ARTICLE IN PRESS
PTEC-10938; No of Pages 8
Powder Technology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Powder Technology

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

Effect of process scale-up on the dissolution of granules with a high content of active pharmaceutical ingredient

David Smrčka [a], Jiří Dohnal [b], František Štěpánek [a,*]

[a] Department of Chemical Engineering, University of Chemistry and Technology Prague, Technicka 3, 166 28 Prague 6, Czech Republic
[b] Zentiva k.s., U kabelovny 130/22, 102 00 Prague 10, Czech Republic

ARTICLE INFO

Available online xxxx

Keywords:
High-shear wet granulation
Froude number
Granulation kinetics
Bulk density
Size distribution
Binder/solids ratio

ABSTRACT

The robustness and parametric sensitivity of a high-shear wet granulation process during scale-up were investigated for a formulation containing over 50% by weight of a hydrophobic active pharmaceutical ingredient (API). The sensitivity of granule properties such as particle size distribution, bulk density and dissolution rate with respect to both formulation (binder/solids ratio) and process parameters (agitation rate and wet massing time) was determined at three different scales (0.5, 4.0 and 25.0 L). For a fixed impeller speed at a given granulator scale, the dissolution rate was found to be strongly correlated with bulk density, and both parameters could be controlled relatively precisely by the wet massing time. However, during scale-up and for variable agitation rates (expressed by the dimensionless Froude number) dissolution rate was found to be a non-trivial function of both granule size distribution and granule density. A set of process parameters for which the formulation was robust during scale-up was identified.

1. Introduction

The formulation and processing of hydrophobic, poorly water-soluble substances is a challenge for the pharmaceutical industry. The low bioavailability of such active pharmaceutical ingredients (APIs) can be compensated either by using a high API load in traditional formulations or by developing new formulations based e.g., on amorphous solid dispersions [1,2]. When hydrophobic powders interact with an aqueous binder during granulation, unusual phenomena such as nucleation by droplet coating [3] or non-monotonic dependence of granule growth on contact angle [4] can occur. For a relatively low API content in the formulation, the granulation behaviour of the powder can be derived from that of the excipients, and therefore to some extent generalised [5]. However, if the API content in the formulation is high, the overall behaviour of the powder becomes dominated by the highly compound-specific properties of the API [6,7], and this reduces the chances of successfully re-using process parameters from previous formulations with only minor adjustments. A more rigorous analysis of the design space in search for a new set of formulation and process parameters that meet the specifications on the product properties is then required [8].

The first step is typically the evaluation of parametric sensitivity in small-scale laboratory granulation equipment [9,10], followed by scale-up to production-scale equipment, which usually goes through several intermediate scales [11]. This activity involves answering two key questions: (*i*) what is the minimum set of granule characteristics or critical quality attributes [12] that should be monitored and preserved during scale-up; and (*ii*) what are the scale-up rules [13,14]. The issue of scale-up of high-shear wet granulation processes has been treated extensively in the literature, focussing on scale-up rules based on constant swept volume, constant impeller tip speed [15], specific power input [16,17], or flow regime characterised by the dimensionless Froude number [18]. A recent study [19] considered a combination of several scale-up rules and concluded that scale-up based on the Froude number was able to preserve the particle size distribution (PSD) but not micro-scale properties.

Although in many cases the conservation of macroscopic granule properties such as PSD during granulation process scale-up can be sufficient, important product properties such as granule strength [20] or dissolution [21] are strongly dependent on the internal microstructure of granules. It has been shown recently by a parametric sensitivity study in small-scale high-shear granulation that even relatively minor changes in process parameters that did not cause any significant changes in the product PSD have led to dramatic variation in dissolution behaviour, which was caused by changing granule microstructure [22]. Product properties that depend on the granule microstructure – such as dissolution – need not be automatically conserved during scale-up even if PSD is. Therefore, the aim of the present work was to investigate the robustness of granule dissolution during process scale-up, and to compare the variation of bulk properties (density and PSD) with that of dissolution characteristics. For this purpose, a formulation containing a high loading

---

* Corresponding author. Tel.: +420 220 443 236.
E-mail address: Frantisek.Stepanek@vscht.cz (F. Štěpánek).

http://dx.doi.org/10.1016/j.powtec.2015.04.028
0032-5910/

Please cite this article as: D. Smrčka, et al., Effect of process scale-up on the dissolution of granules with a high content of active pharmaceutical ingredient, Powder Technol. (2015), http://dx.doi.org/10.1016/j.powtec.2015.04.028

Table 1
Mass fractions (on dry basis) of components in the formulation.

Component	Mass fraction [−]	Mean particle size [μm]
API	0.58	3.3
Prosolv	0.24	63.8
Neosorb	0.07	96.5
Povidone	0.05	72.5
Sodium lauryl sulfate	0.01	42.5
Crospovidone	0.05	73.5

Table 2
Set-up of default values ($Fr = 1.63$) for granulation experiments at different scales.

Vessel volume [dm^3]	Agitator diameter [cm]	Batch size [g]	Agitation rate [rpm]	Chopper speed [rpm]	Massing time [min]	L/S ratio [−]
0.5	14	92	642	3000	3	0.39
4.0	21	735	534	2500	3	0.39
25	38	4592	392	2273	3	0.39

of a hydrophobic API was subjected to parametric sensitivity studies at the smallest scale (0.5 L granulation vessel), followed by granulation studies at two larger scales (4.0 L and 25 L vessels).

2. Experimental methodology

2.1. Formulation

This work is based on a pharmaceutical formulation containing a hydrophobic, poorly water-soluble active ingredient (API) that represents more than half of the formulation by weight. The mass fractions of individual components, specified in Table 1, were kept constant throughout the study. This formulation is specific not only by a relatively high mass fraction of the API but also by a fairly high liquid-to-solid ratio that is required during wet granulation (L/S = 0.39, which is almost a 1:1 ratio with respect to hydrophilic components of the formulation). The API itself has poor aqueous solubility (approx. 0.18 g/L at 25 °C), equilibrium contact angle of water approx. 35°, and a material density of approx. 980 kg/m^3. Its particle size (approx. 3 μm) is significantly lower than that of the excipients — cf. Table 1. The roles of individual formulation components can be briefly described as follows. Povidone (PVP) acts as a binder together with water. Prosolv is silicified microcrystalline cellulose, which improves the physical properties of the powder, such as flowability. Neosorb is a crystallised sorbitol powder, which has good tableting properties as well as a cool taste and a pleasant mouthfeel. Sodium lauryl sulfate is a surface-active agent that improves wettability. Crospovidone has good swelling characteristics and acts as a disintegrant.

2.2. Granulation process

Granules were produced by high-shear wet granulation. A typical granulation protocol consisted of the following three steps: homogenization of the dry powder (always 3 min); water addition (3 min, except for experiments investigating the influence of the binder addition mode); and wet massing (3 min, except for experiments investigating the influence of massing time). Granulation was carried out at three different scales using the Glatt TMG (0.5 L and 4.0 L vessels) and Glatt VG (25.0 L vessel) high-shear mixer granulators. The granulation bowls for all three scales were geometrically similar, consisting of a conical top section and a cylindrical base section, equipped with the Glatt "Z-rotor" three-blade main impeller that spanned across the entire vessel diameter. During homogenization the chopper was off and for the next two phases 100% of the target rate was set. The agitator was set to 50% during homogenization and binder addition, and to 100% for massing.

The chopper rate at different scales was set based on the constant tip speed, whereas for the main impeller, the Froude number was used as a criterion for recalculating the agitation rate at different scales. The Froude number takes into account the ratio of inertial and gravitational forces:

$$Fr = \frac{N^2 d}{g} \tag{1}$$

where N is the number of revolutions per second; d is the impeller diameter; and g is acceleration due to gravity. The midpoint values of the process parameters as well as the batch sizes used at different scales are given in Table 2. The midpoint values were derived from previous experience with pilot batches of the same formulation. The reason for choosing the Froude number as a scale-up parameter in this work was based on preliminary trials where the conservation of Fr (rather than RPM or tip speed) provided the most consistent values of granule properties.

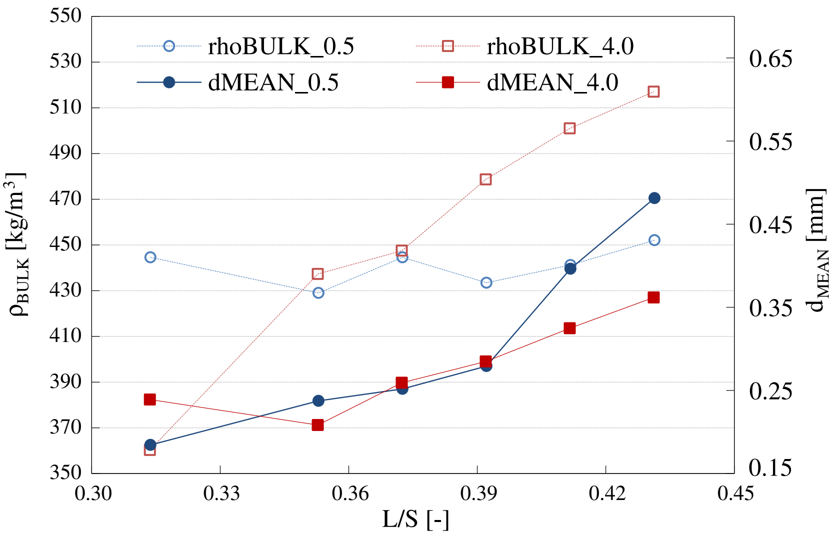

Fig. 1. Effect of binder/solids ratio on the bulk granule properties at the 0.5 L and 4.0 L scales.

Please cite this article as: D. Smrčka, et al., Effect of process scale-up on the dissolution of granules with a high content of active pharmaceutical ingredient, Powder Technol. (2015), http://dx.doi.org/10.1016/j.powtec.2015.04.028