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Original Research Paper

A quantitative study of the effect of process parameters on key granule characteristics in a high shear wet granulation process involving a two component pharmaceutical blend

Sarang Oka [a], Ondřej Kašpar [b], Viola Tokárová [b], Koushik Sowrirajan [a], Huiquan Wu [c], Mansoor Khan [c], Fernando Muzzio [a], František Štěpánek [b], Rohit Ramachandran [a,*]

[a] Department of Chemical & Biochemical Engineering Rutgers, The State University of New Jersey, United States
[b] Department of Chemical Engineering, Institute of Chemical Technology Prague, Czech Republic
[c] Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Science, CDER, FDA, Silver Spring, MD, United States

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ABSTRACT

The objective of the current work was to investigate the effect of liquid to solid ratio (L/S), impeller speed and the wet massing time on the critical quality attributes of granules in a high shear wet granulation process for a two component (API and excipient) system. The parameters were evaluated for their effect on granule properties using a design of experiment based approach. Granules were characterized for their particle size distribution, content uniformity, morphology and porosity.

The liquid to solid (L/S) ratio was found to have a dominant effect on the median particle size and exhibited a clear trend. The system was found to be extremely well mixed for all conditions thus implying robust composition uniformity within and between batches, independent of process parameters. The release kinetics of granules within the batch were found to be identical, independent of particle size. The granules were found to be fairly spherical as observed through a scanning electron microscope with no distinct agglomeration. The images indicate granulation by layering and consolidation. All three process parameters were found to have an effect on granule porosity, with the wet massing time having the most pronounced effect. A judicious selection of the afore mentioned process parameters will enable a balance between granule growth and porosity to be achieved without compromising on the mixing efficiency of the process thereby allowing one to build quality into the final product.

1. Introduction and objectives

Granulation is a particle size enlargement process employed in a variety of industries to convert fine powders into granules. In high shear wet granulation, this is performed by spraying a liquid binder onto the powder mass which is being mixed in a high shear blending environment [1,2]. The process finds extensive application in the pharmaceutical industry since it provides superior control of drug content uniformity at low drug concentrations, bulk density and compactibility. Improved bulk density and flow make these granulated formulations compatible for high speed tableting operations [3]. Consequently, granule properties like particle size, density, morphology, content uniformity and porosity are critical quality attributes (CQAs), the dependence of which on process parameters must be well understood.

Regarding Quality-by-Design (QbD), there are several definitions available in the regulatory guidelines (such as ICH Q8(R2)) and publications. One is that quality should be built into a product by a thorough understanding of the product and the process by which it is manufactured along with knowledge of the risks involved and how best to mitigate those risks [4]. To improve quality, it must be built into the product and to be able to achieve this requires an understanding of how formulation and manufacturing process variables affect product quality. A thorough comprehension of the granulation process and its underlying mechanisms is thus critical.

A number of rate processes, occurring simultaneously contribute to the evolution of the final product attributes in high shear wet granulation. The rate processes can be divided into three classes, namely, nucleation and wetting, growth and consolidation,

* Corresponding author. Tel.: +1 848 445 6278.
E-mail address: rohitrr@rci.rutgers.edu (R. Ramachandran).

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and attrition and breakage [5]. The final product attributes are dictated by the nature of the dominant rate process or processes, which in turn are dependent on the material properties of the formulation and the process parameters. Often, there is little leeway for a formulator to modify material properties of the formulation and thus mapping of the design space of the process parameters remains a key to achieving granules with desired properties.

Given the large number of process variables that can affect product performance in a high shear wet granulation process, it is critical to identify the ones that have the most significant impact on product performance. This is synonymous to identifying factors that maximize risk (ICH Q9). The guidance document states that in order to minimize risk, it is necessary to identify critical process variables that have the most impact on product performance.

Researchers [6,7] have shown that the wet massing time, the binder amount and the impeller speed have the most significant impact on the granule CQAs, namely their size distribution, content uniformity, morphology and porosity. Woyna-Orlewicz and Jachowicz [6] used a Plackett–Burman type design to show that the wet massing time, L/S ratio and the impeller speed were the most critical from a total of 7 factors. Recently, Pandey et al. [7] reported that the wet massing time, binder amount and impeller speed were statistically significant in terms of their effect on particle growth ratios, the amount of fines, bulk density and granule porosity for a 2:1 ratio of microcrystalline cellulose (MCC), lactose system. Badawy and coworkers [8] reported a similar finding for three weak bases which were used as model compounds and showed that the water amount, impeller speed and wet massing time have a significant effect on granule particle size, growth ratio, density and the amount of fines.

However, for a rational Quality by Design, not only is it important to establish a relationship between process parameters and bulk granule properties but it is equally important to understand the quantitative relationship between process parameters and the resulting product microstructure. Rahmanian et al. [9,10] studied in detail, the effect of process parameters on the internal structure of granules. They reported that although the impeller speed did not have a significant effect on the granule size distribution, the sphericity of granules increased with increase in impeller tip speeds. The increase in sphericity translated into an increase in granule strength. Granule porosity was found to decrease with increasing impeller speeds and thus granule porosity and strength were found to be inversely related.

Of equal importance is the content uniformity of the API in granules. Measuring and ensuring content uniformity of the intermediates ensures process robustness and is in lockstep with concepts of QbD. This has resulted in an increased interest from the industry to understand the phenomenon of mixing (or demixing) during the granulation process. van den Dries and Vromans [11] reported that the extent of demixing depends on the difference in particle size between the excipient and the active ingredient while Cavinato and coworkers [12] reported that the granule growth and uniformity were competing attributes dependent on liquid penetration time of the binder.

The process development effort in high shear wet granulation is thus nontrivial. Researchers have also employed a design of experiment [DOE] based approach to understand the effect of process parameters on the above mentioned product attributes [7,8,11,12] and there has been a significant advancement in the understanding of fundamental physical phenomena that govern granulation behavior [13–16]. An effort that quantifies rate processes by the use of dimensionless numbers to enable rational process development is the regime map approach [17–19]. The approach allows one to make an a priori estimate of the dominant granulation mechanism for a given system, but the method is yet to be fully investigated for multi-component systems.

Thus, despite the recent advances, process development continues to occur via heuristic experimentation. This is contradictory to the premise of QbD and there thus exists a need to connect granule properties (bulk and internal) to process parameters with granulation mechanisms through the course of the process development. In an attempt to achieve the same, a systematic exercise has been undertaken to map the critical design space, quantify the effect of key process variables on CQAs and to identify underlying granulation mechanisms in a two-component high shear wet granulation system. The current work focuses on the wet massing time, L/S ratio and impeller speed for previously mentioned reasons. The uniqueness of the work lies in the comprehensive characterization of granules comprising of two components manufactured by a high shear wet granulation process for its internal structure, content, bulk properties and release kinetics. Relations between these properties have also been investigated. To investigate the variability of the granulation mechanism in the same batch, classic dissolution tests have been performed. The granules have been characterized to determine their particle size and shape, content uniformity, release kinetics, morphology and the porosity to achieve the objectives listed below.

The objective of the present work were: (1) to investigate the effect of impeller speed, the liquid to solid ratio (L/S) and wet massing time on the granule size distribution, content uniformity, granule porosity, release kinetics and morphology of granules generated by a high shear granulation process; (2) to quantify the dependence of granule properties on process parameters and propose mechanisms for the observed results; (3) to indicate co-relations between granule properties, if any, and their application in the design of high shear granulation systems.

2. Materials and methods

Semi-fine acetaminophen (Mallinckrodt Inc, Raleigh, NC) was used as the active pharmaceutical ingredient (API) and microcrystalline cellulose (Avicel PH-102, FMC BioPolymer, Philadelphia, PA) was used as the excipient. The API load in all cases was 30% (w/w). The drug load was not selected as a representative of any specific product but as a representative of typical drug loads used in most pharmaceutical formulations currently. Water was used as the binder. Ethyl alcohol for UV/VIS spectroscopy (>99.8%) was purchased from Lachner. Water needed for the same was purified by a demineralized water generator (Aqual 25) to a conductivity of $\sim$1 $\mu S\,cm^{-1}$. All experiments were performed at room temperature.

The particle size distribution of the primary particles was measured using a laser diffraction technique (Beckman Coulter LS 13 320). Each measurement was performed thrice and the average value has been reported in Table 1. Bulk density of the ingredients was measured by calculating the volume occupied by a known mass of material as it was poured in a graduated cylinder using a funnel. Each measurement was repeated thrice and the average value has been reported in Table 1.

2.1. Experimental design

The design space was chosen based on several experimental trials to obtain granules of reasonable quality in terms of size and strength. For L/S ratios less than 60%, granules were found to be flaky while for L/S ratios of more than 80%, the batch was found to be over granulated. The impeller speed was decided with an objective to achieve good mixing keeping in mind that a high impeller speed will lead to vortex like formation of the powder mass which could compromise mixing efficiency and granulation behavior. The wet massing time was selected with an aim to