International Journal of Pharmaceutics 519 (2017) 165–177

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Use of the channel fill level in defining a design space for twin screw wet granulation

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ARTICLE INFO

Article history:
Received 26 September 2016
Received in revised form 23 December 2016
Accepted 13 January 2017
Available online 15 January 2017

Keywords:
Continuous manufacturing
Channel fill
Twin screw granulation
Design space
Residence time

ABSTRACT

Twin screw wet granulation is a key process in the continuous manufacture of oral solid dosage forms. Previous research has qualitatively suggested that the channel fill level influences the granules produced. In this paper a quantitative measure of the total volumetric fraction of the conveying element channels of the screw filled with powder (φ) was used. Experimental results are shown which demonstrate that very similar particle size distributions can be obtained at the same φ with the same material and screw configuration but radically different solids feed rates and screw speeds. Morphology of the granules also correlates with φ. This is consistent with previous observations in the literature correlating granule attributes with powder feed rate and screw speed but also considers the two parameters in combination. A process design space approach based on φ is proposed. This can be determined empirically, and potentially has value in setting process control strategies, assuring process robustness and allowing process flexibility during the product lifecycle.

1. Introduction

In the pharmaceutical industry there is a strategic shift towards continuous manufacturing technologies for the production of oral solid dosage forms. Continuous manufacturing not only offers the prospect of enhanced product quality, control & assurance and reduced production costs but also simplifies the development process by enabling the same equipment to be used throughout the product development process to the product launch. Granulation is often required to increase the density and improve the powder flow characteristics of the active pharmaceutical ingredient in addition to reduce the risk of segregation through the process. In the continuous manufacturing of oral solid dosage forms a twin screw granulator is commonly used for wet granulation.

There is currently a lot of research activity to investigate the aspects of the twin screw wet granulation process that determine the quality attributes of the manufactured granules. The powder ingredients along with the screw configuration are the most important influences on granule attributes (Thompson, 2015) and a considerable proportion of the studies investigating twin screw granulation have focused in these factors. In a commercial manufacturing scenario, these are both likely to be fixed as part of the registered process. The process parameters are also known to influence the attributes of the granules. By developing and registering a design space based on the process parameters, flexibility in the process such as changing the throughput could be enabled. The literature suggests that in order to establish a design space for the process, the liquid solid ratio and the process parameters (screw speed and the material feed rate) require consideration (Dhenge et al., 2010; El Hagrasy et al., 2013; El Hagrasy and Litster, 2013; Keleb et al., 2004; Lee et al., 2012; Saleh et al., 2015; Thompson and Sun, 2010).

Changes in powder feed rate have been widely observed to change the granule particle size distribution, for example, Dhenge et al. (2010) found that increasing the feed rate from 2 kg/h to 5 kg/h, resulted in smaller granules as there was a shift from bimodal to mono-modal size distribution. This was attributed to the reduction of residence time, which led to production of a lower fraction of the larger granules (Dhenge et al., 2010; Keleb et al., 2002, 2004). These findings were in accordance with those found by Lee et al. (2012) who used similar formulation.

However, Djuric et al. (2009) found that increasing the feed rate resulted in a reduction of fine powder production, which increased the median size of granules. The difference in these results from Dhenge et al. (2010) was related to the difference in the size of the granulator, the screw configuration and materials used. Furthermore, Vercruysse et al. (2012) concluded that increasing the feed rate did not show a significant effect on the size distribution of

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http://dx.doi.org/10.1016/j.ijpharm.2017.01.029

Nomenclature

a	Gradient of the linear function of mass hold-up as a function of φ (g^{-1})
c	Constant representing mass hold-up in non-conveying elements (kg)
$f_i(\ln x)$	Normalized mass frequency of the logarithm of particle size (−)
L	Length of the screw formed of conveying elements (m)
L/D	Length to diameter ratio of the screw (−)
$\dot{m}$	Powder mass feed rate (kg s^{-1})
m_H	Material hold up (kg)
N	Screw speed (rev s^{-1})
φ	Total volumetric fraction of the conveying element channels filled with powder (−)
S_L	Lead length of the screw (m)
V_F	Conveyer free volume (m^3)
$\bar{x}_i$	Mid-point of the size interval i (μm)
y_i	Mass fraction in the size interval i (−)
η_v	Volumetric efficiency of the screw to convey powder (−)
$\overline{\rho_B}$	Mean bulk density of the powder in the channels of the screw (kg m^{-3})
$\bar{\tau}$	Mean residence time (s)

granules, although they noticed a variation in the degrees of barrel filling and torque values. However, this insignificance could be related to using different formulation. The differences to changes in the feed rate observed in both the sensitivity and the effect emphasises that trends in granule attributes are dominated by influence of the formulation, the granulator size and screw configuration.

In contrast the effect of screw speed on the size distribution has generally been seen as minimal (Dhenge et al., 2010; Djuric et al., 2009; Keleb et al., 2004). However, the screw speed influence becomes greater with a change in other parameters such as L/S ratio (Tu et al., 2013). Nevertheless, Dhenge et al. (2010) found that using a slow speed of the screw (250 rpm) showed an increase in the size of the granules. This size increase was attributed by the authors to the increase in residence time and the degree of fill level within the granulator. The additional residence time was postulated to allow more solid particles to bind together resulting in the granule growth. This was in accordance with other studies (Dhenge et al., 2010; Djuric, 2008; Keleb, 2004; Reitz et al., 2013; Unlu and Faller, 2002). Lee et al. (2013) also found that the screw speed did not affect the granule growth when the L/S ratio is low. However, when increasing the L/S ratio, the screw speed showed an influence on the d_{50} of the granules, where increasing the screw speed gave a decrease in the d_{50} value (Djuric, 2008; Lee et al., 2012, 2013). The literature review by Thompson (2015) concluded that too little work had explored operating states at high channel fill where screw speed may have a stronger influence on granulation.

It is known that the channel fill level, or as it is sometimes referred to, barrel fill, is the interaction of process parameters screw speed and feed rate, in addition to the barrel geometry and powder properties (Seem et al., 2015). It has been observed that there is a qualitative relationship between the channel fill level and the produced granule attributes. Furthermore a number of mechanistic dependencies on the channel fill level have been proposed throughout the literature to explain and suit individual observations.

Several studies have attributed changes in the granule particles size distribution to the changes in channel fill (Dhenge et al., 2013; Fonteyne et al., 2013; Keleb et al., 2004; Thompson and Sun, 2010; Tu et al., 2013). The authors suggested several possible mechanisms that vary with the channel fill level for their observations, such as changes to the friction and collision, liquid distribution or compaction and mixing within the barrel. Kumar et al. (2014) demonstrated that the channel fill level influences the residence time distribution as the axial mixing, decreases and the process becomes more plug flow in character at higher channel fill levels. However, these effects are not universally seen for all powder formulations as Vercruysse et al. (2014) did not observe any change in granule particle size distribution although the channel fill level was varied by changing both the powder feed rate and screw speed of the process.

The channel fill level has been observed to influence the morphology and the strength of the granules. Dhenge et al. (2010) demonstrated that increasing the fill level through higher feed rate resulted in an increase of the strength of the granules while also improving their sphericity (i.e. becoming more spherical). Additionally, they observed increasing the screw speed and thereby decreasing the channel fill level resulted in more rough and elongated granules. They attributed this to the increased shear forces on the granules and the different residence time experienced at different channel fill levels.

Although the concept of channel fill is frequently used in the literature to aid the interpretation of the attributes of the produced granules, Seem et al. (2015) noted that a quantifiable determination of the fill level has been noticeably absent from previous work. The reliance on qualitative observations rather than a quantitative measure may explain some of the lack of consistency seen between the channel fill level and granulation attributes seen in the literature. Furthermore, Thompson (2015) expressed a concern that not evaluating the degree of channel fill may make it difficult to track the understanding between different sized machines or when going from low to high flow rates on the same sized machine.

Subsequently, Osorio et al. (2016) investigated a series of dimensionless numbers including the powder feed number with the purpose in investigating the scalability of twin screw granulation between different sized equipment. The powder feed number, they combined with corrections for the geometry of the screw and a term that uses the net forward velocity, to describe the channel fill of the different parts of the screw along its axial length. The net forward velocity term is required as the mixing elements have no or minimal conveying capability; flow through these elements are as a result of powder being fed by the upstream conveying. As observed by Thompson and Sun (2010), these elements operate completely filled and therefore they did not consider them in their consideration of channel fill. However, the resistance to powder flow they cause can also result in an increased level of fill in the upstream conveying elements; the level in these conveying elements is dependent on the feed rate and screw speed. It is this variation that is likely to cause the visual change in channel fill frequently observed in the literature.

In this paper a measure of the total volumetric fraction of conveying element channels of the screw filled with powder (φ) was utilised. This is a simplified measure when compared to that given by Osorio et al. (2016), as it considers the channel fill level as a fraction of the capacity of the screw, which is a more practical measure in an industrial application to optimise the throughput of the equipment.

Experimentation was conducted to validate the calculation of φ by analytically measuring the quantity of powder in the screw. Furthermore, the trends of granule particle size distribution and morphology with this quantity were investigated. Moreover this allowed the previously suggested