Effects of Blade Design in Wet Granulation in a High Shear Mixer Determined by Positron Emission Particle Tracking*

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Abstract

Wet granulation in high shear mixer is important in reducing potential environmental and safety hazards. A complex mechanism dominates high shear mixer granulation because there is an enormous range of geometries and designs for the mixer. This study is the first report of the effects of blade design on wet granulation in high shear mixer. In this study, two designs of blade were used to compare the granulation, and it was determined that the flat blade resulted in no granule or lump formation, while the beveled blade resulted in good granule formation. Positron emission particle tracking was used in order to investigate the effects of different impeller designs in wet granulation in a high shear mixer. These results should prove useful in improving process design in order to optimize the final granules, and in improving the quality of the resultant product.

Key words: Positron Emission Particle Tracking, High Shear Mixer, Particulate Motion, Granule motion, Wet Granulation

1. Introduction

In the last few years have seen a spectacular growth of interest in the field of aerosol science. Research in this field has focused on the role of aerosols in such topical areas as heavy metal pollution, acid rain, photochemical smog and global warming. Atmospheric Particles examines the fundamental aspects of aerosol science relating to particles in the atmosphere, including the sources and size distribution of airborne particles, the means of sampling and chemical analysis, and the serious health implications of particles in the urban atmosphere.

Inhalation aerosols have been also used in the asthmatic and bronchial therapies because good clinical effects and reductions of systemic side effects are achieved by delivering moderate amount of drugs directly to the affected parts. Among the aerosol inhalation systems, much attention has been paid to dry powder inhalation aerosols as alternatives to pressurized metered dose inhalation aerosols. The particle size of aerosols is one of the key factors that determine the deposition site of inhaled particles in the human respiratory tract on inhalation. Micronization leads to the difficulty in the handling of drug particles caused by their strong adhesive and cohesive properties. To solve these problems, physical
properties of finer particles are modified by granulation.

High shear mixers are exceedingly useful in achieving high performance dry powder mixing, wet powder mixing and granulation. These types of powder mixing technologies have been advantageously used in a variety of industries in order to reduce production times, to improve process hygiene and powder/liquid mixing, to produce stable emulsions, to dissolve powders or disintegrate solids, to blend liquids of different viscosities, to disperse and hydrate gums, or to dilute high active surfactants, thickeners and stabilizers. Wet granulation is a particularly important step, as it involves taking a homogenous, dry mix of active substances and excipients, and then adding a binder liquid in order to create agglomerates. However, many factors involved in the mixing can affect the quality of the product: the physical properties of the processed materials affects the design of the mixer selected for use, the properties of the source materials can affect the flow pattern within the mixer, the nature of the mixing procedure influences the homogeneity of the resulting mixture, and the degree of mixing of the constituent materials influences the quality of the product.

A high shear mixer is able to handle fine cohesive powders as well as high viscosity binder liquids. Compared to fluid bed granulation, high shear mixer granulation usually results in more spherical, better compacted granules with a wider particle size distribution. However, a complex mechanism dominates high shear mixer granulation because there is an enormous range of geometries and designs for the mixer, with a very wide range of agitation intensities (i.e. shear rates). The mechanisms for powder flow behavior within a high shear mixer are still poorly understood because mixers are considered to be the most complicated of all granulators for analyzing product attributes (1). Positron Emission Particle Tracking (PEPT) can provide quantitative information on the motion of particles in granular and fluid systems, such as in a mixer, and is a powerful tool for non-invasively exploring the dynamic behavior of a single particle in an opaque system.

In recent years, finer resin tracer particles have been developed, which has made it possible to mimic the fine cohesive particles used in high shear mixers. Although various methods have been used to examine the effectiveness of granulation in high shear mixers, these studies have generally focused on variables other than the design of the impellers themselves. Darelius et al (2) used laser Doppler anemometry to measure particle velocity distributions within a high shear mixer during wet granulation at various impeller speeds (450, 600, and 750 rpm) using 3 blades. Ghorab et al (3) reported the liquid-to-solid ratio, impeller speed, binder flow rate, and wet massing time as important factors that can affect granule formation in a high shear mixer, but made no mention of the impeller design itself. Lu et al (4) examined the effects of impeller blade number on mixing using 2, 4, 6, and 8 straight blades, although these experiments focused on gas dispersion and mass transfer in mechanically agitated vessels using Rushton-type turbine impellers, not high shear mixers, and did not examine different blade designs. Sinnott and Cleary (5), however, investigated high shear mixing of dry materials by using two different blade configurations—a disc impeller and a rectangular blade impeller, with effectively 2 blades—and discrete element method (DEM) simulations. They found that the use of a blade impeller resulted in complex flow behavior: particles flowing over the first blade were deposited in the void following the movement of the impeller and fell to the bottom of the mixer. The action of the blade meant that surface particles are thrown radically outwards, resulting in rapid mixing in the top and bottom layers. Sinnott and Cleary found that the rate of mixing was quicker with the rectangular paddle-type blade than with the disc impeller, with steady radial and circumferential mixing observed when the rectangular blade was used, while no radial mixing was observed when the disc impeller was used.

The purpose of this study was to investigate the effects of two different blade designs in wet granulation using PEPT. As a result, it was possible to determine that a beveled
design resulted in good granule formation, while neither granules nor lumps were formed when using a flat blade.

Nomenclature

- \( V \): velocity, m/s
- \( p \): particle track location, m
- \( t \): time of particle track location, s

Subscripts

- \( i,j \): corresponding to \( i \)th, \( j \)th particle track location
- \( j \) is also used as a summation index, in difference equations
- \( r \): \( r \)-direction component
- \( z \): \( z \)-direction component

2. Experimental

Microcrystalline cellulose powder (MCC, Avicel PH102, Merck, UK) was used as a starting material, and polyvinyl alcohol (PVA, 87-89% hydrolyzed, Sigma-Aldrich, UK) was used as a binder. The viscosity of the PVA water solution depends on the average molecular weight of the PVA. The PVA was dissolved in distilled water at 60-80°C while stirring the solution for 3 hours with a magnetic stirrer, resulting in a PVA concentration of mass% in the solution. As shown in Table 1, the viscosity for each 4% PVA solution was provided by Sigma-Aldrich and measured with a rheometer (Cone shape rheometer, CVO50, Bohlin Instruments).

Table 1  The relationship between molecular weight and viscosity in 4% PVA solution

<table>
<thead>
<tr>
<th>Molecular weight</th>
<th>85,000-124,000</th>
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<tbody>
<tr>
<td>Viscosity, ( \mu )/mPa ( \cdot ) s</td>
<td>20</td>
</tr>
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</table>

Two types of high shear mixers, horizontally shafted and vertically shafted mixers, are commonly used in industrial applications. The former are generally used in continuous mode, and the latter in batch processing. In this study, a vertically shafted mixer was used, as is commonly used in the pharmaceutical industry.

The high shear mixer used in this study was fitted with a stainless steel bowl (internal diameter 210 mm, vertical height 200 mm) attached with a centrally mounted impeller rotating around a vertical axis (Fig. 1). The experiments were carried out using two
different blade designs for the agitator: three beveled blades and three flat blades (see Table 2 and Fig. 2).

<table>
<thead>
<tr>
<th>Table 2 The geometry of blades</th>
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<tbody>
<tr>
<td>Beveled blade</td>
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<tr>
<td>Angle of the leading edge, $\theta$ /deg.</td>
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<tr>
<td>Number of blade</td>
</tr>
<tr>
<td>The length of blade, L/mm</td>
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<tr>
<td>The thickness of blade, T/mm</td>
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MCC powder (500 g) was placed into the bowl of the mixer. A transparent glass lid was placed over the top of the bowl to support a silicon tube with a diameter of 1 mm that was used to add the PVA binder. A peristaltic-tube-pump (Type 502S, Watson Marlow, UK) was used to perform continuous addition at a constant rate, which made it possible to determine objectively the amount of binder and to achieve saturation of the binder in the granulation process based on the torque measurements. The binder flow rate was 14 g min$^{-1}$. The granules were produced at an impeller speed of 600 rpm in order to investigate the effect of the impeller design on granulation behavior, in which the tip speed of the impeller was 6,600 mm/s ($6.6$ m s$^{-1}$).

PEPT is a method in which a single labeled radioactive tracer mixes with a bed of particulate and granules and is tracked in three dimensions with granulation time. The radionuclide in the tracer undergoes $\beta^+$ decay, that is, a proton is converted to a neutron, which is accompanied by the release of a positron (6). Following its emission, the positron will slow down over a small stopping distance and then annihilate with a neighboring electron. This electron-positron annihilation is possible only when the momentum and energy conservation laws have been met. Each annihilation will result in a pair of 511 keV $\gamma$-rays which, in order to conserve momentum, are emitted back-to-back, 180° apart (to within approximately 0.3°) (7). Detection of coincident pairs of gamma photons on the two camera detectors provides a straight line along which the particle lies, and lines generated from subsequent pairs will intercept at the source, enabling determination of the particle positrons by geometric triangulation.

It is necessary for the size and density of the tracer to be close to that of the bed materials, and therefore a resin particle (strong base anion ion exchanger) with a diameter of $\mu$m and a density of 1100 kg m$^{-3}$ was used as the tracer particle in order to match the diameter and density of the MCC powder. The tracer particles were labeled using a radioisotope $^{18}$F via the ion exchange technique. During granulation, the tracer particle rapidly stuck to the finer MCC particles, thereby providing visualization of the bulk of the
3. Results and Discussion

Knight (8) noted that thin, flat blades with a vertical front surface (90° angle on the front surface) would result in torque that increases with rotational speed, where the torque is the sum of the inertial impact and frictional interactions. He noted that beveled blades with large angles would behave similarly to flat blades, while beveled blades with small angles (approximately 17°) would result in more complex behavior, mimicking the flat blades at lower speeds. However, beveled blades with very small angles (approximately 11°) would show a sharp decrease in the torque at the critical speed, with greater effects of impact forces at lower speeds and with greater effects of frictional forces at higher speeds. The beveled blade used in the present study had an angle which fell between the two examples noted by Knight, and therefore, it would be expected that the results from this study would similarly fall somewhere between the results predicted by Knight. In a previous study of the effects of blade design in dry granulation (unpublished data), we discovered that particularly near the blade, the flow pattern in the flat blade was extremely different from that observed with the beveled blades. In the region near the blade, the powder flow was mainly directed towards the wall of the mixer. There was less upward flow with the flat blade than with the beveled blade, which was determined to be likely due to the difference in the angle of the blades.

In the present study of wet granulation, Figures 3 and 4 show occupancy plots during the granulation for the two blade designs used in this experiment. These figures show the particle motion during each time period in the mixing process, and in these figures, the pink color indicates that the majority of the region within the mixer will show good mixing behavior, while the length of the arrows indicate the velocity of the particle flow. The results displayed are averaged over all the passes of the tracer through each individual pixel. The quantity in this occupancy plot represents the fraction of the selected time range that the tracer was located in each pixel. Occupancy \( O \) is defined as \( O = \frac{t_{\text{pixel}}}{t_{\text{total}}} \) where \( t_{\text{pixel}} \) is the time the trace spends within an individual pixel, and \( t_{\text{total}} \) is the total time range. The length of the arrows

![Fig.3 Occupancy plot in wet granulation - flat blade](image-url)
corresponds to velocity of the flow.

The velocities were calculated using the six point method for PEPT (9). The six point method is the most commonly used method due to the fact that it can reduce the effect of error in the PEPT measurements. \( V_j \) is the velocity at the \( j \)th particle track location, which is point \( p_i \) in space and at time \( t_i \). The velocity \( V_j \) at point \( p_i \) and time \( t_i \) can be calculated from six data points using the following formula.

\[
v_j = 0.1 \left( \frac{p_{i+5} - p_i}{t_i} \right) + 0.15 \left( \frac{p_{i+4} - p_{i-1}}{t_{i+4} - t_{i-1}} \right) + 0.25 \left( \frac{p_{i+3} - p_i}{t_{i+3} - t_{i-2}} \right) + 0.25 \left( \frac{p_{i+2} - p_{i-3}}{t_{i+2} - t_{i-3}} \right) + 0.15 \left( \frac{p_{i+1} - p_{i-4}}{t_{i+1} - t_{i-4}} \right) + 0.1 \left( \frac{p_{i+4} - p_{i-5}}{t_{i+4} - t_{i-5}} \right)
\]  \( \text{(1)} \)

This six point method provides an unbiased estimate of instantaneous speed with an rms error of fewer than 10% of the true speed over the range of speed from 0.1 to 2 m/s (10). The R-Z plane is horizontal and the R plane is parallel to the blades. It is clear that the bed height significantly increased after the induction period, as can be determined from the torque curve for the beveled blade. However, no significant change in the bed height was observed with the flat blade.

This velocity distribution was calculated using the six point method (9), as described above. Figure 5 shows the velocity histograms for the beveled blade design. These velocity histograms were obtained using the “Track” program for Windows (a Track program on PC Windows is used for the visualization and initial analysis of these transferred PEPT results files. This Track program was produced by Dr. David Parker who is a professor of Birmingham University although this software has not been published.), which is used for the visualization and initial analysis of PEPT data. The histograms of the velocity distribution or residence time distribution within a specified region were obtained using “Track” because the “Track” analysis covers the history of the particle’s location over time. As is clear from these figures, the average axial velocity and mean radial velocity for the beveled blade design were -11.11 mm/s and -50.62 mm/s, respectively, with an average velocity of 630.79 mm/s."

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**Fig.4 Occupancy plot in wet granulation - beveled blade**

\[ V_x 2.0 \text{ m/s}^2 \]

\[ V_r 2.0 \text{ m/s} \]
Figure 6 shows a comparison of the velocity distributions in the axial direction (Z) for the two blade designs. In Figure 6, the powder and granule bed were divided layer by layer at every 10 mm of depth in the axial direction in order to obtain the average velocities along the bed height. For instance, the average velocity at the axial position of 50 mm corresponded to the velocity averaged between 45 and 55 mm. As is clear from this figure, the velocity near the blade was significantly higher with the flat blade design than with the beveled blade, but the flow of the material was mainly directed radially outwards, towards the wall of the mixer, and this flow was insufficient to disperse the powder in the axial direction. Figure 7 shows scanning electron microscope (SEM) photographs of the product of the wet granulation process using the two different blade designs. The flat blade design resulted in poor aggregation of the materials, with neither granules nor lumps of material formed. In contrast, the beveled blade design resulted in good granule formation, with
granules of uniform size and shape. Figure 8 shows the granule growth in the granulation process using the beveled blade. Of course, the SEM photographs do not represent the whole of particles and granules. However, this shows that the granules can be formed by the beveled blades.

The new findings should prove extremely useful for the design, operation and scale-up of high-shear mixers. To obtain additional corroborative data, similar experiments should be performed using different powders/binders and different types of mixer designs.

![Granulation time=1800 sec.](image)

Flat blade, Granulation time=1800 sec.

![Granulation time=1800 sec.](image)

Beveled blade, Granulation time=1800 sec.

Fig. 7 SEM photographs after granulation

![Granulation time=720 sec.](image)

Granulation time=720 sec.

![Granulation time=1440 sec.](image)

Granulation time=1440 sec.

Fig. 8 SEM photographs of granules formed by beveled blade
4. Summary

Wet granulation modifies physical properties of finer particles, which is one of key technologies in solving environmental and human health problems. High shear mixer granulation is a particularly important step, as it involves taking a homogenous, dry mix of active substances and excipients, and then adding a binder liquid in order to create granules. In this study, blade design can have a significant effect on granule formation, and a beveled blade design result in the formation of uniform granules during wet granulation, while a flat blade design result in poor aggregation of the materials, with neither granules nor lumps of material formed. The use of PEPT provided useful information on powder flow in mixers beneath the powder surface, which will be helpful in more accurately modeling high shear mixer processing, making it possible to improve mixer design and quality control.

References