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Assessment of predictive models for characterizing the atomization process in a spray dryer's bi-fluid nozzle

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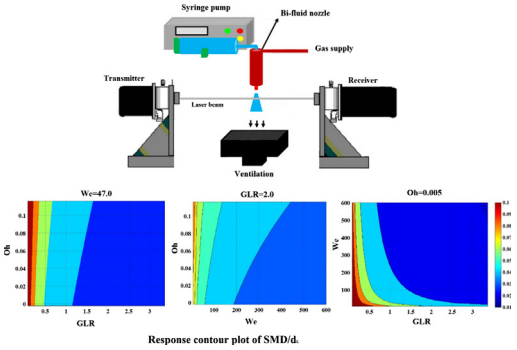
HIGHLIGHTS

- A spray dryer's nozzle with different designs, able to atomize polymers dissolved in solvents under versatile conditions is investigated.
- Scale analysis is utilized to relate non-scaled parameters to droplet size distribution.
- Models are provided to describe both the droplet Sauter mean diameter and the span of the droplet size distribution.

GRAPHICAL ABSTRACT

Droplet size distribution which is a pivotal factor affecting both size and morphology distribution of the final dried particle is investigated and characterized utilizing non-scaled parameters.



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ABSTRACT

Spray drying as a commonly used process to produce amorphous solid dispersions of poorly water soluble active pharmaceutical ingredients (API) involves dissolution of the API and often a polymer, surfactant, and/or other functional excipient(s) into a volatile solvent. This feed solution is then pumped to an atomizing nozzle to produce droplets inside the drying chamber. The current paper aims to utilize non-scaled parameters to characterize the atomization process. A bi-fluid nozzle with two different designs commonly used in a lab-scale spray dryer was investigated under different operating conditions. The feed solutions were made of several excipients commonly used to produce amorphous solid dispersion composites. Atomization characterization is presented via both mean droplet size and size distribution. Various models are evaluated for predicting droplet mean diameter and span suitable for extrapolating atomization in the spray drying process. These approaches may be extended to other nozzles and across scales.

1. Introduction

Poorly soluble APIs are often prepared as amorphous solid dispersion composites whereby the API (i.e. the drug) is combined with one or more excipients. Via this approach, the API may achieve improved thermodynamic activity in solution so as to increase the driving force for absorption and therefore the oral bioavailability. Pharmaceutical spray drying is commonly used to make amorphous solid dispersions (Beyerinck et al., 2010; Paudel et al., 2013) of the drug by combining with polymers and often other functional excipients such as surfactants. The steps in a pharmaceutical spray drying process include the following (Masters,

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1979): (i) Preparation of a feed solution using a solvent or solvent system that can readily dissolve the drug, polymer and other functional excipients, (ii) Atomization of the feed solution into the drying chamber where it is mixed with the heated drying gas, (iii) Evaporation of the fine spray droplets to produce solid particles, and (iv) Separation of the processing gas and the particles in a cyclone placed downstream of the main spray drying chamber. The formation of droplets via atomization is a critical step directly influencing the size and porosity of the resulting particles (Sander and Penović, 2014), the droplet size distribution may impact residence time and drying rates which may impact particulate physical structure and chemical homogeneity in space (Poozesh et al., 2017). Understanding the relationship between the processing conditions and resultant droplet size distribution and evaporation rate is therefore essential to identifying acceptable process ranges for various instrument scales. The purpose of this paper is to highlight those properties of the feed solution that impact the droplet size distribution for a given nozzle design and generate some guidance for understanding associated process sensitivity.

Although the pharmaceutical literature has limited focus on the atomization process, many pharmaceutical unit operations rely heavily on the associated theory and application. Atomization is considered as one of the key steps in several pharmaceutical unit operations such as spray drying (Vicente et al., 2013), spray-freeze drying (Wanning et al., 2015), tablet coating for elegance, modified, and controlled release formulations (Dennison et al., 2016), and fluidized bed granulation (Burggraeve et al., 2013) among others. For all applications, reproducibility must be achieved if consistent functional outcomes are expected. The atomization process must be well controlled, efficient, and reproducible across the controlled operational space. That is, performance measures must not be greatly influenced by expected fluctuations in the process conditions. As an example, it was shown that for a given batch of spray dried felodipine and poly(vinyl) pyrrolidone, large particles (presumably originating from large droplets) showed amorphous-amorphous phase separation while small droplets (presumably originating from small droplets) existing as a single homogeneous phase (Poozesh et al., 2017). Further, it was shown in the same publication that the morphology can be impacted by the distribution in droplet size. Clearly, a fundamental understanding of the spray drying process must start with an understanding of atomization phenomena.

The process of droplet inception (atomization) to particle birth (solidification of the dissolved species) involves interacted fluid dynamic, heat and mass transfer phenomena, mandates step by step research throughout the spray dryer. First and foremost, the atomization process must be understood. Atomization is the process by which a liquid jet disintegrates into unstable sheets, then ligaments and finally droplets. Focusing on the left panel of Fig. 1, sheet formation exists immediately adjacent to the nozzle tip and is difficult to capture – even via high speed imaging. Nevertheless, a continuous liquid is observed at the regions close to the nozzle tip; then by gradually going downward, the ligaments are more easily visualized. Finally, droplets are more easily identified as shown in this figure. The position and timescale of these breakup processes (i.e. sheet formation, ligament formation and droplet generation) are functions of nozzle design, operating condition, viscosity, density, and surface tension of the feed solution, among other variables. Obtaining meaningful droplet size distribution measurements must include consideration of the location of each of these transition points. Specifically, if measurements are focused on the region where sheet formation or ligaments dominate, the meaning of "droplet size" is unclear. Therefore, measurements should be made as a function of distance from the nozzle tip as will be shown below. Further, high speed imaging (the topic of a subsequent paper) may be coupled with droplet size measurements to ensure appropriate interpretation. According to Babinsky and Sojka (2002) there exist three available methods for modeling droplet size distribution: the maximum entropy method, the discrete probability function method, and the empirical method. Based on maximum entropy method the most likely droplet size distribution is the one that maximizes the entropy function under a set of physical constraints (e.g. conservation of spray mass, minimization of surface energy, etc.). These constraints are relied on at least two representative diameters of the droplet size distribution calculated via instability analysis by which only one diameter can be obtained. This shortcoming makes this method less favorable for practical applications. On the other hand, in discrete probability function method, a droplet size distribution is obtained from applying deterministic linear or non-linear breakup models on non-deterministic initial conditions that depend on variety of factors (such as turbulence, surface roughness, vortex shedding, mixture composition, etc.). This method can be used only for the initial stage (i.e. primary breakup) in atomization process; so its application is limited particularly for our bi-fluid nozzle whereby the secondary breakup controls the droplet size. Finally, there is classical method of modeling droplet size distributions: a curve is fit to data collected for a wide range of

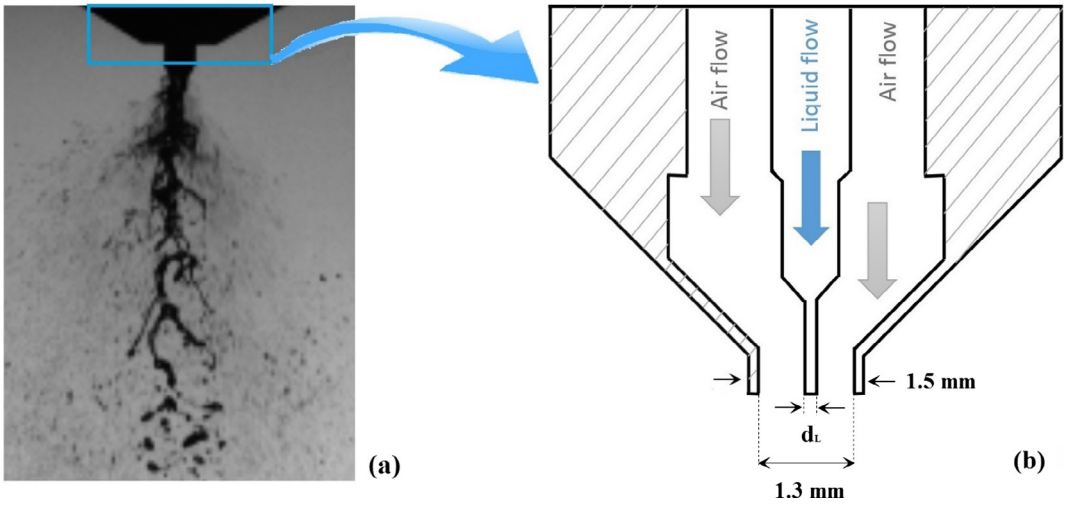

Fig. 1. Left: breakup mechanism, right: configuration of the bi-fluid nozzle.