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Impact of impeller design on high-shear wet granulation

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ABSTRACT

In recent decades, three-blade impellers have been well-established in pharmaceutical high-shear granulation. However, three-blade impellers often require high rotation speeds to initiate product circulation and to provide proper granulation performance. With high rotation speeds much energy is introduced, which is indeed favourable for granule consolidation, however it comes with undesirable thermal stressing and increased granule breakage rates. In order to improve the mixing and granulation behaviour for a more robust process, a new impeller design has been developed that works at lower rotation speeds. The impeller consists of two blades with elongated side wings. In this work, the performance of both impeller designs is intensively studied. Firstly, the mixing behaviour is experimentally investigated in a laboratory mixer (10 L in volume) and at production scale (600 L). The mixing homogeneity of coloured sugar pellets is examined by the digital image analysis (DIA) for several impeller rotation speeds. In a second study, discrete element method (DEM) simulations are employed to obtain shear forces and force distributions at a single-particle scale. The third study is the comparison of granulation performance using a placebo formulation in the frame of a full factorial design of experiments (DoEs). The mixing investigations show that the two-blade impeller has great potential for scale-up. The DEM simulation confirms that both impeller types investigated apply almost the same shear forces on particles. The granulation performance in the DoE is proven to be better for the two-blade impeller. Larger drive torque is measured, product temperature increases significantly less with reduced thermal stressing, and larger granules are produced. Additionally, particle growth behaviour is more robust as it depends only on the amount of liquid added and is unaffected by the impeller's rotation speed.

1. Introduction

High-shear wet granulation has often been applied in pharmaceutical production for many decades. In the high-shear process, strong and dense granules can be formed to achieve improved product properties for compaction, dosing, or transportation. Furthermore, granulation allows the mixing ratio of different powder components to be fixed, avoiding later segregation into single components and resulting inhomogeneous tablet qualities. High-shear wet granulation is primarily based on three major steps: (1) efficient mixing between the dry powder and the sprayed liquid, (2) formation of granules by liquid bridges and bonds between primary powder particles and finally, and (3) the consolidation of formed granules. Therefore, the granulation is mainly driven by applied shear and normal strain. For many decades, several research activities have been carried out on the fundamental understanding and mechanisms of high-shear wet granulation, as summarized by Parikh [1] and Reynolds et al. [2]. In addition to actual process conditions, such as liquid-to-solid ratio [3], fill factor [4] or impeller rotation speed [5], and material properties of the liquid binder [6,7] and of solids formulation [8], the design of an impeller can have a tremendous influence on granulation performance. The impeller design affects applied forces and energy input into the particle bed. The amount of applied stress manipulates granule densification in the consolidation phase [9]. In principle, differentiation can be made between low-shear granulators (pan granulators or kneaders) and high-shear granulators (impeller systems and extruders), according to the amount of introduced stress [10]. An unambiguous delineation between low- and high-shear granulators has not been made so far. The effect of shear rate on granule properties has been studied by Oulahna et al. [11] equating rotation speed with applied shear. Chan et al. [12] showed by force measurements on the impeller tip that the blade profile exerts stress on the granules that is transmitted through the entire bed. Consequently, applied stress is not only a function of rotation speed; it further depends on the fill level, the blade geometry, and product properties such as bulk density.

The scope of this work is the comparison of a novel two-blade impeller design against a traditional three-blade impeller in high-shear wet granulation. The target in the development of the two-blade impeller was to improve process robustness. The granulation is mainly driven by the mixing of powder and liquid, which should be enhanced by forced axial and radial product circulation. This results in a z-shaped impeller with elongated wings. The wings feature mixing behaviour

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similar to the mixing of non-Newtonian fluids and reduced wall caking. Granule breakage rates should be reduced at lower impeller rotation speeds, achieving uniform particle size distributions with less thermal stressing of the product.

In order to highlight differences between the impeller designs, an intensive study has been performed focusing on the key influences in high-shear wet granulation. The high-shear wet granulation procedure can be divided into three phases: (I) the mixing phase, (II) wetting phase, and (III) wet massing/-granulation phase. The mixing performance is thereby the most decisive key influence for initially creating a homogeneous blend of raw materials that will be fixed by the two subsequent phases. The mixing performance further determines the even distribution of sprayed liquid in bulk during the wetting phase. In the granulation phase, the introduction of force and energy governs growth and consolidation. To expose all key influences with impact on high-shear wet granulation, state-of-the-art analytics have been applied.

The first part of the current study was the investigation of the mixing performance of both considered impellers. The scale-up ability from laboratory- to production-size has been proven; this is important, since scale-up is always challenging in high-shear granulation [13]. Mixing investigations have been performed by the digital image analysis (DIA). The DIA is a powerful tool for any kind of visual inspection, e.g. Daumann et al. [14]. It has been successfully applied for mixing investigations of cement components. Previous work used optically well-identifiable tracer material and determined dispersion coefficients in a twin-shaft-paddle laboratory mixer.

Energy introduced by the impeller during granulation has a decisive influence on granule properties. However, stress and energy input on the single-particle scale is almost impossible to measure within the high-shear process. To identify applied forces on the particle scale, the discrete element method (DEM) has proven to be an effective and established approach to study stress and motion in particulate systems. The DEM approaches traces to the theory of Cundall and Strack [15]. Recently, several researchers have applied DEM for the study of mixing processes [16,17]. However, the method is computationally very expensive. Radeke et al. [18] improved DEM computation time by transferring the computational power from central processing units (CPUs) to massively parallelised graphical processing units (GPUs) on graphic cards. In this way, particle numbers far beyond 1 million can be simulated in reasonable time scales.

Besides the fundamental understanding of the previously mentioned impact of mixing behaviour and energy input, granulation performance is of utmost interest in the comparison of both impeller designs. Mirza et al. [19] proved the influence of different impeller designs on granule properties. They experimentally showed for a variety of very simple blade geometries that a two-blade impeller can provide the best results in terms of granule size distribution and granule strength. Within the frame of the following work, the granulation performance has been investigated by applying a design of experiment (DoE) approach. The basic DoE theory has been well summarized by Antony [20]. Design space analyses were obtained in terms of dependence on impeller design, impeller rotation speed, and liquid-to-solid ratio (L/S). DoEs are often applied in pharmaceutical engineering to improve process understanding and to optimize process performance. For example, Oka et al. [21] applied the DoE approach to show the effect of process parameters on key granule characteristics in high-shear wet granulation.

By means of experimental mixing and granulation investigations and further DEM simulations a fundamental understanding of the performance differences of both impeller designs shall be pursued in detail.

2. Material and methods

2.1. High-shear granulator and impeller

Investigations were performed in a laboratory high-shear granulator (Mycromix, Bosch Packaging Technology, Schopfheim, Germany), as illustrated in Fig. 1. The product container had a volume of 10 L with an inner diameter of $d_m = 0.28$ m. The bottom drive granulator featured a replaceable impeller that rotated between 0 and 500 min^{-1}. A chopper was mounted in the upper lid with speeds of up to 3000 min^{-1}. To disturb the tangential product flow, a baffle was installed in the upper lid, as well. At the bottom end of the baffle, a PT100 temperature sensor measured the instantaneous product temperature. The liquid was introduced into the granulator by a one-component full-cone spray nozzle supplied by a peristaltic pump. The liquid reservoir was connected to a balance controlling the liquid mass flow rate. Besides the laboratory scale, mixing trials were also performed in a 600 L production-scale granulator (HTG600, Bosch Packaging Technology, Schopfheim, Germany), as presented in Fig. 2. The production-scale granulator had an inner diameter of $d_m = 1.05$ m and offered, in principle, the same design and equipment as in a typical laboratory granulator.

Two different impeller designs were thoroughly compared in this work. A standard three-blade impeller, as shown in Fig. 3, consisting of three single blades 120° apart, was incorporated close to the bottom of the granulator. The edges of the impeller blades were raised alongside the bottom radius of the vessel. The front side of the blades had a 45° slant. In Fig. 4 the two-blade impeller is illustrated. Besides the number of blades (decreased by one) and the 180° blade arrangement, the bottom design was identical to the three-blade impeller. However, the outer parts of the blades had elongated side wings that reached up to the lid of granulator. The upper parts of the wings were broadened. At the ends, the wings were reduced in width to avoid product transport against the lid, causing additional wall-wiping and avoiding product adhesion at the wall. In the laboratory granulator, the three-blade impeller had a total blade surface area of 588 cm^2. The total blade surface area for the two-blade impeller was 1.05 larger, at 622 cm^2. This higher surface area was located more toward the outer radius of the impeller. At this location, the largest circumferential velocities occur.

2.2. Materials

In the mixing trials, spherical sugar pellets (Pharm-a-spheres, Hanns G. Werner, Germany) with an average particle size of $d_p = 1$ mm were used. The sugar pellets had a pure white colour. In order to achieve optical identification in the DIA investigation of mixing homogeneity 20% of the white sugar pellets were blue-coated (Kollicoat IR Brilliant Blue, BASF SE, Germany) in an upstream fluid bed coating process. The coating solution consisted of 10 wt% Kollicoat and 90 wt% water. A weight

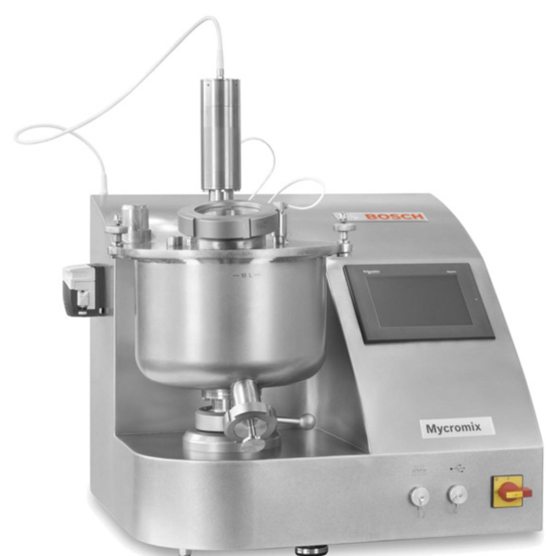

Fig. 1. A 10 L laboratory high-shear granulator.