A Statistical Method for Velocity Detection in Moving Powder Beds Using Image Analysis

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DOI 10.1002/aic.12624
Published online April 22, 2011 in Wiley Online Library (wileyonlinelibrary.com).

An existing method to measure particle velocity is particle image velocimetry which requires presence of tracer materials. This method of contrast enhancement is not always applicable in an industrial setting. Therefore a method to assess the movement of small, structures has been introduced, called powder surface velocimetry (PSV). The principle of PSV is to follow the movement of small structures on the surface of the powder bed. The displacement of the structure is correlated with velocity. The rate of the blade of a blender was quantified to assess the validity of PSV. Next the powder surface velocity of lactose 100 M was measured by PSV and was found to be in line with expected values and flow regimes. *AIChE J*, 58: 690–696, 2012
Keywords: powder surface velocity, dry powder, excipient, impeller speed, PSV

Introduction

Dry blending of powders is an extremely important unit operation in industry. Obviously, blend uniformity is a basic product quality attribute.[1–4] The homogeneity of a blend is influenced both by the blender and the components of the powder. With regard to the latter, especially the cohesiveness of the powder is relevant.[5–9] A typical example is when a small amount of a cohesive, micronised drug is blended in noncohesive diluents such as lactose. The drug then tends to form lumps or aggregates. Clearly, these aggregates need to be broken. Prescreening of aggregates is a common approach, but do not prevent the powder to reaggregate. From a process quality perspective, the blending conditions need to be such that existing aggregates are broken up sufficiently and that formation of new aggregates is prevented. It has been demonstrated that the speed at which particles move in a mixer is a crucial parameter. Also the filler particle size is of importance here.[10] Measurement of the particle velocity in a moving dry-powder bed is not a trivial operation. For this reason it is often assumed that particle speed in the blender is the same as, or at least proportional with, the impeller (tip) speed.[11] However, it is very reasonable to assume that filler type and fill degree have also a certain impact on the particle velocity. To distinguish impeller speed effects from other effects one should be able to determine particle velocity under different conditions experimentally.

In recent years different techniques like high speed imaging and positron emission particle tracking (PEPT) have been used to measure particle velocities in granulation experiments. PEPT studies were carried out with a single radioactive tracer particle which is followed in space and time. This measurement yields the average velocity patterns within the apparatus. Studies carried out with PEPT have some drawbacks related to cost, spatial resolution, temporal resolution and powder contamination.[12] Until now, only limited studies have been reported on the application of PEPT within dry blending.

Another frequently applied technique to measure particle velocity in granular flows is high speed imaging where individual particles are tracked to measure powder velocities.[13–16]

An alternative to analyze the granular flow is to calculate the velocity using particle image velocimetry (PIV).[12,17] PIV compares two images of subsequent frames at the same location and moves the images over each other until the best match between the images has been found. This matching is quantified using convolution filtering or Fourier transform (FFT). The displacement of the images is proportional with velocity. The images must be large enough to capture the complete path length of the displacement. Furthermore, FFT requires that the number of visible particles or other structures should be sufficiently large in a certain pattern. For example, in the study of Nilpawar et al.[17] it was needed to detect at least 5–10 granules for the detection of velocity with PIV. On the other hand, when the image is over-saturated with visible particles, the field is too busy to distinguish the movement of individual particles.[18]

To solve these issues the granular flow was made visible by addition of tracer particles.[19] A tracer particle is assumed to exhibit similar characteristics and hence the same velocity as the rest of the powder. Of course, the addition of tracer materials is also to be considered as a contamination and therefore not always tolerated.[10]

In this work, we propose the powder structure velocimetry (PSV) method which measures the movement of surface on the powder surface structures. PSV does not require the addition of any tracer.

Experimental

Materials

The material used was lactose monohydrate (Pharmatose® 100M, from DMV Frontera, Goch, Germany).

Equipment

The blending experiments reported in this study were performed in a convective mixer with a bowl volume of 25 L (Fukae Powtec model FS-GS-25J, Japan). The chopper was not installed and the impeller rotated at rates between 50 and 350 rpm corresponding with tip speeds between 1.07 and 7.48 m/s. The fill degree at each experiment was 5 kg powder which corresponds with a relative fill volume of about 27% (V/V).

For capturing the videos of the dry powder bed a Casio-EX-F1, (Casio computer, Tokyo, Japan) Motion Analyzer was used.

Quantitative powder velocity experiments were performed by placing a transparent plexiglass lid on the blender. The camera was placed perpendicular on the bowl. Three large spotlights were used to illuminate the powder surface. The camera operated at a speed of 600 frames per second.

Quantitative image analysis

In this study the method was developed in the empty mixer by measuring displacement velocities of the blades. The impeller arm rotated at rates between 100 and 350 rpm.

Figure 1 schematically depicts the steps applied in PSV. These steps will be described subsequently.

Step 1: Identify Fingerprints of Structures in the Images of the Selected Frames. After selection of two subsequent images the first step in PSV is to identify clearly distinguishable structures (fingerprints). A typical example is depicted in Figure 2. The figure illustrates the initial and following image denoted as $\chi^t_{1:n,1:m}$ (Figure 2a) and $\chi^{t'}_{1:n,1:m}$ (Figure 2b), where t is the initial image at time t and n and m are the number of columns and rows of the image, i.e., 180 × 225 pixels in this case.

Each pixel at location (i, j) in the images has intensity, x^t_{ij} and $x^{t'}_{ij}$.

A subimage of the images at position (i, j), with $\left((i,j)\middle| \begin{array}{l} i \in 1:n \\ j \in 1:m \end{array}\right)$ with a window tile size k is defined as $\chi^t_{ij,k} = \left\{ x^t_{l,p} \middle| \begin{array}{l} l \in (i-k : i+k) \\ p \in (j-k : j+k) \end{array} \right\}$ (Figure 2a) of image $\chi^t_{1:n,1:m}$ and $\chi^{t'}_{ij,k}$ (Figure 2b) of image $\chi^{t'}_{1:n,1:m}$.

The selection of a window-size k depends on the relationship between surface structure and image resolution. This means that in cases that include large structures or low resolution of the image a larger window-size k can be

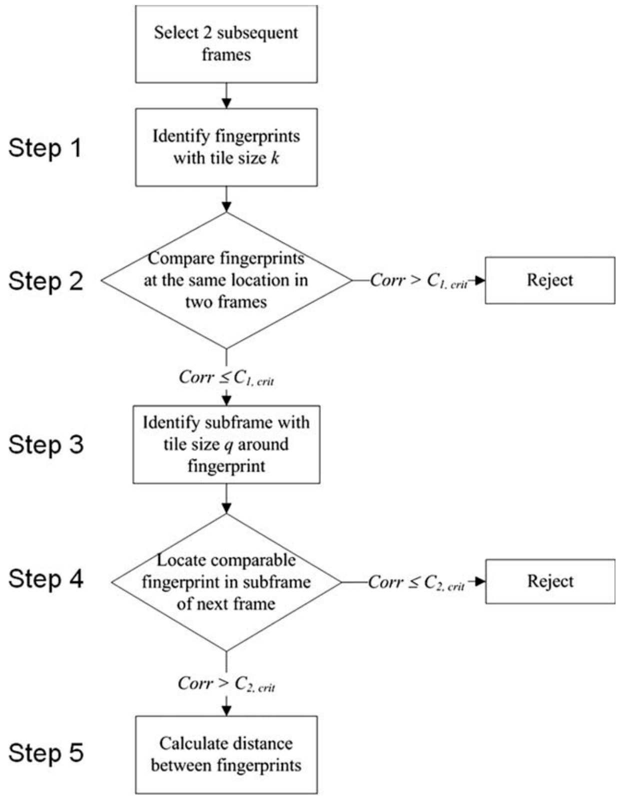

Figure 1. Flow chart applied in PSV.

chosen. In this work, a subimage tile size of 5 by 5 was used that also included taking into account the computational capacity.

The subimages represent a collection of pixel intensities and functions as a fingerprint at a specific location when there is significant variation. This means that a very low intensity variation in the subimage illustrates a nonstructure area and will not be defined as a fingerprint.

Step 2: Detection of Potential Fingerprints for Velocity Calculations. In principle, any subimage pairs $\chi^{t}_{ij,k}$ and $\chi^{t'}_{ij,k}$ at each location $(i,\ j)$ of the two images $\chi^{t}_{1:n,1:m}$ and $\chi^{t'}_{1:n,1:m}$ could be examined for a fingerprint. To speed up the analysis and to make it feasible for a large image data, one can also limit the number of the candidates, which is expected to be statistically significant different between two subimage pairs at the same location for different time points due to the move. This is accomplished by evaluation of the differences between two subsequent subimages, $\chi^{t}_{ij,k}$ and $\chi^{t'}_{ij,k}$, at each location $(i,\ j)$ of the two images. The "corr" statistical correlation command provided by the MATLAB® Statistics toolbox was used for this purpose after reconstruction (unfolding) of the matrices $\chi^{t}_{ij,k}$ and $\chi^{t'}_{ij,k}$ to vectors. In this work a correlation threshold of 0.6 was selected ($C_{1,\ \mathrm{crit}}$ in Figure 1). The subimage pairs that have correlations of less than the threshold $C_{1,\ \mathrm{crit}}$ were considered significant different and were therefore identified as candidate fingerprints in Step 3.

Step 3: Creating a Search Window (in the Next Image) to Find Fingerprints that Moved. The next step in the PSV process is to locate fingerprint $\chi^{t'}_{ij,k}$ in the next image, $\chi^{t'}_{1:n,1:m}$, at a new position in the neighborhood of the initial location $(i,\ j)$ that possesses the best match with $\chi^{t'}_{ij,k}$.

Again, to speed up the analysis a larger search window, $S^{t'}_{ij,q}$, with size q ($q > k$) around position $(i,\ j)$ around the fingerprint of interest (step 3) is used,

$$S^{t'}_{ij,q}\left\{ x^{t'}_{l,p} \,\middle|\, \begin{array}{l} l \in (i-q : i+q) \\ p \in (j-q : j+q) \end{array} \right\}.$$

In this work a search window size q of 31/31 pixels was used. This was large enough to find fast moving objects but still acceptable in perspective of computational capacity.

Figure 3 illustrates an example of the search window $S^{t'}_{ij,q}$ with size q created around coordination $(i,\ j)$.

Step 4: Identify Replacement Trajectory of Fingerprints—the Best Match in the Search-Window. It is now assumed that fingerprint $\chi^{t}_{ij,k}$ is *visible* (reallocated) at a new location $(a,\ b)$ in the neighborhood of position $(i,\ j)$. A second correlation step was introduced to find a new location $(a,\ b)$ having the best match between fingerprint $\chi^{t}_{ij,k}$ and fingerprint $\chi^{t'}_{ab,k}$ within search window $S^{t'}_{ij,q}$, $\chi^{t'}_{ab,k}\left\{ x^{t'}_{l,p} \,\middle|\, \begin{array}{l} l \in (a-k : a+k) \\ p \in (b-k : b+k) \end{array} \right\}$. The corr command (MATLAB® Statistics toolbox, corr($\chi^{t'}_{ij,k}$, $\chi^{t'}_{ab,k}$) was applied again.

A high correlation threshold (e.g., >0.95) (($C_{2,\ \mathrm{crit}}$ in Figure 1) tolerates no or very limited additional changes of the original fingerprint in the initial image, like noise in image signals, other small changes such as light condition or the structure itself which results in a limited number of matched fingerprint pairs.

A relatively low correlation threshold (e.g., 0.7) allows (accepts) more noise or changes to the original fingerprint which results in a high number of matched fingerprint pairs but with low reliability (low confidence). A balance must be chosen depending on the prior knowledge or estimation of, for example, signal noise or other changes. In this work the correlation threshold of 0.9 was selected.

This process was repeated for all selected fingerprints.

Step 5: Calculating the Velocities. The final step in PSV is calculating the velocity based on the displacement of the fingerprints in two subsequent frames.

The displacements ($d_{\chi^{t}_{ij,k}}$) were determined using the distance of two correlating fingerprints, $\chi^{t}_{ij,k}$ and $\chi^{t'}_{ab,k}$:

$$d_{\chi^{t}_{ij,k}} = \sqrt{(i-a)^2 + (j-b)^2} \tag{1}$$

The velocities (v) are now calculated based on the frame rate of the camera ($f = 600$ frames per second) and the size of the pixels (Ψ) (1.3 mm/pixel).

$$v = \frac{d_{\chi^{t}_{ij,k}} * \Psi}{f} \tag{2}$$

The procedure explained so far describes the displacement of structures in two subsequent images. For a complete analysis the structure movement has been detected for 10 subsequent images.

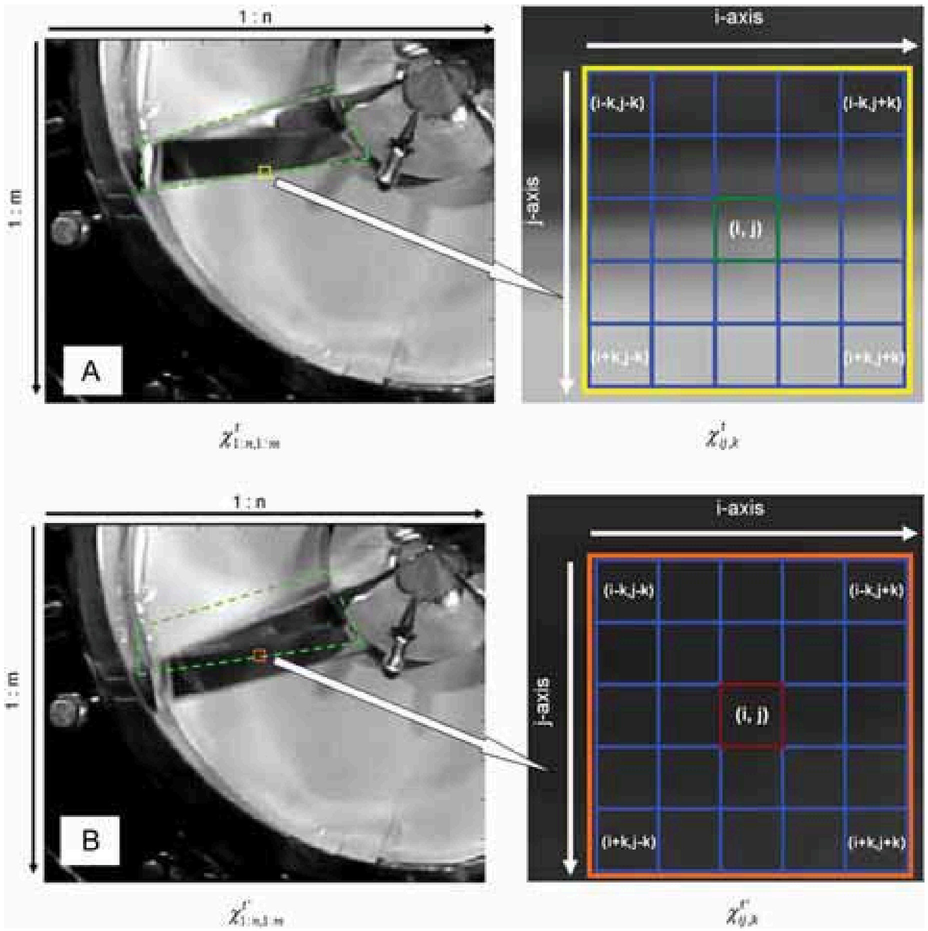

Figure 2. Example of subimages in the initial (A) and following (B) images.

Explanation see text. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

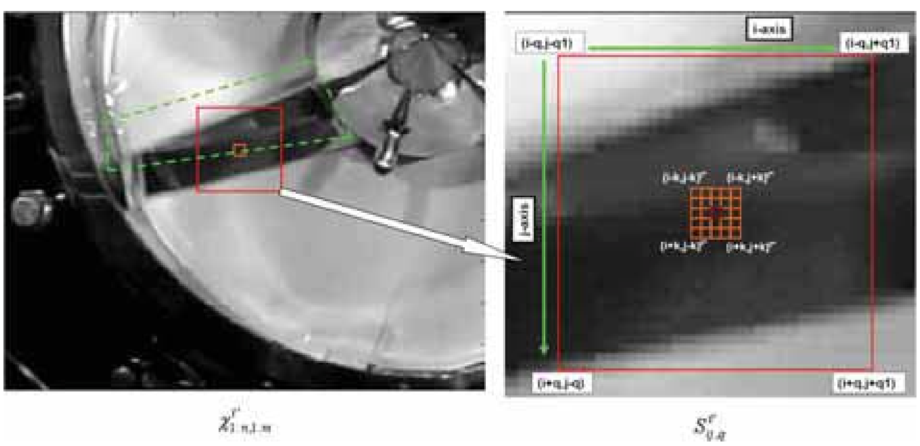

Figure 3. Example of the search window $S^{t'}_{ij,q}$ with size q created around fingerprint $X^{t'}_{ij,k}$.

The left-hand figure depicts a snap-shot at t', the green dashed line depict the impeller position at time t and the small orange box the finger print at time t. The right-hand figure shows the search window and the original finger print. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Results and Discussion

Movement of the impeller; empty container

The velocity of the impeller was determined using the PSV method described in the previous section. This was done to assess the validity of the method and to obtain an impression of the accuracy of the technique.

Obviously, the movement of the impeller in an empty blender is precisely known. After analysis there are a

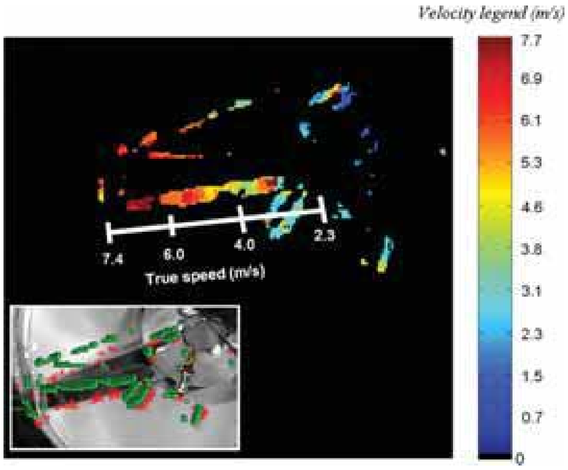

Figure 4. Velocity map of the impeller at 350 rpm ($v_{tipspeed}$ = 7.4 m/s).

The insert shows the (green squares) fingerprints with their identified best match fingerprints (red crosses). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

number of matching fingerprints. Figure 4 gives a typical example of the measurement of the blade speed using PSV. The insert in this figure shows that the technique predominantly identifies structures that are moving and ignores the structures that do not. From this experiment, the quantitative image analysis method was shown to be able to detect differences in the speed of moving objects.

Figure 5 compares the real velocity of the impeller and the velocity of the blade measured by PSV. An exact correlation was achieved. A least square analysis assuming a linear relationship of the data points lead to a slope of 0.993. Hence, the figure shows that the method is able to measure the speed of the impellor very precisely. The variation shown is probably also due to the noise in the light field such as background speckle, aberrations of the lenses, or noise in the image recording medium. Another reason could be found in the calculation of the velocity applied in PSV. The powder velocities in PSV are calculated by dividing the linear displacement $d_{\chi_{ij,k}^t}$ of the fingerprints by time. Since it is not exactly known if the structures travel the shortest path between the two points the calculation inherently yields a value with an undefined error. However, this particular error is thought to be negligible, since the forced flow is large in comparison to the dynamics of the structure as such.[18,20]

Therefore, based on the results depicted in Figure 5, the method presented here is considered suitable for structure (fingerprint) velocity measurements.

Filled container; visual observation

The powder movement of the blender filled with lactose monohydrate was monitored at different impeller speeds and the data were analyzed using PSV. Figure 6 gives typical examples of the analyses. The fingerprints that are suitable for velocity analysis were identified at locations close to the position of the blade. Furthermore the number of identified fingerprints is relatively low at low impeller speed (Figure 6a). This could be explained by the bumping behavior described by Litster et al.[15] who observed two distinct flow regimes in a moving powder bed, called bumping and roping flow, respectively. The bumping flow regime occurs at low impeller speeds in which the powder bumped up and down when the impeller passes underneath. Within this regime the bed rotates slowly and there is little vertical turn over. The roping flow regime occurs at high impeller speeds in which the powder shows similarities to a toroidal flow. Within this regime the powder bed is forced up the vessel wall and then tumbles down the angled bed surface towards the centre of the bowl.

The higher number of fingerprints identified with increasing impeller speed is explained by the roping flow behavior of the powder (Figures 6b,c). Under these conditions the whole powder bed behaves in a chaotic manner resulting in an image with more contrast.

As can be seen, PSV is well able to quantify local speeds, even when impeller speeds are low. Visual assessment of the powder bed revealed that the bumping pattern was only observed at impeller speeds below 110 rpm and a clear roping pattern was observed at impeller speeds above 200 rpm.

Powder surface velocity

It is interesting to note that the differences in powder surface velocities at different areas of the powder bed are considerable. Therefore, five areas were defined around the impeller to assess the local differences in powder velocity. This is illustrated in Figure 7a. The local particle velocities are depicted as a function of the impeller speed in Figure 7b. This figure shows that below an impeller speed of 200 rpm the powder surface velocities of the entire powder bed increases proportionally with impeller speed which agrees with the findings of Muguruma et al.[14] and corresponds to a bumping flow regime at impeller speed below 110 rpm and a regime with a mixture of the roping and bumping pattern at an impeller speed between 110 and 200 rpm as described by Litster et al.[15] Above an impeller speed of 200 rpm the mixture of bumping and

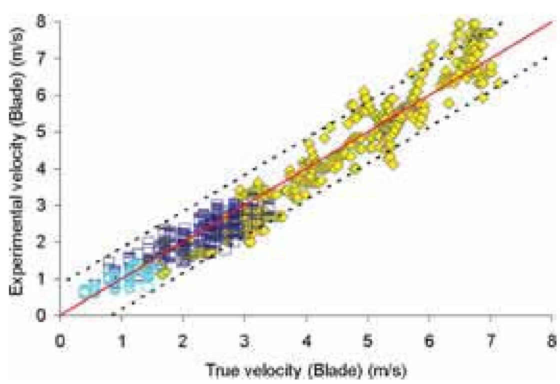

Figure 5. True velocity vs. experimental velocity of the blade at 75 rpm (○, turquoise), 155 rpm (□, blue) and 335 rpm (◇, yellow).

Dashed lines indicate the 99% confidence limits. Correlation coefficient = 0.98. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

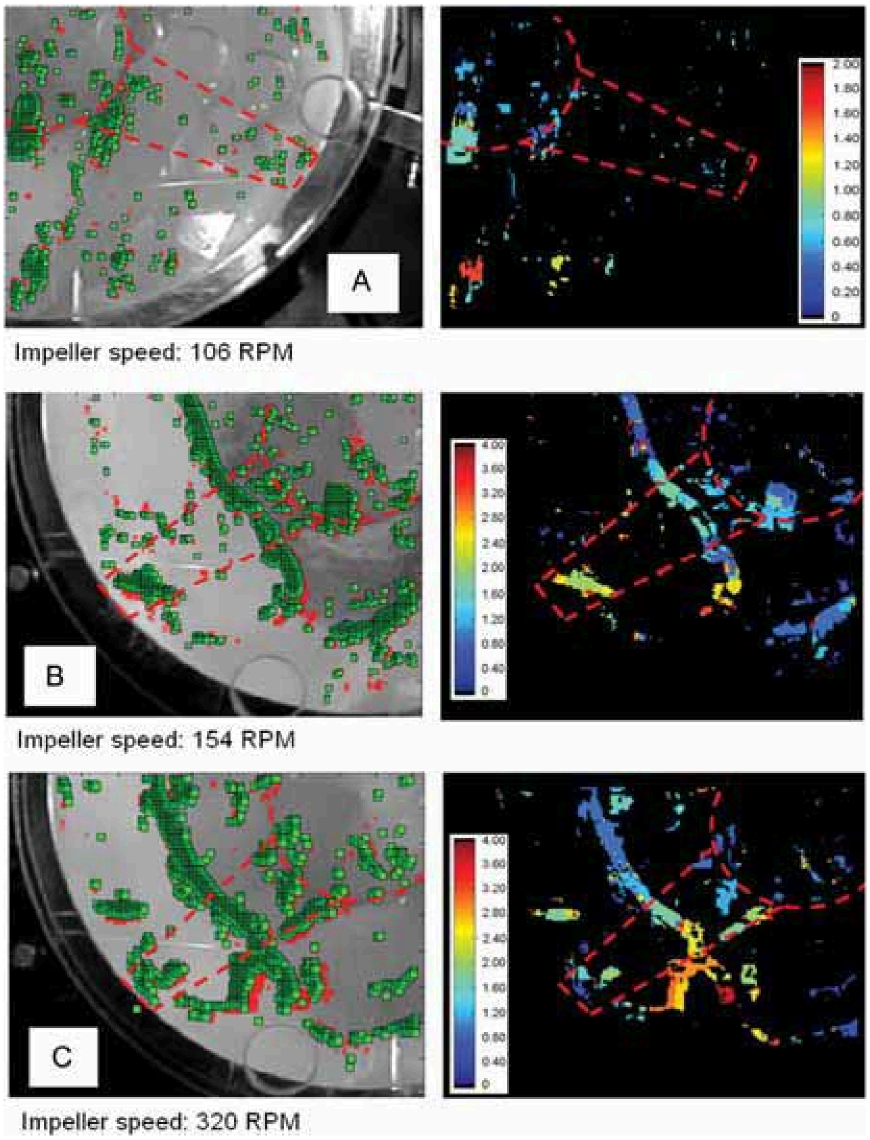

Figure 6. Typical examples of powder surface velocities at various impeller rotational speeds.

Color bars indicate the powder surface velocities in m/s. Green square symbols indicate the initial position of the powder pattern. Red cross symbols indicate the position of the powder pattern in the following frame. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

roping flow patterns changed to a full roping flow regime. This regime is characterized by the powder surface velocities that do not increase with impeller speed but stabilize to a certain level. These findings are also in agreement with the findings by Litster et al.[15]

Figure 7a shows that the highest powder surface velocities are found in the vicinity of the blade (area I). This implies that the particles in that area contain the highest kinetic energy since they are exposed to the propulsive and dissipation mechanisms between impeller and particle, and in between particles.[13,21]

Conclusion

In this study lactose 100 M with a constant fill level was used as a model excipient to introduce PSV for powder surface velocity measurements in a moving bed. PSV is a method based on mapping the movement of small structures called fingerprints. Identification of these structures is based on a statistical correlation function. The method is able to identify sufficient structures to assess the velocity of a powder under conditions of low contrast, i.e., a powder bed. Addition of tracer particles is not necessary, which is an advantage when the tests need to be performed in an industrial setting.

The validity of the method presented in this article is assessed by quantifying the rate of movement of the blade of a blender. The method enabled measurement of blade speed with reasonable accuracy.

The powder speeds of lactose monohydrate 100 M detected with PSV are in line with those reported in literature and showed that the powder surface velocity is location dependent.

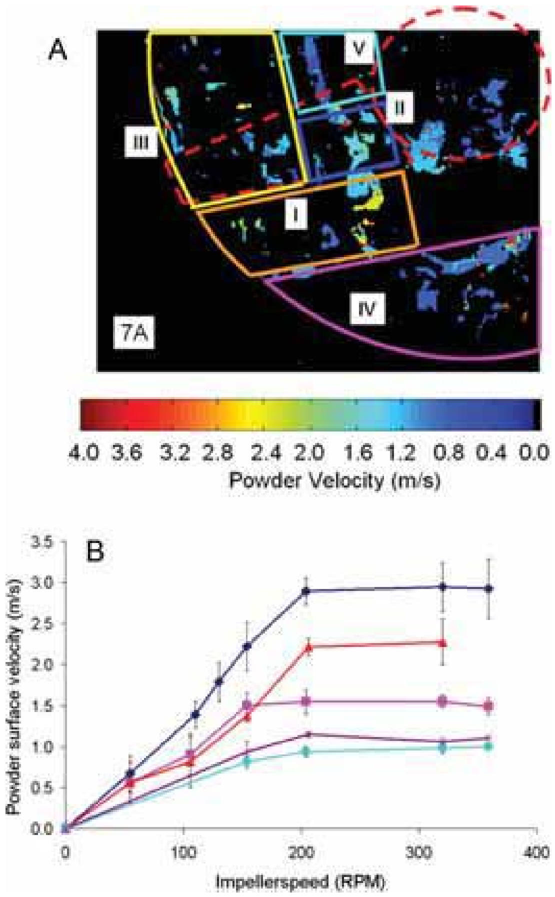

Figure 7. Powder surface velocities at increasing impeller speeds at areas I (◆), II (■), III (▲), IV (●), and V (X).

Error bars represent the standard deviation of four subsequent images of two individual experiments and the dashed lines indicate the blade and the centre of the impeller. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The analytical technique described in this study forms the basis of further investigation into powder motion. The technique seems to be possible for monitoring processes to investigate critical steps, understanding mixing mechanisms and material parameters. With the concept of quality by design being embraced by the pharmaceutical industry there is a need to understand mixing mechanisms.[22,23] The method described in this paper offers a relatively simple tool to do the required investigations.

Acknowledgments

This study was performed within the framework of Top Institute Pharma project number D6-203.

Literature Cited

1. Sudah OS, Coffin-Beach D, Muzzio FJ. Effects of blender rotational speed and discharge on the homogeneity of cohesive and free flowing mixtures. *Int J Pharm*. 2002a;247:57–68.
2. Sudah OS, Coffin-Beach D, Muzzio FJ. Quantitative characterization of mixing of free-flowing granular material in tote (bin)-blenders. *Powder Technol*. 2002b;126:191–200.
3. Das Gupta S, Khakhar DV, Bhatia SK. Axial segregation of particles in a horizontal rotating cylinder. *Chem Eng Sci*. 1991;46: 1513–1517.
4. Donald MB, Roseman B. Mixing and demixing of solid particles: Part 1 Mechanisms in a horizontal drum mixer. *Br Chem Eng*. 1962; 7:749–753.
5. Knight JB, Jaeger HM, Nagel SR. Vibration-induced size separation in granular media: the convection connection. *Phys Rev Lett*. 1993;70:3728–3731.
6. Nase ST, Vargas WL, Abatan AA, McCarthy JJ. Discrete characterization tools for cohesive granular material. *Powder Technol*. 2001; 116:214–223
7. McCarthy JJ. Micro-modelling of cohesive mixing processes. *Powder Technol*. 2003;138:63–67.
8. Li H, McCarthy JJ. Controlling cohesive particle mixing and segregation. *Phys Rev Lett*. 2003;90:1–4.
9. Kuwagi K, Horio M. A numerical study on agglomerate formation in a fluidized bed of fine cohesive particles. *Chem Eng Sci*. 2002; 57:4737–4744.
10. Willemsz TA, Oostra W, Hooijmaijers R, de Vegt O, Morad N, Vromans H, Frijlink HW, van der Voort Maarschalk K. Blending of agglomerates into powders 1: quantification of abrasion rate. *Int J Pharm*. 2010;387:87–92.
11. Iveson SM, Wauters PAL, Forrest S, Litster JD, Meesters GMH, Scarlett B. Growth regime map for liquid-bound granules: further development and experimental validation. *Powder Technol*. 2001; 117:83–97.
12. Lueptow RM, Akonur A, Shinbrot T. PIV for granulation flows. *Exp Fluids*. 2000;28:183–186.
13. Ramaker JS, Jelgersma MA, Vonk P, Kossen NWF. Scale-down of a high-shear pelletization process: flow profile and growth kinetics. *Int J Pharm*. 1998;166:89–97.
14. Muguruma Y, Tanaka T, Tsuji Y. Numerical simulation of particulate flow with liquid bridge between particles (simulation of centrifugal tumbling granulator). *Powder Technol*. 2000;109:49–57.
15. Litster JD, Hapgood KP, Michaels JN, Sims A, Roberts M, Kameneni SK. Scale-up of mixer granulators for effective liquid distribution. *Powder Technol*. 2002;124:272–280.
16. Russell P, Diehl B, Grinstead H, Zega J. Quantifying liquid coverage and powder flux in high-shear granulators. *Powder Technol*. 2003;134:223–234.
17. Nilpawar AM, Reynolds GK, Salman AD, Hounslow MJ. Surface velocity measurement in a high shear mixer. *Chem Eng Sci*. 2006; 61:4172–4178.
18. Adrian RJ. Particle-imaging techniques for experimental fluid mechanics. *Ann Rev Fluid Mech*. 1991;23:261–304.
19. Melling A. Tracer particles and seeding for particle image velocimetry. *Meas Sci Technol*. 1997;8:1406–1416.
20. Westerweel J. Fundamentals of digital particle velocimetry. *Meas Sci Technol*. 1997;8:1379–1392.
21. Vromans H, Poels-Janssen HGM, Egermann H. Effects of high shear granulation on granulate homogeneity. *Pharm Dev Technol*. 1999; 4:297–303.
22. Landin M, York P, Cliff MJ, Rowe RC, Wigmore AJ. Scale-up of a pharmaceutical granulation in fixed bowl mixer-granulators. *Int J Pharm*. 1996;133:127–131.
23. Portillo PM, Ierapetritou M, Tomassone S, McDade C, Clancy D, Avontuur PPC, Muzzio FJ. Quality by design methodology for development and scale-up of batch mixing processes. *J Pharm Innov*. 2008;3:258–270.

Manuscript received Nov. 15, 2010, revision received Jan. 27, 2011, and final revision received Mar. 15, 2011.