soluble |
| $D_{10}$, $D_{50}$ and $D_{90}$ (microns)[c] | 7.8, 40.8 and 123.7 | 26.1, 71.3 and 156.9 | – |

[a] Based on number distribution.
[b] Found from the MSDS sheet of the materials.
[c] Malvern 2000S (dry system) based on volume distribution.

## 2. Materials and methodology

### 2.1. Materials

A number of commercial powders were used as shown in Table 1. Alpha lactose monohydrate ($C_{12}H_{22}O_{11}H_{2O}$) and Avicel PH-101 (microcrystalline cellulose $(C_6H_{10}O_5)_n$) were used as primary particles and hydroxypropyl methylcellulose (HPMC, $C_{56}H_{108}O_{30}$) was used as the binder. All materials were supplied by Sigma–Aldrich Co., Ltd., UK. Fig. 1 shows the SEM images of both primary powders, where the particles of lactose have a relatively wide size distribution as compared to Avicel. The Micromeritics Tristar 3000 was used to measure the BET Surface Area (m$^2$/g) for the materials. While the density of solids was found using Micromeritics Acupyc 1330 device. Furthermore, particle size, mean aspect ratio, circularity and elongation were measured using the Malvern

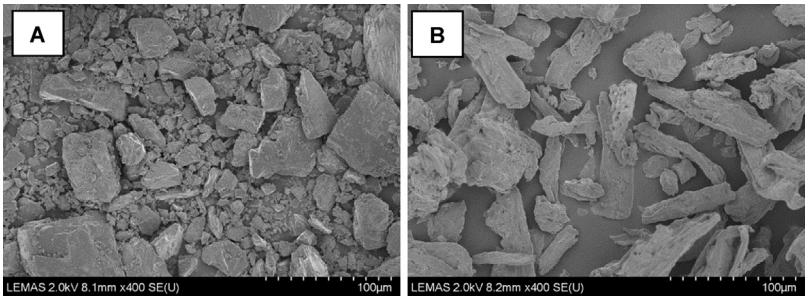


**Fig. 1 – SEM images of A) α-lactose monohydrate and B) avicel PH-101 cellulose microcrystalline.**