SPRAY CHARACTERIZATION FOR FLUIDIZED BED GRANULATION PROCESSES

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Abstract
The fluidized bed granulation process is used in various applications in areas like pharmaceuticals, chemical, food and dairy industries. This process takes place inside a fluidized bed column where a binder solution is sprayed onto the fluidized powder in order to granulate the powder. Controlled spraying and atomization of the binder solution is necessary for an optimal process. It is important to determine dependence of spray properties on the atomization parameters at different scales used during development, as this information can be used as a basis for establishing process parameters for the manufacturing process. This paper presents the spray characteristics of hydroxypropyl Cellulose (HPC) solution sprayed through two different size nozzles used for the top spray granulation process in a fluidized bed column.

Introduction

Fluidized bed processing is used for drying, cooling, agglomeration, granulation, and coating of particulate materials or coating of tablets [1]. Agglomeration and granulation of particulates may be performed in a number of ways depending upon the feed to be processed and the product properties to be achieved. The use of fluidized beds for granulation was first described by Wurster based on his work on air suspension coating [9]. In the last twenty years, this granulation technique has received significant attention in the pharmaceutical industry since it offers a number of advantages such as better dust control and reduced powder handling over conventional wet granulation processes [2-8]. The most common method of fluid bed granulation is top spray granulation where the binder solution is spread from a nozzle located above the fluidized bed [3-4]. Droplets from the spray nozzle get deposited onto the solids in the bed below. The fluidization is carried out using hot air, and hence liquid from the droplets (before and after deposition onto solids) is evaporated. The purpose of this process of droplet deposition followed by evaporation of liquid is the formation and growth of granules.

The granulation process in the fluidized bed is a complex process since there are a number of parameters that can affect it. A list of most of the important process and apparatus parameters is presented by Rambali and co workers, which includes atomization nozzle parameters such as nozzle air pressure, nozzle height position, nozzle air cap position, nozzle diameter and spray rate of binder solution [7]. They showed that atomization pressure and air cap position were significant parameters affecting the geometric mean granule size.

In order to develop a robust pharmaceutical manufacturing process, it is important to determine all the process parameters affecting critical quality attributes of the final product. The effect of these parameters on the final product and interactions amongst them should be determined at small scale since drug requirements to conduct these tests is manageable at this scale. This data can be used to predict parameter values for processing at manufacturing scale.

Experiments were carried out to test spray characteristics of HydroxypropylCellulose (HPC) solution using two different size nozzles commonly used for top spray granulation. The effect of atomization air flow rate, liquid flow rate and air cap position on the droplet size distribution was studied.

Experimental Setup

Table 1 presents dimensions of nozzles used during these experiments. Nozzles were tested using water and 3.93 % (w/w) HPC solution in water (see Table 2). For the droplet size measurement, a laser diffraction particle analyzer from Malvern Instruments (model # 2600) was used. This particle sizer is based on the principal of laser ensemble light scattering. Droplet size distributions are inferred from the measured scattered light distribution on an array of ring diodes. The instrument does not measure individual drop size directly, nor does it measure drop velocity. It measures a 13 mm diameter x 230 mm length cylindrical portion of the spray from the nozzle. A 300 mm lens was used which limits the measurement capability of the equipment to a size range of 5.8 μm to 564 μm. This lens was chosen as an optimum between the size range to be studied and the width of the spray that can be used for the measurement.

Nozzle #	1	2
Column	GPCG- 200	GPCG-15
Nozzle model #	937-7-1S12	940-43-7-1
Air cap size [mm]	6	4.95
Area of annular gap for air flow [cm^2]	0.15	0.11
Liquid tip size [mm]	1.2	0.76

Table 1. Dimensions of tested nozzles

Nozzle #1: Schlick 937-7-1S12 (GPCG-200)					
3.94% (w/w) HPC			**Water**		
Z, [inch]	Liquid, [g/min]	Atomization air, [scfm]	Z, [inch]	Liquid, g/min]	Atomization air, [scfm]
10	351	10, 12, 13	10	383	8, 10, 11, 12, 13
10	405	8, 10, 12, 13	15	383	8, 10, 11, 12, 13
15	405	8, 10, 12, 13	10, 15	437	8, 10, 11, 12, 13
10	463	10, 12, 13	10, 15	473	8, 10, 11, 12, 13

Nozzle #2: Schlick 940-43-7-1 (GPCG-15)				
Z, [inch]	Liquid, [g/min]	Liquid Tip Setting	**Atomization air [scfm]**	
			3.94% (w/w) HPC	Water
10	312	Extended	6.6, 8.1, 9.7, 11.8	6.6, 8.3, 10.5, 12.6
10	209	Flush	6.3, 7.9, 9.4, 11.8	7.0, 8.7, 10.1, 12.0
10	312	Flush	6.5, 8.1, 9.9, 11.6	6.6, 8.3, 10.1, 12.0
15	312	Flush	6.8, 8.1, 9.7, 11.0	7.0, 8.9, 10.5,13.0
10	405	Flush	6.4, 8.1, 9.7, 11.4	6.3, 8.1, 9.7, 11.8

Table 2. Test conditions of both nozzles for the water and 3.94% HPC solution (Z=distance from nozzle tip).

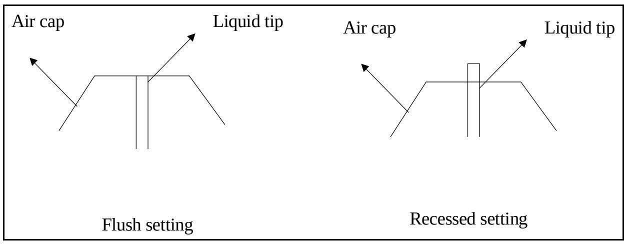

Figure1. Two nozzle tip settings for Glatt GPCG 15 (Nozzle #2)

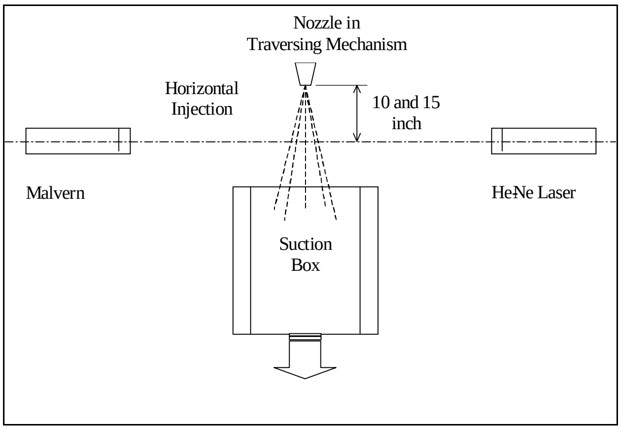

Figure 2. Experimental set-up for drop size measurements with Malvern 2600

The nozzle head for the GPCG-200 column consists of three “The Schlick 937-7-1S12” nozzles. For these experiments, two of the nozzles were blocked off and only one nozzle was tested due to airflow limitations of the set-up. Most of the Schlick nozzles used in Glatt columns have air caps, which can be adjusted in height with respect to the liquid tip. Setting of the liquid tip in line with the air cap is typically called a "flush" setting. If the air cap is set back in comparison to the liquid tip, the setting is defined as "recessed". These two types of settings are shown in Figure 1. The measurements were made at ambient temperature and pressure while the spray was directed in the horizontal direction into a collecting chamber, which was connected to an exhaust fan. The measurements were made at a distance (Z) of 10 inches and 15 inches from the nozzle tip. Figure 2 shows the experimental set-up. The droplet size distribution is discussed with respect to Sauter Mean Diameter (SMD) and 95th percentile for Volume Mean Diameter (VMD).

Results

The droplet size distribution is an important processing variable in the top spray granulation process. It is important for droplets to hit the powder bed for formation of granule nuclei. Smaller droplets, due to their high surface area to mass ratio, may evaporate before reaching the powder bed. Droplets larger than 4 to 5 times the mean diameter of the powder can result in formation of agglomerates. As presented by Parikh, liquid droplets form nuclei from particles in the powder bed, and the size of these nuclei depends on droplet size [6]. These nuclei then grow into granules or break up, depending on various factors such as binding force between particles, surface properties of primary particles, fluidization forces in the bed, etc.

The left frame in Figure 3 demonstrates change in SMD as a function of liquid flow rate at different atomization airflow rates 10 inches downstream from the exit of Nozzle #1. The fluid being atomized is 3.94% HPC solution. As expected, the SMD increases slightly with increase in liquid flow rate. Also, the SMD decreased by increasing atomization airflow rate at a given liquid flow rate. This figure also shows that SMD is higher at 15 inches from the nozzle as compared to SMD at 10 inches. This indicates coalescence in the spray development zone. The right frame in Figure 3 shows the same results for the 95th percentile of VMD. Increase in 95th percentile size is more dramatic than SMD. Increase in this size indicates presence of larger droplets, which will in turn result in formation of larger aggregates of particles. Hence this variable has to be analyzed carefully during process development in addition to SMD.

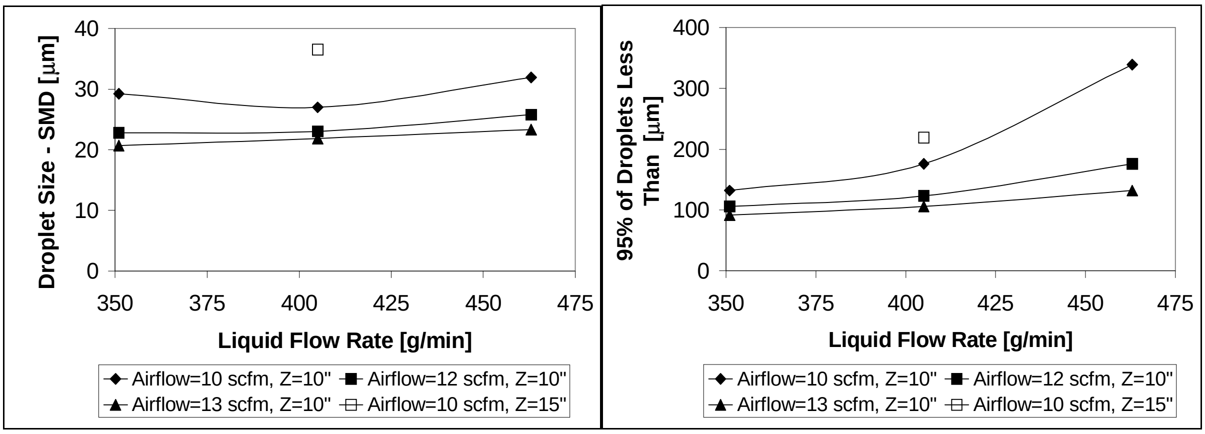

Figure 3. Effect of liquid flow rate on SMD (left frame) and 95th percentile drop size (right frame) for HPC atomization with Nozzle #1

The left frame in Figure 4 shows the effect of the atomization air velocity on the SMD for the HPC solution atomized through Nozzle #1 at different liquid flow rates. At all liquid flow rates, SMD decreases rapidly with increase in air velocity from about 50000 standard ft/min (sfm) to 82000 sfm. As expected, this is caused by providing more atomization energy per unit liquid mass available for the spray break-up. At liquid flow rate of 405 g/min, SMD increases when the size measurement location was moved from Z=10 inch to 15 inches. This is caused by the droplet coalescence in the further spray development zone. The SMD can be reduced approximately 40% for the flow rate 405 g/min, at both measurement locations of Z=10 and 15 inches, by increasing the air velocity from 50000 to 82000 sfm. The right frame in Figure 4 shows 95th percentile of VMD as a function of the atomization air velocity and the downstream distance from the nozzle. The data indicates that there is an increased risk of over granulation if the process is run at 70000 sfm or lower due to a sharp increase in the size of larger droplets. It also indicates that the process should be run above 70000 sfm since the effect of air velocity on 95th percentile is minimal in this region and hence normal fluctuations in the air velocity during manufacturing will not impact the product quality. The effect of increase in viscosity due to addition of HPC to water is shown in Figure 5. Adding hydroxypropyl cellulose causes an increase in the SMD at all liquid flow rates because of increased viscosity and surface tension.

Figure 6 and 7 present results for Nozzle #2, which is typically used in column GPCG-15 used at pilot scale. The SMD and 95th percentile for VMD show similar trends as seem for Nozzle #2 used in column GPCG-200 used at manufacturing scale. The right frame in Figure 6 indicates that, similar to Nozzle #1, risk of over granulation due to increase in size of larger droplets increases significantly below air velocity of 70000 sfm. This is especially true at higher liquid flow rates. This data also corroborates the fact that it is essential to consider 95th percentile of VMD as one of the parameters to study during process development.

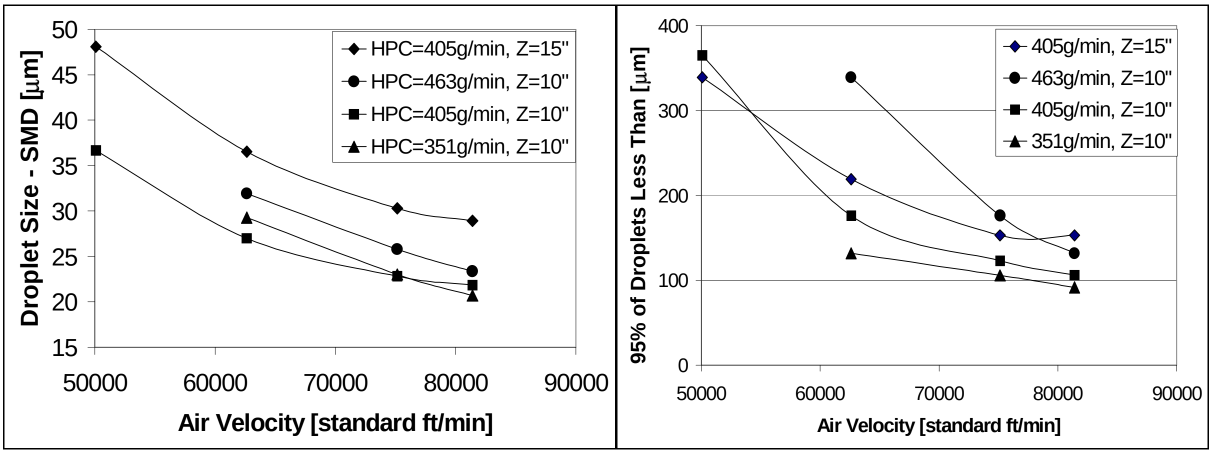

Figure 4. Effect of air velocity on SMD (left) and 95th percentile drop size (right) for HPC with Nozzle #1

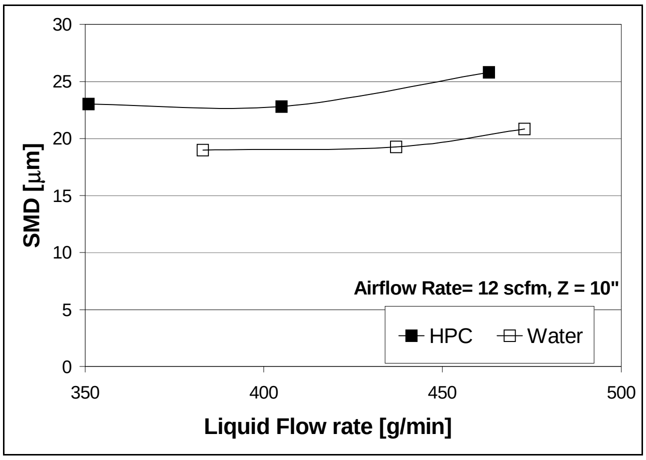

Figure 5. SMD vs. liquid flow rate comparison of water and HPC atomization for Nozzle #1

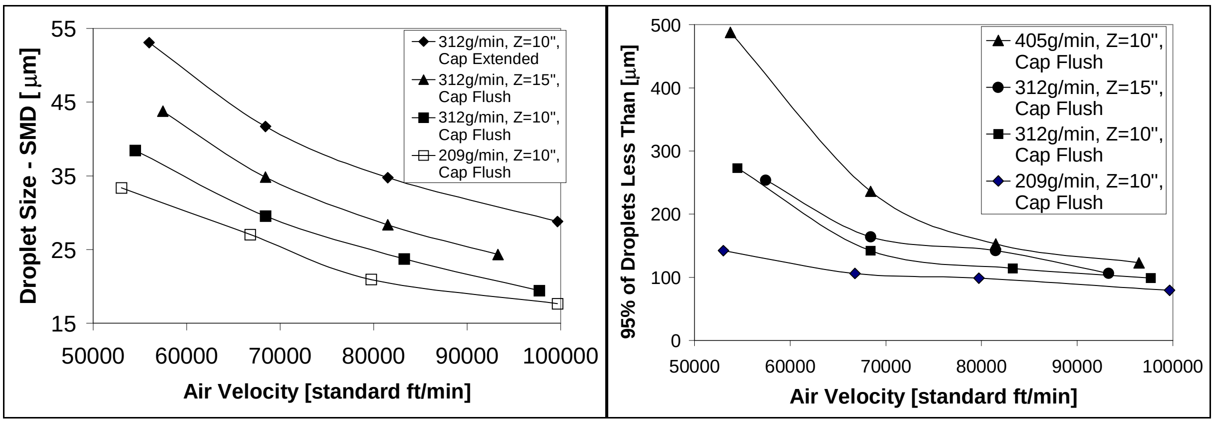

Figure 6. Effect of air velocity and liquid tip setting on SMD (left frame) and 95th percentile droplet size (right frame) for HPC atomization with Nozzle #2

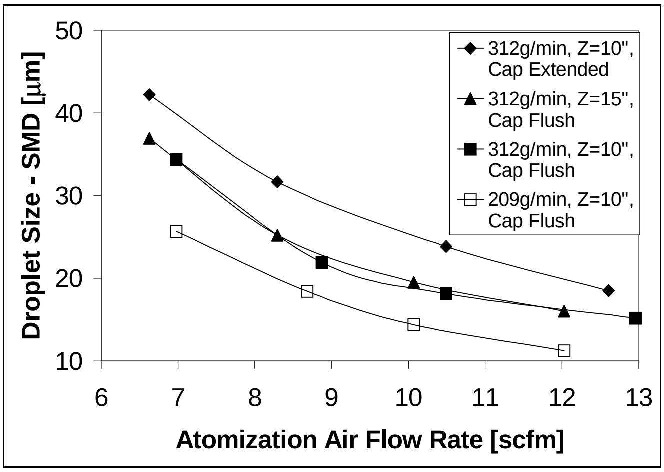

Figure 7. Effect of atomization airflow rate and liquid tip setting on SMD for water with Nozzle #2

Figure 8 compares SMD sizes as a function of atomization airflow rate for two nozzles with the HPC atomization at a liquid flow rate of 405 g/min and 10 inch downstream location. Nozzle #2 generates smaller droplets than Nozzle#1.

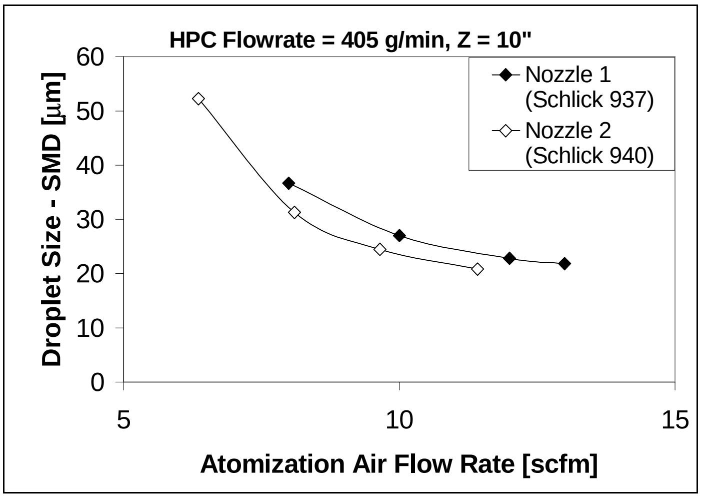

Figure 8. Comparison of the two nozzles with regard to droplet size vs. airflow rate

An experiment was conducted using Schlick nozzle #940-43-7-1 used in the GPCG-15 column to determine the effect of flush vs. extended liquid cap setting on droplet size distribution. The air cap was set to 2.5 mm recessed with respect to the liquid tip. The data from this experiment is presented in Table 3. As seen from the results in Table 3, there is a drastic increase in the 95th percentile for VMD although increase in SMD is not significant when the nozzle setting is changed from flush to recessed air cap setting. In fact, formation of very large droplets was observed (D>200 μm) when the air cap is set recessed with respect to the liquid tip. A plausible explanation is that with the recessed setting, the air hits the liquid tip and gets deflected away from the liquid stream, thus imparting less energy to the liquid. This results in the formation of larger droplets. This data again proves the importance of 95th percentile for VMD as an important parameter in addition to SMD for

Liquid	Air cap setting	Liquid flow rate / # of nozzles, [g/min]	Atomization air pressure, [psig]	95th percentile diameter, [μm]	% less than 10 [μm]	SMD [μm]
Water	Flush	312 / 1	64	63.8	17	15.2
Water	Recessed	312 / 1	64	422	14.4	18.5
HPC solution	Flush	312 / 1	64	98.6	11	19.4
HPC solution	Recessed	312 / 1	64	488	6.7	28.8

Table 3. Results of flush vs. extended liquid cap settings

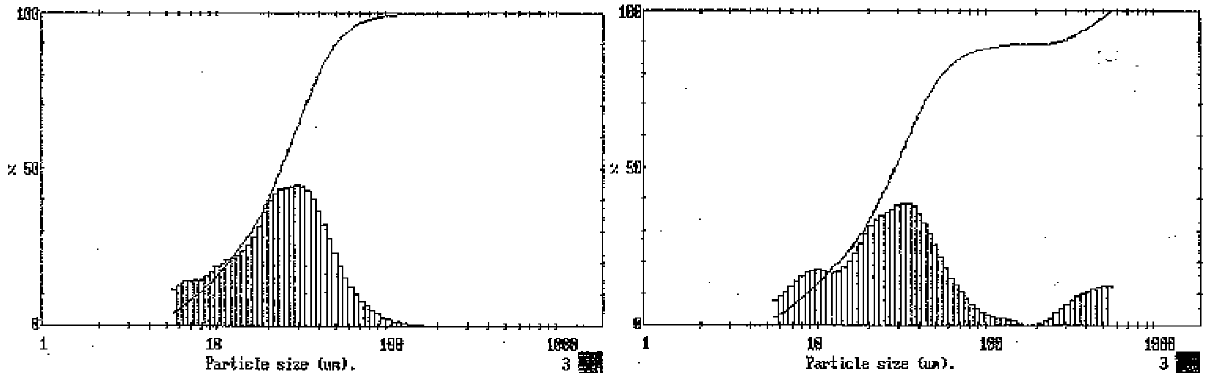

Figure 9. Effect of flush (left) and recessed (right) air cap settings on particle size distributions

characterizing droplet size distribution during development of top spray granulation process. Figure 9 gives a comparison between the droplet size distributions for the flush setting vs. recessed air cap setting at a water flow rate of 312 g/minute and atomization air pressure of 64 psig.

Conclusions

The top spray granulation process in a fluidized bed coater is a complex process including heat, mass, and momentum transfer in addition to spray dynamics. Since droplet size distribution directly impacts granulation properties, it is important to optimize atomization variables for the manufacturing process at different scales. In general, increase in atomization airflow rate at a given air flow rate decreases SMD. Increasing the liquid flow rate increases the SMD. However, of the two fluid flow rates – liquid and air – from the nozzle, change in airflow rate has the dominant effect on droplet size distribution. In fact, to obtain a desired droplet size distribution, airflow rate can be used as a primary control variable. In addition to SMD, 95^{th} percentile of VMD is a useful variable to characterize droplet size distribution. This parameter is indicative of size of large droplets, which are mainly responsible for large aggregate formations. Position of air cap with respect to the liquid tip is an important variable and should be optimized during process development. It should be kept constant from batch to batch for a given product.

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