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Characterization of Particle Sizes in Bulk Pharmaceutical Solids Using Digital Image Information

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ABSTRACT

The purpose of this study was to demonstrate a novel method of extracting relevant information from undispersed bulk powder surfaces to be used in particle size analysis. A new surface imaging approach for undispersed powders combined with multivariate modeling was used. Digital surface images of various granule batches were captured using an inventive optical setup in controlled illumination conditions. A descriptor, the gray scale difference matrix (GSDM), which describes the particle size of granular material was generated and extracted from the powder surface image information. Partial least squares (PLS) modeling was used to create a model between the GSDM and the particle size distribution of granules measured with sieving. The use of lateral illumination and the combining of information from 2 surface images strengthened the shading effects on the powder surfaces. The shading effects exposed the topography or the visual texture of the powder surfaces. This textural information was efficiently extracted using the GSDM descriptor. The goodness-of-fit (R^2) for the created PLS model was 0.91 and the predicted variation (Q^2) was 0.87, indicating a good model. The model covered granule sizes in the size range of approximately 20 to 2500 μm. The extracted descriptor was effectively used in particle size measurement. This study confirms that digital images taken from undispersed bulk powder surfaces contain substantial information needed for particle size distribution analysis. The use of the GSDM enabled the utilization of bulk powder surface information and provided a fast method for particle size measurement.

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INTRODUCTION

Whenever visual or image information is used in science, exact descriptors for this information are needed. The utilization of descriptive image information in pharmaceutical technology is rather limited. Consequently, the development of this discipline is a challenge within physical characterization of pharmaceutical solids. There is a growing importance of quantitative analysis of digital images in industries handling bulk powders.[1] Particle size analysis is one important field within particulate characterization using image information. The aim of this study was to demonstrate the use of a novel approach in the utilization of image information in pharmaceutical powder technology. A recently introduced method to extract relevant information from undispersed bulk powder surfaces to be used in particle size analysis is explained. The main purpose was to exemplify how a descriptor called the Gray Scale Difference Matrix (GSDM) was formed and used in particle size measurement of granules produced with fluidized bed granulation.

The most common particle-sizing methods for pharmaceutical dry powders and granules are sieve analysis, laser diffraction, and computerized image analysis techniques.[2] Microscopy or computer-assisted microscopy is often considered as a reference method in particle size analysis as it enables visual inspection of particles. The use of complementary techniques is most often recommended. Visual and microscopic inspection of any material is essential in powder characterization. Relatively fast and versatile approaches of microscopy and image analysis (IA) have been described in the literature.[3] Nevertheless, particle size analysis is often difficult using traditional image analysis, since the measurement of individual particles of powders and granules can be very time consuming because of operating slowness and problems in sample dispersion.

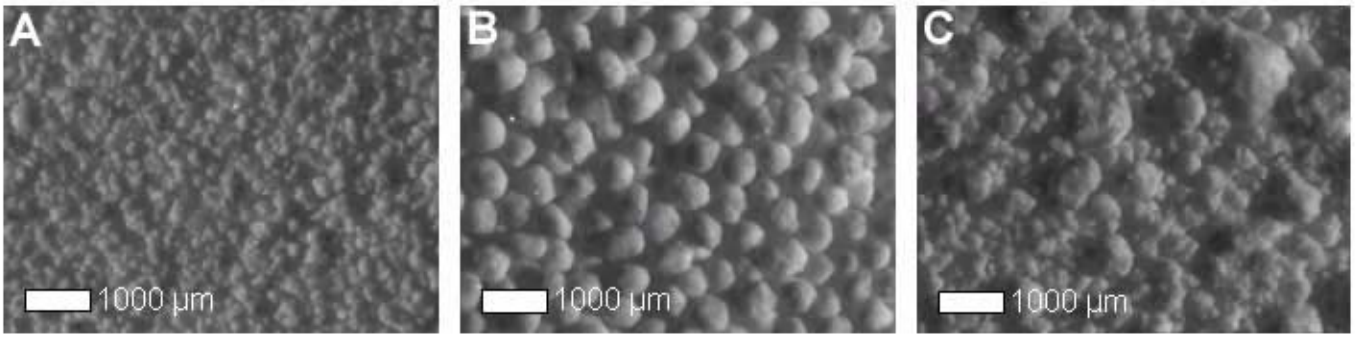

Figure 1. Demonstration of textural differences in a set of 3 different granules (A-C) with dissimilar size characteristics. Smaller particles have finer textures and larger particles coarser textures. The image surfaces' dimensions are 8.2 × 6.1 mm.

Pons et al[4] have addressed the reluctance to use IA in routine analysis of particle morphology. The relative slowness of the process and the large size of the image as a data set create problems. However, considerable advances to solve the problems with dispersion of particles and automation of image processing have been made.[5] Many current IA systems are reliable and fast, with the possibility of online and real-time analysis. Still, sample preparation and the dispersion of powder samples often remain as a difficulty in routine IA. Therefore, new approaches using image information in particle size analysis should be studied and developed. A key issue is the opportunity for real-time measurement and the reduction of various image preprocessing tasks. Naturally, the extraction of substantial information from images is essential. Therefore, the development of useful image information descriptors is critical.

A key property of a bulk particulate material is a typical pattern of the field-of-view image called texture. Texture is related to the distribution of the spatial variation in gray scale levels (or color levels in color images) and can be connected to general bulk-particle characteristics.[6,7] Global measurements of the texture that is observed in an image can portray information about the size of the particles.[8] Smaller particles lead to finer textures and larger particles to coarser textures. Russ[9] has described the general concept of texture and different texture operators. An advantage of textural methods is that particles do not have to be identified individually. The concept of comparing image information of pharmaceutical powder surfaces has been introduced earlier.[10] This concept is based on the idea that image information of undispersed powder surfaces with similar visual appearances could be linked to related material properties. A content-based image retrieval (CBIR) system, which extracted texture feature information from images in large image databases,[11-13] was used. The results showed that digital images of powder surfaces contain substantial textural information that can be linked to particle size. More recently, a novel particle size descriptor GSDM was derived from surface images of undispersed granules.[14] This approach removes the problems related to powder dispersion, which often adds the time-consuming step of sample preparation and can be very problematic for many particles. As sample preparation is made easier, surface imaging in particle size analysis enables faster measurements. Nitta and Asakura[15,16] have also introduced a method for measuring the mean particle size of bulk powders using a speckle correlation technique.

One fundamental question has to be raised: if a material is handled as bulk powder during processing, is it always necessary to measure properties of single particles? Is it possible to assess the bulk properties as such, using visual information? Humans have an immense capability to understand this visual information. **Figure 1** illustrates 3 different kinds of digital surface images of granular material. Differentiation between the 3 is easy and can probably give an estimate of the flow properties for each granule batch by the appearing particle size. The edges of particles contribute to the formation of a certain kind of texture in the image. **Figure 1A** has a finer textural appearance, thus a smaller particle size. **Figure 1B** consists of larger particles forming a coarser texture, and **Figure 1C** has a less regular texture with a larger range of particles with different sizes. These images demonstrate that a bulk surface already tells us a great deal about a powder system. Naturally, depending on the material, factors that contribute to its behavior cannot always be detected visually. The challenge is to find descriptors for this visual information. Once substantial descriptors are developed, image information can be used for decision-making purposes. The large image databases that are created can thereaf-

ter be used, taking advantage of content-based image retrieval techniques or multivariate means.

The fields of pharmaceutical product development and manufacturing, which mostly deal with particle technology, would benefit from focusing more on physical characterization of pharmaceutical solids, especially powders and granules.[17]

MATERIALS AND METHODS

Materials

Granules from approximately 100 different batches prepared with fluidized bed granulation were used for imaging. The granules consisted of several different model formulations that have been produced during a period of several years at the Pharmaceutical Technology Division (University of Helsinki, Finland). All granulations were made in a bench-scale fluidized bed granulator (Glatt WSG 5, Glatt GmbH, Binzen, Germany). The granulation setup has been described in detail by Rantanen et al.[18]

Methods

Sieving

The particle sizes of all granules were measured with sieve analysis (Fritsch Analysette, Fritsch, Idar-Oberstein, Germany) using the following sieves: 0.045, 0.071, 0.090, 0.125, 0.160, 0.250, 0.355, 0.500, 0.710, 1.000, 1.400, and 2.000 mm. The sample size was 20 g (5 minutes with amplitude 6). Pure sieve fractions of a model granule formulation were also made by sieving in order to demonstrate the visual differences in the extracted image descriptor when the particle size varies. The used sieve fractions were of the following sizes: 0.09 to 0.125 mm; 0.125 to 0.18 mm; 0.18 to 0.25 mm; 0.25 to 0.355 mm; 0.71 to 1 mm; 1.4 to 2 mm.

Sample Preparation

The samples for imaging were prepared by pouring material in a sample cup (cup dimensions; height 1 cm, circular diameter 1.2 cm) followed by the leveling of the surface with a glass plate. The leveling of the surface was made by striking off the excess powder with the plate.

Surface Imaging

Imaging Setup

In order to create reproducible and controllable imaging conditions, an optical setup with the following components was constructed during the study.

The imaging unit, with a light source, a monochrome CCD (charged coupled device) camera (JAI, CV-M50, Copenhagen, Denmark), and a lens objective, is connected to a frame grabber (WinTV, Hauppauge Computer Works, Hauppauge, NY) and a personal computer (PC). On opposite sides of the sample, the symmetrically positioned, bilateral light sources stand on rails on which they can be accurately positioned. The illumination system includes 2 lamp housings, 100 W quartz tungsten halogen lamps, and 2 collimating lens assemblies (Oriel Instruments, Stratford, CT). The collimated output beam can be turned 90 degrees with a beam turning assembly. The light sources are connected to stabilized direct current power supplies (Oriel Instruments). The imaging setup is presented in **Figure 2**.

Imaging Settings

Extensive optimizing studies concerning the illumination and imaging conditions have been performed previously.[14] Consequently, the following imaging settings were established for powder surface imaging. A 50-mm lens objective with an additional 40-mm extension tube was used. The light source distance from the sample was 20 cm. The angle of illumination was 30°. The power source voltage was 5.5 V, and the image resolution in the frame grabber was 600 × 800 pixels. The dimensions of each sample surface in the taken images were 8.2 × 6.1 mm, approximately 10 μm/pixel. All images were taken in a dark room with no disturbing light sources. The calibration of the imaging conditions was made with a smooth white calibration board (Xerox Premier, batch 11/DD/YKD/1, Xerox, Stamford, CT).

Two images of each sample surface were taken. The 2 light sources were used to illuminate the sample from opposite sides. A digital image of the sample was first captured by using 1 light source. Then, another image was taken by illuminating the sample with the other light source. In total, more than 2000 images in bit map picture (bmp) format were captured.

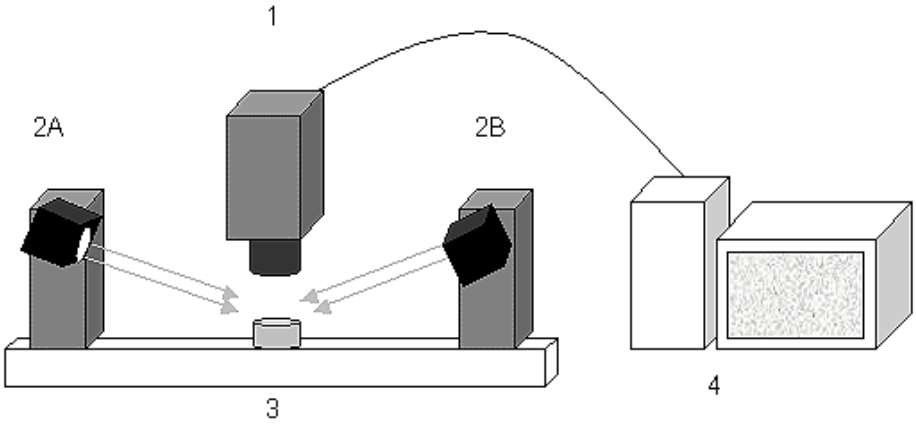

Figure 2. Imaging setup. (1) CCD camera with optics; (2A) and (2B) light sources on rails with collimated light beams; (3) Powder sample in sample cup; (4) PC and frame grabber.

Calculation of the GSDM Particle Size Descriptor

The particle size descriptor GSDM was created from surface images. The following steps are taken in the creation of the GSDM. The 2 captured surface images of each sample are used. The 2 digital images consist of 2 matrices (600 × 800) with gray-scale values of zero to 255. The difference between these 2 matrices is calculated. The operation of matrix subtraction is explained by Equation 1 using a 2 × 2 example matrix.

$$GSDM = M1 - M2 = \begin{bmatrix} 4 & 6 \\ 9 & 5 \end{bmatrix} - \begin{bmatrix} 8 & 6 \\ 5 & 11 \end{bmatrix} = \begin{bmatrix} -4 & 0 \\ 4 & -6 \end{bmatrix} \quad (1)$$

where $M1$ is the gray-scale matrix of an image 1 and $M2$ is the gray-scale matrix of an image 2. The difference is calculated for each corresponding pixel in $M1$ and $M2$.

For a theoretically completely smooth surface, the difference between the 2 matrices consists of zeros. For a real surface, the difference matrix can have values from -255 to +255. In the next step, a distribution of the difference matrix is formed (ie, how many numbers represent each of the possible 511 values). The particle size distributions were created from the GSDM using PLS modeling.

Partial Least Squares Modeling

PLS modeling was made using Simca-P software (Simca-P, version 8.0, Umetrics, Umeå, Sweden). The vector with 511 values consisting of the GSDM distribution data was used as explanatory variables (predictors), and sieve analysis size fractions were used as the response variables in the creation of a PLS model. The GSDM from 3 sample surfaces of 33 (= 99 × 2 images) batches were used to create the model. PLS relates 2 data matrices, X and Y, to each other by a multivariate model. In this study X was the GSDM and Y was the sieve analysis results. The PLS method allows modeling of data in which the number of variables exceeds the number of observations.[19] The created model was evaluated by inspecting the goodness of fit (R^2) and the predicted variation (Q^2).

RESULTS AND DISCUSSION

The GSDM for Surface Images of Specific Size Fractions

Figure 3 shows the image pairs of 6 different granule sample surfaces for the specific size fractions obtained by sieving. The different samples belong to the following size fractions: s4 (0.125-0.160 mm), s5 (0.16-0.25 mm), s6 (0.25-0.355 mm), s7 (0.355-0.5 mm), s9 (0.71-1 mm), s11 (1.4-2 mm). In addition, on the top of the figure, the characteristic shape of the GSDM distribution for each surface is shown. A smoother surface with smaller particles creates a more peaked GSDM distribution. With large particles, the GSDM distribution is flatter.

Descriptors of the PLS Model

The goodness-of-fit or the R^2 for the PLS model was 0.91 and the Q^2 was 0.87. R^2 is the fraction of the variation that is explained by the model, and Q^2 indicates the fraction of the variation that can be predicted

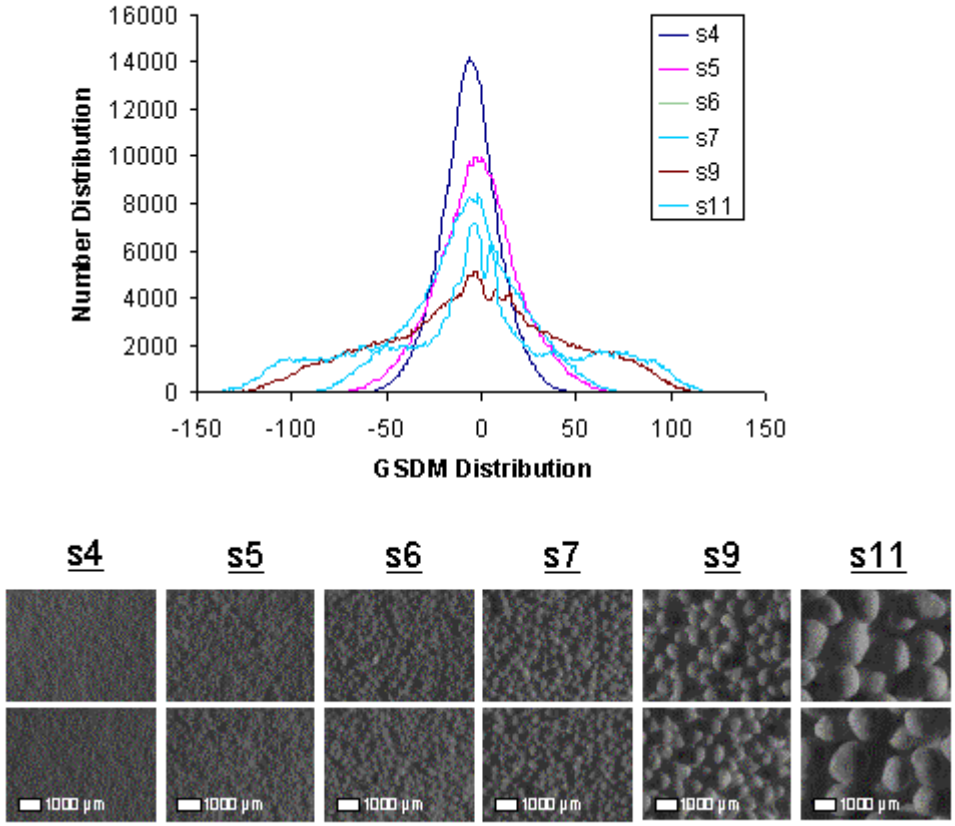

Figure 3. The GSDM distribution calculated from different kind of surfaces. Bottom, image pairs of 6 different granule sample surfaces for the specific size fractions obtained by sieving are shown. The different samples belong to the following size fractions: s4 (0.125-0.160 mm), s5 (0.160-0.250 mm), s6 (0.250-0.355 mm), s7 (0.355-0.500 mm), s9 (0.710-1.0 mm), s11 (1.4-2.0 mm). The characteristic shape of the GSDM distribution for each surface is shown above the surface images. The number distribution shows the count of each number between -255 and +255 in the GSDM.

by the model. Possible values will be in the range of zero to 1, where 1 represents a model with excellent predictive power. The median particle sizes measured with sieve analysis of the granules used in the model are presented in **Table 1**.

Particle Size Measurement Using Surface Images of Granules

Figures 4A and **4B** illustrate 2 example batches (G1 and G2) of granules. The median size for batch G1 was 236.4 µm and for batch G2, 430.6 µm. We examined the figures starting from the left. First, the pair of images used to calculate the GSDM is shown. Next, the resulting GSDM distribution is shown. Then, for each batch, 2 size distribution histograms are shown. The one received from the surface information is on the top; the other represents the distribution measured with sieve analysis. Finally, the cumulative size for both surface imaging and sieve analysis are shown. **Table 2** shows the percentage mass of each of 13 fractions of the particle size distributions of the 2 example batches (G1 and G2) measured from the surface image information and with sieve analysis.

In an image the 3-dimensional (3-D) reality is projected on a plane. A certain number of 3-D characteristics are often required in order to get quantitative information about particle morphology. In order to acquire 3-dimensionality in images one method is to view a surface from different angles.[9] Furthermore, depending on

Table 1. Particle Mean Sizes for the Batches Used in the PLS Model Measured With Sieve Analysis*

Batch	SA	SD
R1	339	6.9
R2	1147	44.5
R3	622	15.2
R4	260	9.2
R5	266	7.2
R6	236	2.8
R7	1413	202
R8	1057	17
R9	241	3.6
R10	246	5.8
R11	282	6.3
R12	273	2.7
R13	289	1.0
R14	331	5.5
R15	390	3.2
R16	293	8.8
R17	412	25.1
R18	441	5.2
R19	279	9.1
R20	276	70.3
R21	571	69.2
R22	592	76.6
R23	603	21.8
R24	223	7.2
R25	616	14.3
R26	237	11.4
R27	557	39.7
R28	292	11.9
R29	260	10.3
R30	356	25
R31	233	7.2
R32	294	3.9
R33	295	4.8

*Particle mean sizes are given in μm. PLS indicates partial least squares; and SA, sieve analysis.

how the picture is produced, different numbers of 3-D features can be distinguished. For example, optical microscopy has a poorer depth of field than scanning electron microscopy. Lateral illumination can also reveal 3-D features.[4] These features are connected to shading effects that expose the topography or the visual texture of an object or a surface. A rough structure produces an image with large gray-scale variations, while smoother structures generate images with smaller gray-scale variations. If particulate analysis is considered, controlled illumination conditions enable comparisons between materials. The challenge is to find, extract, and quantify the information that is produced. In this study, shading effects were exploited and used to produce images with distinct textural information. This information was then assessed by a GSDM.

This study confirms that digital images taken from undispersed powder surfaces contain substantial information that is needed for particle size distribution analysis. To obtain this information reproducibly from images, careful consideration has to be given to the imaging conditions. When the GSDM is calculated, image subtraction is used. Subtraction is primarily a way to discover differences between images.[9] In the present approach, the combining of information from 2 images strengthens the shading effects. The observation and the mathematical representation of the shading effects set the basis for the use of the GSDM in powder characterization and in particle size analysis in particular.

The sieve range used was from 0 to 3000 μm. However, the model covers granule sizes in the size range of approximately 20 to 2500 μm, since no very fine (<20 μm) or very large (>2500 μm) particles were present, according to a visual inspection of the surface images used in the creation of the model. The median particle size of the granules in this study (determined by sieve analysis) varied roughly between 200 and 1400 μm. The model in this study was an improvement in the model used in our previous study.[14] A wider granule size range and a larger set of model surface images were used. The previous model consisted of only 31 surface image pairs. In this study, 3 surfaces from each of 33 batches were used in the creation of the model. Therefore, 99 image pairs were used in the creation of the model. The R^2 and Q^2 values indicate good model behavior. It is important to bear in mind that when a model is created using a reference method, the quality of the model is dependent on the quality of the measurements of the reference technique used.

Figure 4 demonstrates the use of the PLS model for 2 model batches of granules. They were chosen to exemplify the flow of measurement of granules with different kinds of size characteristics. By visual inspection one can already see distinct differences between the materials. The GSDM distribution, resulting from the image matrix subtraction, provides an exact descriptor for both materials in question. By feeding this GSDM information into the model, a size distribution is received. The upper distribution for each material in **Figures 4A** and **4B** was received from the surface information. In both cases, this distribution is very similar to the distribution measured with sieve analysis, (shown below the former histogram). The cumulative graphs also confirm this finding.

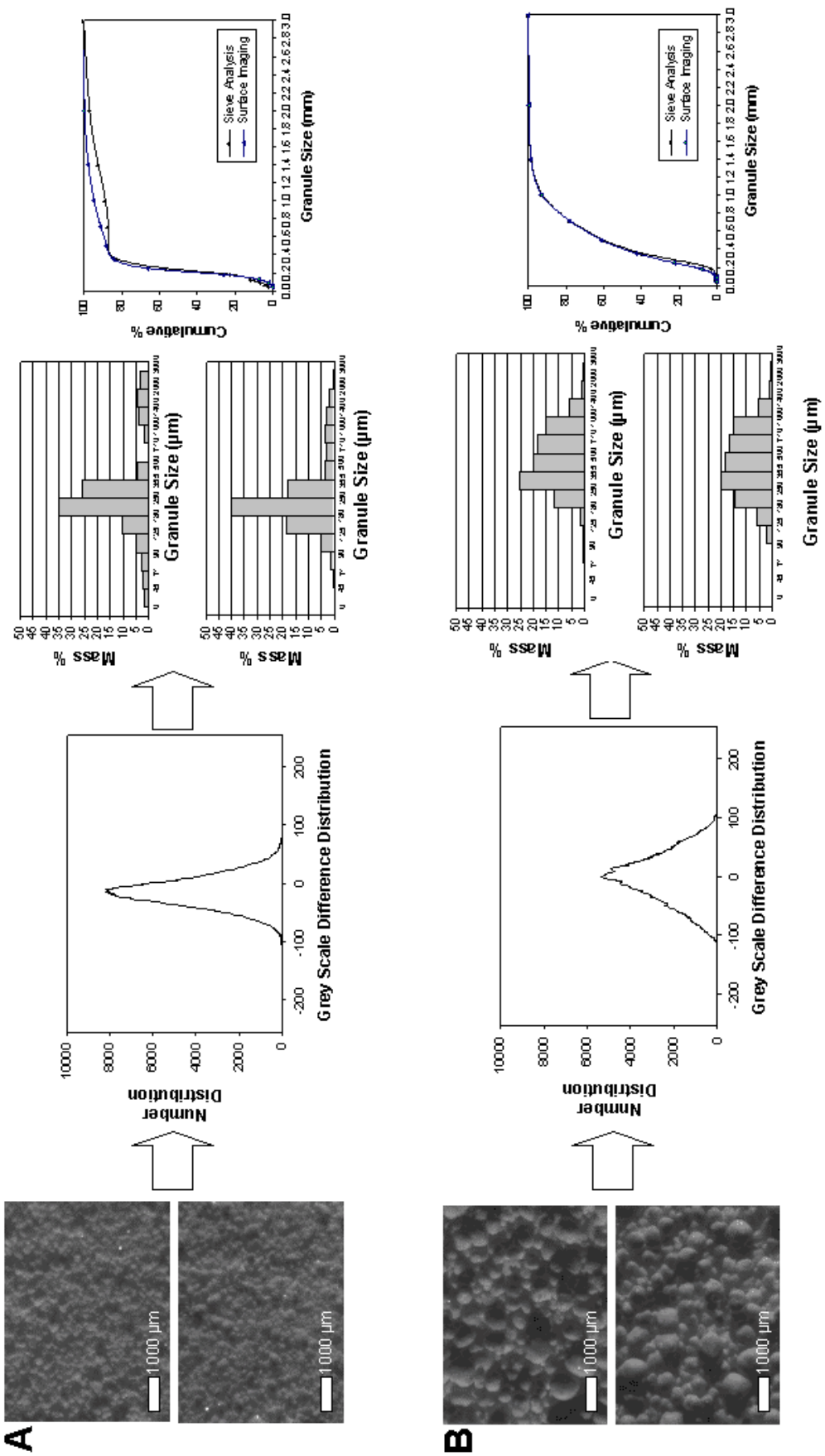

Figure 4. The flow of measurement of the particle size distribution from powder surface images. (1) A captured pair of surface images of granule batches (A) G1 and (B) G2; (2) GSDM distribution for each batch; (3) Two size-distribution histograms: top, generated using the PLS-model from surface information; bottom, measured with sieve analysis; (4) Cumulative size graphs for surface imaging and sieve analysis.

Table 2. The Particle Size Fractions (Mass %) From the Sieve Analysis Measurements and Generated From the Surface Image Information From One Sample for Each Granule Batch, G1 and G2

	Size Fractions (mm)												
	0.0–0.045	**0.045–0.071**	**0.071–0.09**	**0.09–0.125**	**0.125–0.160**	**0.160–0.250**	**0.250–0.355**	**0.355–0.500**	**0.500–0.710**	**0.710–1.0**	**1.0–1.4**	**1.4 – 2.0**	**2.0 – 3.1**
G1 (surface image)	1.9	2.0	2.5	5.1	10.4	34.9	26, 1	4.2	0.0	1.4	3.7	4.6	3.1
G1 (sieve analysis)	0.0	0.5	1.5	5.4	18.8	40.1	18, 3	3.5	3.0	3.5	3.0	2.0	0.5
G2 (surface image)	0.0	0.1	0.2	0.7	1.5	12.0	25.1	20.1	18.0	14.8	6.0	1.1	0.5
G2 (sieve analysis)	0.0	0.0	0.0	2.0	6.1	14.7	19.8	18.3	16.8	15.2	5.6	1.0	0.5

Compared with sieve analysis, the use of GSDM is very fast. The time of analysis is approximately 30 seconds, including the sample preparation, imaging, and achieving the result. In practice, the analysis of 3 samples with 1 sieve required several hours, including the time for cleaning and drying of equipment. In addition, if particle size determination using surface imaging is compared with traditional image analysis, the examination in surface imaging is easier as the sample does not have to be dispersed. Extensive image preprocessing is also avoided when analysis is made directly from a surface image of undispersed particles. Image processing steps, such as noise reduction, binarization, and filtering are often needed to obtain results when measuring single particles.

Another advantage of the surface imaging approach described here is that the analyzed sample is not destroyed. This is particularly an advantage when the analyzed particles are brittle. A particle sizing method, such as sieve analysis, might break larger granules into smaller units, thus achieving erroneous results. Maintaining the integrity of the sample is also valuable because it can then be used for other purposes after the analysis. Another difficulty encountered in sieving is the blockage or blinding of the sieves.[20] In addition, static attraction of particles on sieves may create a problem. Depending on the material, static problems naturally can arise with surface imaging as well; however, since every sample leaves a visual trace in terms of a digital image, erroneous results can be found visually. Regardless of the method, sample preparation is always a source of error and has to be performed with care. In the preparation of granule surface samples, we have determined that approximately 5% variability in results is due to sample preparation. Consequently, this variability has to be linked to data interpretation as well.

It is important to be aware that extrapolations to materials that are different in nature cannot always be made because the presented surface imaging approach is based on a model or an empirical library of certain kinds of granules. However, if one deals with similar types of materials, such as granules with similar shapes, the presented approach should not be formulation specific. Different formulations of granules prepared with the same granulation techniques are often visually alike. Naturally, material properties that can cause limitations have to be understood and studied.

The sample size, when using the introduced imaging method can be very small (a few milligrams). However, the sample has to be large enough to completely cover the field-of-view of the camera used. Samples for sieve analysis and usually for laser diffraction have to be much larger. The requirement of a very small quantity makes the technique suitable for samples and materials that are expensive or available in small quantities only.

In future studies, larger magnifications and a smaller particle size range have to be investigated in order to find out the applicability of this surface imaging approach to the particle size range of inhalation powders. The limiting factor for very small particles will be the wavelength of electromagnetic light. Larger particles can be measured representatively by taking images of a larger powder surface area. Some improvements in the imaging can be made with increased resolution of the system. Further, using more advanced cameras can increase the number of gray-scale levels distinguished at each point. The drawbacks of high-resolution imaging are slower image acquisition, slower digitization, and overall increased data processing times as well as higher costs of equipment.[9]

Since this is a very new field within powder technology, various aspects of this approach have to be assessed. First of all, material dependency of surface im-

aging should be studied. Also, the effects of particle shape and the relation of shape on shade formation in particle size measurement from powder surface images have to be examined. Most important, new descriptors for surface image information have to be created. All these further prospects will enable the evaluation of the possibilities and limitations of the introduced GSDM approach in bulk powder characterization.

CONCLUSION

This study shows that it is possible to create substantial algorithms that describe the particle size information found on undispersed bulk powder surfaces. The use of the GSDM enabled the utilization of bulk powder surface information and provided a fast method for particle size measurement. In general, as humans have a great sense for visual information, image information should be utilized more comprehensively. New ideas in the field of visual characterization broaden the scope of analytical techniques used in pharmaceutical powder technology.

REFERENCES

1. Grasa G, Abanades JC. A calibration procedure to obtain solid concentrations from digital images of bulk powders. Powder Technol. 2001;114:125-128.

2. Washington C. Particle Size Analysis in Pharmaceutics and Other Industries: Theory and Practice. West Sussex, UK: Ellis Horwood Ltd; 1992.

3. Houghton ME, Amidon GE. Microscopic characterization of particle size and shape: an inexpensive and versatile method. Pharm Res. 1992;9(7):856-859.

4. Pons MN, Vivier H, Belaroui K, Bernard-Michel B, Cordier F, Oulhana D, Dodds JA. Particle morphology: from visualisation to measurement. Powder Technol. 1999;103:44-57.

5. Hammond S, Egelberg P. 1999. Particle size and shape measurement by automated microscopy. Eur Pharm Rev. 1999;4(4):16-20.Lucke A, Gopferich A. Acylation of peptides by lactic acid solutions. Eur J Pharm Biopharm. 2003;55(1):27-33.

6. Bonifazi, G. Particulate solids control in bulk by image analysis. Paper presented at: Proceedings of Powder and Bulk Solids Conference; May 5-8, 1997; Rosemont, IL. 337-348. Publisher: Reed Exhibition Companies, Norwalk, Conn.

7. Bonifazi G, La Marca F, Massacci P. Characterization of bulk particles in real time. Part Part Syst Char. 2002;19:240-246.

8. Novales B, Guillaume S, Devaux MF, Chaurand M. Particle size characterisation of in-flow milling products by video image anlysis using global features. J Sci Food Agric. 1998;78:187-195.

9. Russ J. The Image Processing Handbook. 3rd ed. Boca Raton, FL: CRC Press; 1999.

10. Laitinen N, Antikainen O, Mannermaa JP, Yliruusi J. Content-based image retrieval: a new promising technique in powder technology. Pharm Dev Tech. 2000;5(2):171-179.

11. Niblack W, Barber R, Equitz W, Flickner MB, Glasman E, Petkovic D, Yanker P, Faloutsos C, Taubin G. The QBIC project: querying images by content using colour, texture and shape: storage and retrieval for image and video databases. Paper presented at: International Symposium on Optical Engineering, February 1993. SPIE. 1993;1908:173-87.

12. Faloutsos C, Barber R, Flickner M, Hafner J, Niblack W, Petkovic D. Efficient and effective querying by image content. J Intell Inf Syst. 1994;3:231-262.

13. Flickner M, Sawhney H, Niblack W, Ashley J, Huang Q, Dom B, Gorkani M, Hafner J, Lee D, Petkovic D, Steele D, Yanker P. Query by image and video content: the QBIC system. Computer. 1995;28(9):23-31.

14. Laitinen N, Antikainen O, Yliruusi J. Does a powder surface contain all necessary information for particle size distribution analysis? Eur J Pharm Sci. 2002;17(4-5):217-227.

15. Nitta H, Asakura T. Measurements of fine particle size using a speckle correlation technique. Meas Sci Technol. 1990;1(2):131-135.

16. Nitta H, Asakura T. Method for measuring mean particle size of the bulk powder using speckle patterns. Appl Optics. 1991;30(33):4854-4858.

17. Muzzio FJ, Shinbrot T, Glasser BJ. Powder technology in the pharmaceutical industry: the need to catch up fast. Powder Technol. 2002;124(1-2):1-7.

18. Rantanen J, Känsäkoski M, Suhonen J, Tenhunen J, Lehtonen S, Rajalahti T, Mannermaa J-P, Yliruusi J. Next generation fluidized bed granulator automation. AAPS PharmSciTech. 2000;1(2): article 10.

19. Wold S. PLS for multivariate linear modelling. In: van de Waterbeemd H, ed. QSAR: Chemometric Methods in Molecular Design. Vol 2. Weinheim, Germany: Wiley-VCH; 1995: 195-218.

20. Iacocca RG, German RM. A comparison of powder particle size measuring instruments. Int J Powder Metall. 1997;33(8):35-48.