

Effect of variation of active ingredient particle size on the dimension of granules produced with high shear wet granulation process

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Introduction

Granulation is a particle size enlargement process that converts fine or coarse particles into physically stronger and larger agglomerates. During the granulation, primary powder particles are made to adhere to form multiparticle entities called granules (Shinde et al., 2014). Resulting granules usually have larger particle size and bulk density compared with the starting material (Frag Badawy and Hussain, 2004). The physical properties of produced granules are mostly dependent on the characteristics of starting material particularly within the wet granulation process where particle interfaces are combined with the interaction of primary particles with granulation liquid.

According to Schaefer and Mathiesen (1996), there are two different mechanisms of granule nucleation during the wet granulation process in a high-shear mixer: distribution and immersion. Mechanism of distribution occurs when the particle size of molten binder droplets is smaller than the solid particles whereas the immersion occurs when the molten binder droplets are larger than solid particles for instance, for granulation where high viscosity binders are implemented. In case of the immersion mechanism of granulation, the primary solid particles are deployed around the surface of high viscosity binder's droplets. Consequently, a

slight variation of primary solid particle dimensions will result in changes in the number of particles bind by the same quantity of high viscous binder solution, leading with incensement of un-granulated primary particles at the end of the granulation process.

The aim of this study is to present the differences in particle size distribution of granules (in high dose formulation) produced with high shear wet granulation process using high viscosity binder and three different grades of the active ingredient, all of them satisfying the specification requirements. It is anticipated that this information will be valuable for future prudent selection of an alternative active substance manufacturer during the product lifecycle.

Materials and methods

Materials

The materials used were of pharmaceutical grade and include Anhydrous colloidal silicon dioxide (Aerosil 200, Evonik Industries AG), Croscarmellose sodium (Ac-Di-Sol, DuPont Nutrition & Health), Mannitol (MERCK KGaA), Starch (Binder, BASF). Purified water was used for dispersion of starch and formation of starch paste as granulation liquid. The model drug substance X (from two different API manufacturers) was used in three diverse grades all of them satisfying the specification requirements: $d_{50} < 20 \mu\text{m}$, $d_{90} < 80 \mu\text{m}$.

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The grades of model drug substance X used in the described experiments were: Grade I (d10–1.63 μm , d50–4.15 μm , d90–9.15 μm), Grade II (d10–3.68 μm , d50–12.6 μm , d90–38.1 μm) and Grade III (d10–4.50 μm , d50–21.75 μm , d90–78.75 μm).

Characterization of active ingredient particle size

The particle size of each grade drug substance X was determined by laser diffraction (Mastersizer S, Malvern Instruments Ltd., Worcestershire, UK) dry technique.

Granulation experiments in the high shear mixer

The granulation of the three different grades of the model drug substance X was performed in a laboratory-scale bottom-driven vertical high shear granulator with a horizontal chopper shaft (Diosna 4 L bowl) using a batch size of 1.0 kg.

All three trials were of the same composition, produced with the same process parameters, only the grade of the model drug substance X was varied. The formulation consisted of 97.70% active ingredient, 0.19% anhydrous colloidal silicon dioxide, 0.88% mannitol and 1.23% croscarmellose sodium. 10.43% starch paste was used as a binder.

Re-granulation of the wet granules was performed on Quadro Comil U5 laboratory scale conical mill. Wet granules were dried in Mycrolab fluid bed drier to a moisture content of <1.0 %.

Granule size analysis

The particle size distribution of the granules was determined according to the analytical sieves method from Ph. Eur, using Retsch analytical sieve-shaker AS 400 (Retsch GmbH) with ISO standard sieves.

The particle size distribution of the granules was described as a cumulative fraction under sieve. The granules from all trials were analyzed on a sieve-shaker using a series of sieves with different sizes (80 μm , 125 μm , 250 μm , 315 μm , 630 μm).

Results and discussion

A significant difference between the analyzed samples was obtained within cumulative fraction under sieve size 250 μm . Granules size was found to be smaller (Trial 3 - Cumulative fraction under sieve 250 μm = 85.5%) when the initial mean particle size

of the active ingredient is bigger (grade III - mean particle size = 21.75 μm). Furthermore, the granules produced with a smaller initial particle size of active ingredient (grade I - mean particle size=4.15 μm) tend to form coarse granules (Trial 1 - Cumulative fraction under sieve 250 μm = 48.90%) after granulation with the same process parameters.

The particle size mean diameter of the active ingredient used in trial 2 was intermediate (mean particle size = 12.6 μm) compared to the other two active ingredient grades, consequently producing granules with medium particle size (Trial 2 - Cumulative fraction under sieve 250 μm = 62.80%).

The particle size of granules produced with high viscosity binder as starch paste appeared to be inversely related to the starting material mean particle size. During the wet granulation process with high viscosity binder, granule growth is greater if the initial active ingredient particle size is smaller.

Conclusion

Although, all grades of active ingredient used in this study complied with the specification requirements, changes within the approved particle size distribution criteria lead to the production of final granules with different particle sizes.

Experimental data obtained in this study contribute to the immersion mechanism of granule nucleation. When the droplets of the binder are bigger than the initial solid particle size, the number of particles able to be bounded with the binding material is rising if the mean particle size of the starting material is decreasing. The evaluated influence could be especially important within high dose formulations as the final product quality is particularly based on active ingredient properties.

References

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