International Journal of Pharmaceutics 513 (2016) 357–375

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Statistical analysis and comparison of a continuous high shear granulator with a twin screw granulator: Effect of process parameters on critical granule attributes and granulation mechanisms

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ARTICLE INFO

Article history:
Received 23 May 2016
Received in revised form 25 August 2016
Accepted 10 September 2016
Available online 12 September 2016

Keywords:
Continuous manufacturing
High shear granulation
Twin screw granulation
Design of experiments
Design space
Granulation mechanism

ABSTRACT

This study is concerned with identifying the design space of two different continuous granulators and their respective granulation mechanisms. Performance of a continuous high shear granulator and a twin screw granulator with paracetamol formulations were examined by face-centered cubic design, which focused on investigating key performance metrics, namely, granule size, porosity, flowability and particle morphology of granules as a function of essential input process parameters (liquid content, throughput and rotation speed). Liquid and residence time distribution tests were also performed to gain insights into the liquid-powder mixing and flow behavior. The results indicated that continuous high shear granulation was more sensitive to process variation and produced spherical granules with monomodal size distribution and distinct internal structure and strength variation. Twin screw granulation with such a particular screw configuration showed narrower design space and granules were featured with multimodal size distribution, irregular shape, less detectible porosity difference and tighter range of strength. Granulation mechanisms explored on the basis of nucleation and growth regime maps revealed that for most cases liquid binder was uniformly distributed with fast droplet penetration into the powder bed and that granule consolidation and coalescence mainly took place in the nucleation, steady growth and rapid growth regimes.

1. Introduction

Wet granulation is a particle design process where formulation design (primary particles and liquid properties) and process design (granulator type and operation condition) are combined to produce granulated materials with desirable attributes. While granulation is traditionally considered as a size enlargement process, other particle properties such as porosity, flowability, compressibility and shape can be modified simultaneously to meet specific use requirements. This in turn is driven by the rates of several macroscopic granulation mechanisms: wetting and nucleation, consolidation and coalescence, breakage and attrition (Iveson et al., 2001). In secondary pharmaceuticals manufacturing, wet granulation has been widely carried out to modulate the attributes of in-process intermediates (granules), enabling exquisite control of finished drug product quality (Tan et al., 2014).

For decades, most commercial granulation processes were carried out by batch-wise operation of tumbling, fluidized bed or mixer granulators, largely due to the high profit margins, stringent regulatory framework and limited material throughput (Vervaet and Remon, 2005). Although batch manufacturing still predominates in pharmaceutical industry, nowadays continuous processes are advancing in leaps and bounds, with the imperative necessity to speed up and de-risk process and product development under reduced capital expenditure. Regulatory authorities, such as U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), are also encouraging this paradigm transformation

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http://dx.doi.org/10.1016/j.ijpharm.2016.09.041
0378-5173/

from conventional batch processing to continuous processing. In compliance with the concept of Quality by Design (QbD), continuous manufacturing has inherent advantages to improve production efficiency by mitigating scale-up issues and achieving automated real-time quality monitoring and control by implementing Process Analytical Technologies (PAT), thus facilitating process understanding and technical transfer associated with manageable variability and enhanced product quality.

Twin-screw extrusion/granulation was first introduced for pharmaceutical applications in the late 1980s and over the last decade, considerable attention has been drawn to the extrusion-based continuous granulation. The modular nature of this equipment gives it enormous versatility with respect to screw type selection and configuration (selecting different combinations of conveying, kneading and distributive mixing elements), as well as flexibility in the placement of auxiliary units like feeders and pumps at different zones to accommodate different granule residence times. While enabling optimum throughput with limited materials loss for pharmaceutical manufacturing, twin-screw granulation (TSG) has also demonstrated its robustness towards variation in process and raw materials properties, and consequently maintains consistent product quality against unexpected changes. Recent activities on TSG have extensively investigated the effects of geometry and configuration of screw elements (El Hagrasy and Litster, 2013; Sayin et al., 2015a; Vercruysse et al., 2015), rotation speed (Kumar et al., 2015), binder delivery (Dhenge et al., 2013; Fonteyne et al., 2014a), formulation (El Hagrasy et al., 2013b; Fonteyne et al., 2014b), material feeding (Cartwright et al., 2013; Dhenge et al., 2013) on critical attributes of granules and final tablets as well as mixing and residence time distribution (RTD). In addition, various PAT techniques have been developed for the in-line measurement of granule size and shape (El Hagrasy et al., 2013a; Sayin et al., 2015b), RTD (Laske et al., 2014), moisture content (Chablani et al., 2011; Fonteyne et al., 2012), mixing and flow behavior (Kumar et al., 2014; Vercruysse et al., 2014) and drug solid state (Fonteyne et al., 2012). Regime maps were also explored to gather insights into the working principles underlying granulation process (Dhenge et al., 2012, 2013).

Despite the aforementioned advantages, it is notable that granule size distribution (GSD) from the TSG is highly sensitive to its screw configuration and certain configurations can give rise to broad and multimodal GSD. (El Hagrasy et al., 2013b; El Hagrasy and Litster, 2013; Vercruysse et al., 2014). This is quite undesirable from an industrial perspective in virtue of its serious implication on uniformity of drying process and potential powder segregation in the ensuing processing. Although narrower GSD could be attained at high liquid content, the resultant median diameter (D_{50}) is typically above 1 mm, rendering it less usable in the downstream tableting (Dhenge et al., 2012). Findings by Dhenge et al. (Dhenge et al., 2013) showed that low shear conditions with conveying screws failed to effectively disperse the liquid binder, especially with direct injection delivery method, which eventually resulted in a multitude of un-granulated fines and lumps. Studies undertaken by EI Hagrasy et al. (El Hagrasy and Litster, 2013) reported several configurations of kneading elements that could improve liquid distribution, yet the intensive shear force also induced breakage of granules, leading to the production of smaller granules and bimodal distributions. Recent work from Sayin et al. (Sayin et al., 2015a, 2015b) and Vercruysse et al. (Vercruysse et al., 2015) demonstrated that incorporation of comb mixing elements could allow intimate liquid-powder mixing and optimize granulator performance. As with current implemented TSG, however, it seems challenging to have relatively monomodal GSD and favorable liquid homogeneity without compromising other essential properties like shape and porosity.

Ever since equipment manufacturers were mindful of the specific requirements in pharmaceutical industry, small and versatile continuous granulators tailored for the production at low throughput have been emerging. So far there are very few scientific reports on comparing TSG with other continuous granulation techniques that have also been on market for years. As high-shear granulation (HSG) is the most prevalent granulation approach for batch granulation, it is not uncommon to have continuous granulators devised on the basis of high-shear granulation technology. Therefore, in this study, both TSG and a continuous high-shear mixer granulator, Lödige CoriMix® CM5, were comprehensively characterized with paracetamol formulations. The objectives of the present work were: (1) to bridge the knowledge gap between important process parameters and critical granule attributes using QbD methodologies; (2) to investigate the interplay among different granule properties and identify the granulator design space based desirable specifications; (3) to elucidate the discrepancies in granule properties from different granulators and unveil the underlying granulation mechanisms for better process control in the future.

2. Material and methods

2.1. Materials

The formulation of low-dose drugs was tested on both granulators. It was composed of 8% (w/w) semi-fine acetaminophen (APAP, Mallinckrodt Inc, Raleigh, NC, USA), 44.75% (w/w) α-lactose monohydrate 200 M (Foremost Farms USA, Baraboo, WI, USA) and 44.75% (w/w) microcrystalline cellulose (MCC, Avicel® PH101, FMC Biopolymer, Philadelphia, PA, USA). 2.5% (w/w) binder, Polyvinylpyrrolidone (PVP K29-32, Fisher Scientific, Pittsburgh, PA, USA), was added as dry powders in the blend and distilled water was used as granulation liquid. A high-dose formulation comprising 80% (w/w) semi-fine acetaminophen, 8.75% (w/w) α-lactose monohydrate 200 M, 8.75% (w/w) microcrystalline cellulose and 2.5% (w/w) Polyvinylpyrrolidone K29-32 was further tested on the continuous HSG process. The particle size specifications of each formulation component were shown in Table 1.

2.2. Experimental set-up

2.2.1. Powder mixing

All the excipient ingredients were firstly premixed in a Glatt tumble tote blender (Model TAM 40, Glatt GmbH, Binzen, Germany) for 30 min at 25 rpm, and then transferred into a K-Tron loss-in-weight (LIW) feeder (K-CL-KT 35, K-Tron Soder,

Table 1
Specifications and physical properties of input formulation.

Component	D10 (μm)	D50 (μm)	D90 (μm)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner Ratio
APAP	5.5	29.8	116.4	–	–	–
MCC	19.1	58.7	132.5	–	–	–
Lactose	13.7	78.4	159.5	–	–	–
Low dose premix	14.3	69.8	140.3	0.476	0.629	1.32
High dose premix	9.4	42.6	123.2	0.361	0.586	1.63