Research Article

Process Analytical Technology: Application to Particle Sizing in Spray Drying

L. W. Chan,[1] L. H. Tan,[1] and Paul W. S. Heng[1,2]

Abstract. The purpose of this research was to explore the possibility of employing PAT for particle sizing during spray drying with the use of an in-line and at-line laser diffraction system. Microspheres were made using maltodextrin and modified starch as wall material and size results obtained using PAT compared with those determined with off-line laser diffraction and light microscopy. Median particle size results were highest for in-line laser diffraction, followed by at-line and off-line laser diffraction and finally light microscopy. This was due to the presence of agglomerates which were measured as discrete microspheres in the in-line set-up. At-line and off-line laser diffraction gave results more closely correlated with individual microsphere sizes due to agglomerate breakdown during the measurement process. Light microscopy allowed direct observation of the particle morphology, however, its use for particle sizing was tedious and sample size was much smaller compared to laser diffraction. Although PAT was found to be an efficient and convenient tool, careful data interpretation was needed taking into account the cohesiveness of the material measured. The at-line set-up appeared to be more suitable in this particular application.

KEY WORDS: laser diffraction; particle size; process analytical technology; spray drying.

INTRODUCTION

Process analytical technology (PAT) is defined by the United States Food and Drug Administration as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality" (1). This has been of increasing importance and involves the use of in-, on- or at-line instruments for the collection of "real-time" quality data throughout the entire manufacturing process. In-line process analyzers involve mounting the instrument directly on the process line without any sample extraction. On-line process analyzers incorporate eductors which extract a portion of sample from the main line for measurement, after which the sample is either returned to the main line or discarded. As for at-line process analyzers, the instrument is in close proximity to but physically separate from the process line and samples are removed for testing. The focus of PAT is on building quality into the product and placing greater emphasis on in-process instead of end-product testing and release. The final objectives include decreased cycle times and cost, increased efficiency and batch to batch consistency, improved process understanding, and rapid feedback control (2).

The particle size distribution is one of the most important characteristics of a powder or particulate system affecting both the properties and performance of intermediate and final products (3). It may also greatly impact the nature and efficiency of the manufacturing process (4). Hence, there is a need for appropriate means of characterization, monitoring and control of particle size distributions, preferably using PAT approach. Traditional sizing methods using laboratory instruments such as light microscopes, bench-top laser diffraction equipment and Coulter counters are mainly separate from the process stream (off-line) and are unable to provide "real-time" data (3,5–7). Constant monitoring and feedback control are thus not possible. Focused beam reflectance measurement as a PAT tool has been used in crystallization (8) and high shear wet milling processes (9). A recent review by Yu et al. (10) examined the role of PAT in crystallization of active pharmaceutical ingredients. Potential methods for *in situ* particle size characterization included diffusing wave spectroscopy, turbidity, frequency–domain photon migration, focused beam reflectance measurement and near infrared spectroscopy. These methods varied in usefulness and commercial success. Other on-line particle size analysis methods using electrostatic sensors (11,12) and springs (13) have also been studied. The search is on-going for more reliable, robust, cost-effective and user-friendly particle sizing methods for PAT applications, especially for large-scale industrial productions.

Spray drying transforms fluid feeds into dried particulate products by converting the fluid into droplets using an atomizer in a hot drying medium (14). It is used in many areas including the manufacture of products such as directly compressible lactose (15), industrial production of dry powder aerosols (16), drying of thermosensitive materials (17,18) and microencapsulation among many others. In all of the above mentioned

[1] GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore.
[2] To whom correspondence should be addressed. (e-mail: phapaulh@nus.edu.sg)

applications, the particle size distribution of the spray dried products greatly affects product quality. Microencapsulation, in particular, is frequently carried out for purposes of controlled release, taste masking and protection of encapsulated material from the external environment (19). In all the above applications, microsphere size can have direct and indirect effects on the desired functions. In-, on and at-line process analyzers enable the possibility of continuous particle size control and potentially allow greater understanding of the process. Any potential variations during production and machine start up and shut down could be detected with these real-time process monitoring techniques. They could also allow the determination of how long these variation effects take to appear in the product itself. Periodic sampling and particle sizing using traditional off-line techniques would not be sensitive enough to detect rapid process changes. To date, little information is available on the use of PAT for particle sizing in spray drying for microsphere production, unlike other processes like milling and crystallization.

The aim of the present work was to apply a PAT system in the form of an in- and at-line laser diffraction particle sizer to the spray drying process. Its effectiveness as a real-time monitoring tool in a pilot scale spray dryer for microsphere production was evaluated. Spray drying conditions and feed material were varied to study the sensitivity of the particle sizer to changes. The usefulness and limitations of using the PAT instrument were explored. As a comparison, conventional sizing methods like off-line laser diffraction and light microscopy were performed.

MATERIALS AND METHODS

Materials

A marine fish oil (ROPUFA®) was supplied by Roche Vitamins, UK. Modified starch, (Capsul®), was obtained from National Starch and Chemical, USA. A maltodextrin of 19 dextrose equivalents (Glucidex® IT 19) was a gift from Roquette, France. All other chemicals used were of analytical grade.

Feed Preparation

Maltodextrin was dissolved in deionized water to produce 30% *w/v* solutions. Emulsions were prepared by homogenizing 15% *w/v* suspensions of modified starch with fish oil at oil-to-starch weight ratios of 0.5:1, 1:1 and 1.5:1 using a high speed mixer (Silverson L4RT, UK). The homogenization conditions used were 4,500 rpm for 3 min, followed by 5,000 rpm for 2 min. The modified starch suspensions were made by dispersing the required amounts of modified starch in deionized water and leaving the suspension to hydrate overnight.

Spray Drying

The feed liquid was spray dried using a pilot scale spray dryer (Mobile Minor, Niro A/S, Denmark) equipped with a rotary atomizer. For the maltodextrin solutions, two atomizer wheel speeds of 23,000 and 27,500 rpm were used to produce microspheres of different size ranges. For the emulsions, the atomizer wheel speed was fixed at 27,500 rpm. The inlet and outlet temperatures used for both types of feed were 170°C and 80°C respectively. The emulsions were stirred continuously to ensure a uniform oil droplet distribution prior to feeding into the spray dryer. It was previously shown that oil droplet coalescence did not occur as no change in droplet size was detected throughout the run (20).

Microsphere Sizing

Microspheres were sized using laser diffraction (in-, at- and off-line) and light microscopy. For each laser diffraction technique, the median particle size and span were determined and the average of three batches reported. The span was calculated by the following formula:

$$Span = \frac{Dv(90) \ - \ Dv(10)}{Dv(50)} \qquad (1)$$

where Dv(90), Dv(10) and Dv(50) were the particle sizes at the 90th, 10th and 50th percentiles of the cumulative size distribution respectively. For light microscopy, only the median particle size was reported.

In-Line Laser Diffraction (ILLD)

The in-line laser diffraction system (Insitec®, Malvern Instruments, UK) comprised several parts: the optical head, interface box, computer and data analysis software. The optical head was directly connected in-line to the process stream (Fig. 1). This was unlike other on-line systems fitted with an eductor which extracted part of the product flow for measurement before returning it to the main product line. The optical head consisted of a lens of focal length 100 mm and it functioned as a standard laser diffraction instrument. This was suitable for measuring a particle size range of 0.5 to 200 μm. As particles passed through the optical head, the laser beam from one side of the lenses was diffracted. The diffracted light was collected by the receiver lens on the opposite end and focused onto an array of 32 photodetectors. The scattering pattern was then analyzed and its relationship to particle size obtained using the Mie theory. Details of this theory have been described in detail by other authors (21,22). This was then displayed as real-time size distribution data. The particulate refractive index was set as that of a standard opaque particle. An important part of the in-line system was the purge air flow, set at a velocity greater than that of the primary flow. This was
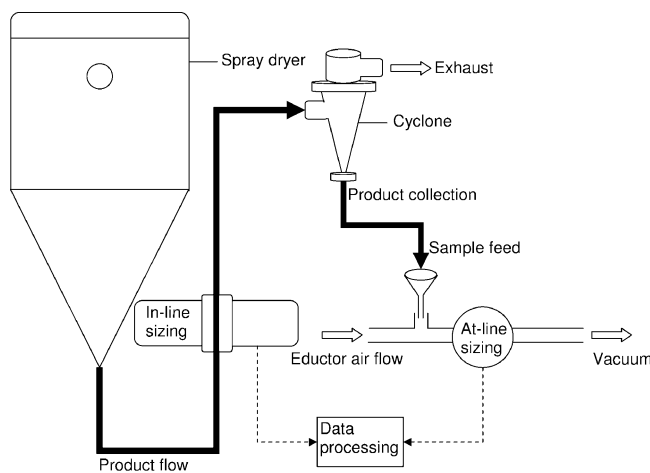

Fig. 1. Layout of the spray dryer with the in-line and at-line laser diffraction set-up

essential to prevent the adherence of particles to the lenses' surfaces. Particles present on the optical windows would produce constant background readings affecting the accuracy of the results obtained (23,24).

At-Line Laser Diffraction (ALLD)

The main components used for the at-line laser diffraction system were the same as those used in the in-line system, except that for the at-line system, the laser module was not physically connected to the product flow stream. Instead, it was positioned adjacent to the spray dryer and worked as a separate system. Sampling and sizing were performed after the product had left the process stream (Fig. 1). The optical head was connected to a venturi which directed in-coming particles to the laser module. After sizing, the particles were removed via a vacuum system. Besides the purge air supplied to prevent particle adherence to the optical windows, an additional purge air, commonly termed the eductor air flow, was supplied via the venturi to aid in particle dispersion. Before actual size analysis was carried out, eductor air flow and sample feed rate were varied to investigate their effects on particle size results. The eductor air flow rate to be used for the actual runs was determined to be 5 m^3/h for maltodextrin microspheres and 7 m^3/h for microspheres of modified starch.

Off-Line Laser Diffraction (OLLD)

The dry powder module of a Coulter LS230™ system (Coulter Corporation, USA) was used as the off-line laser diffraction system. This system was suitable for measuring particles in the size range between 0.04 to 2,000 μm, and size results were based on both the Fraunhofer and Mie theories. About 15 g of sample was used for each run and three replicates were performed for each batch. Each analysis lasted a duration of 60 s. This method was not used to size oil-loaded microspheres mainly due to practical limitations associated with oil contamination along the sample conduit which required extensive cleaning after each size determination.

Light Microscopy (LM)

A light microscope (BX61TRF, Olympus, Japan) interfaced with an image analysis system (MicroImage™, Olympus, Japan) was used. This was intended to size only oil-loaded microspheres. However, maltodextrin microspheres were also sized to allow a three-way comparison. At least 625 microspheres were measured using a lens of ×40 magnification for each batch. Samples were mounted on glass slides and dispersed using liquid paraffin. Only discrete microspheres were sized.

RESULTS AND DISCUSSION

For microspheres made of modified starch as wall material, median microsphere size increased as oil loading increased (Table I). The effect was greater when the oil-to-starch weight ratio was increased from 0.5:1 to 1:1. This was also reported in a previous paper (20). A similar trend was observed regardless of the sizing method used. During the spray drying process, microspheres shrank as moisture evaporation occurred. With more oil present within the microsphere core, less shrinkage took place during drying as the oil remained and occupied the voids within the microspheres. This resulted in the formation of larger microspheres. Higher atomizer wheel speeds produced smaller microspheres, as shown by the maltodextrin microspheres (Table I). This was due to a greater centrifugal force available to break up the feed into fine droplets. These trends for the particle size distributions obtained were consistent regardless of the sizing technique used. However, there were quantitative differences in size measurements obtained using the four methods. For all types of microspheres produced, median particle size results were in the order ILLD > ALLD ≈ OLLD > LM.

In-Line Laser Diffraction

In-line size analysis gave rise to very large Dv(50) and standard deviation values for microspheres produced using modified starch as coat wall material (Table I). These values were unlikely to be representative of the true individual microsphere size. The broad, bimodal size distributions (Fig. 2) were likely due to microsphere agglomeration, with discrete microspheres forming the smaller mode and agglomerates contributing to the larger mode value. This was because agglomerates were not differentiated from discrete microspheres during measurement. As oil loading increased, so did the extent of agglomeration, as could be seen from the sizing results obtained. This was also observed under light microscopy. It was mainly

Table I. Dv(50) and Span Values Measured Using In-Line Laser Diffraction (ILLD), At-line Laser Diffraction (ALLD), Off-line Laser Diffraction (OLLD) and Light Microscopy (LM; Mean±S.D., $n=3$)

Measurement technique	Dv(50; μm)[a]					
	Blank[b]	Oil-to-starch 0.5:1[b]	Oil-to-starch 1:1[b]	Oil-to-starch 1.5:1[b]	Low Wheel Speed[c]	High Wheel Speed[c]
ILLD	37.7±13.4 (4.5±2.5)	44.8±14.9 (7.3±2.9)	119.3±16.2 (2.7±0.7)	157.3±13.3 (2.0±0.1)	22.3±3.4 (9.6±6.9)	19.3±1.1 (5.2±0.7)
ALLD	18.5±0.1 (1.6±0.1)	19.3±0.1 (1.8±0.1)	19.7±0.1 (1.6±0.1)	20.7±0.4 (2.1±0.0)	19.2±0.4 (3.6±0.4)	17.4±0.1 (2.9±0.2)
OLLD	–	–	–	–	18.3±1.3 (1.7±0.2)	16.9±0.8 (1.7±0.2)
LM	13.4±0.3	15.5±0.2	19.3±0.4	18.7±0.4	16.3±3.8	15.5±1.0
	–	–	–	–	–	–

[a] Values in parentheses represent the Span values
[b] Microspheres made of modified starch as wall material
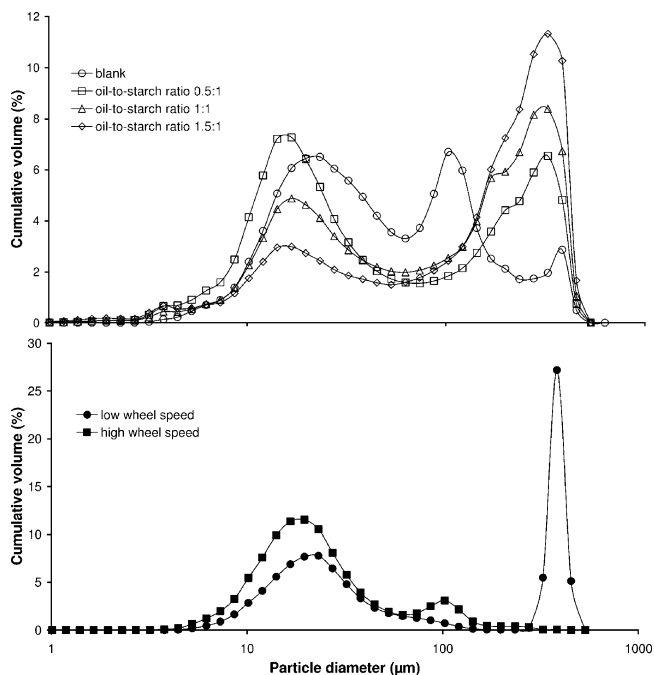[c] Microspheres made of maltodextrin as wall material

Fig. 2. Representative particle size distribution curves for microspheres obtained from in-line laser diffraction (*open symbols*, microspheres produced using modified starch as wall material; *filled symbols*, microspheres produced using maltodextrin as wall material)

than those obtained by the other techniques as a result of broader size distributions due to microsphere agglomeration.

For the in-line set up used in this study, spray dried microspheres from the drying chamber entered the measurement zone without any prior particle dispersion stage. This was unlike on-line PAT systems with eductors which extracted a portion of the product from the main process line for size analysis allowing additional sample dilution and dispersion (23,24). For the in-line setup in this study, agglomerates were not broken up and were thus taken to be single particles, resulting in grossly elevated particle size values. Since agglomeration was a random process, the incidences, sizes and shapes of agglomerates varied. This could explain the unusually high second mode seen in Fig. 2. It could also potentially affect the accuracy of the in-line particle size measurement results, as laser diffraction data analysis algorithms usually relied on spherical and discrete particle models (25,26). Besides this, the quality of data collected by any laser diffraction instrument could be affected by high particle concentrations due to multiple scattering effects (21), although algorithms were available to correct for this. Multiple scattering reduces estimated median values and extends the span in the direction of smaller particle sizes. However, the aforementioned phenomenon was not a problem in this study as particle concentrations were relatively low as compared to large-scale industrial processes. This could be seen from the high average light transmission values (>90%) obtained during the size measurements (Fig. 3), implying that less than 10% of the light from the laser beam was scattered by the particles. This was within the limits of the single scattering region.

Another potential disadvantage with the use of the in-line system, as opposed to the use of at-, on- or off-line systems, was that production would be affected in the event of optical window contamination, as the process had to be stopped before the lenses could be cleaned. This would be minimized if the purge air system was properly maintained. On-line systems with a bypass design or at-line set-ups which allow cleaning of the lenses without interrupting the main production process are superior in this aspect. The bypass design would also be the only method to fit a sizing system for larger production
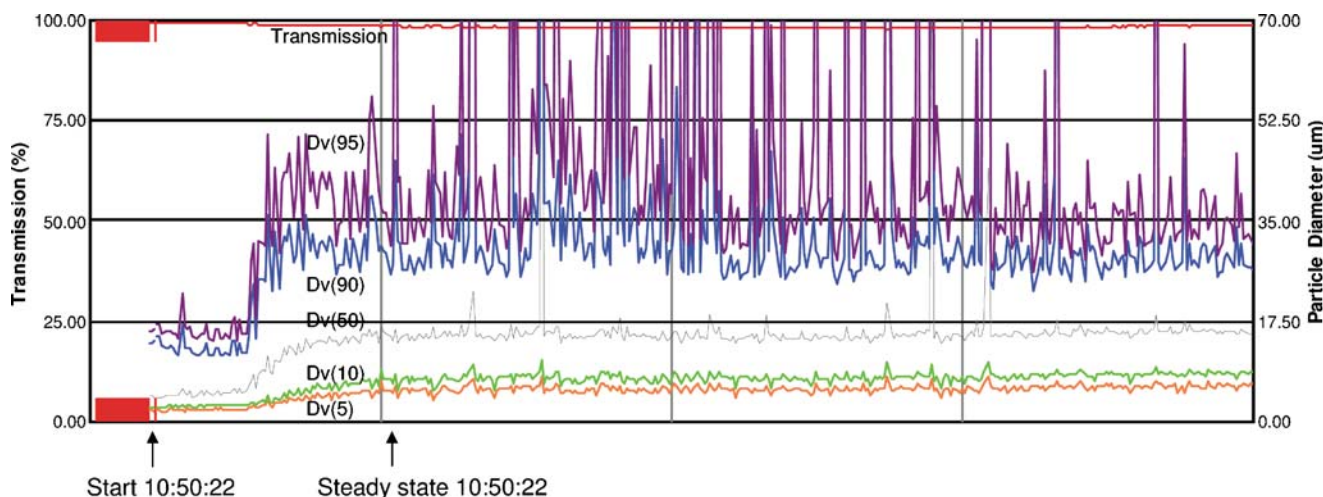
due to the presence of a greater amount of surface oil resulting in more sticky microspheres. The poor flowability of the wall material was also a contributing factor. Microspheres produced using maltodextrin as wall material, in comparison, gave rise to a narrower particle size distribution (Fig. 2) although the size distribution curves were also bimodal. Median particle size values (Table I) were not excessively elevated. This was due to the absence of oil and the more flowable nature of the material, forming microspheres which had fewer tendencies to agglomerate. Span values (Table I) for ILLD were generally higher

Fig. 3. Particle size history during process start-up obtained from in-line laser diffraction

machines where the throughputs per unit time are just too high to be sized whole and reliably in-line. In-line systems would, however, be very useful in areas like crystallization and flocculation, where an accurate reflection of agglomeration behaviour is desired. In the present study, it also allowed the qualitative determination of the propensity of the microspheres to agglomerate. Such systems would also be useful for friable materials which could be broken down by the eductor air flows of the off-line and on-line sizers.

One of the most important characteristics of the in-line set-up was its sensitivity to product changes during the production process. In this case, the measurement update period was set at 1 second, which meant that sizing was performed at 1-s intervals. This would not be practically possible with off-line techniques. It allows the system to provide valuable information in optimization processes and in detecting intermittent process upsets which may be missed by off-line measurements. Non-destructive throughput allowed full recovery of the product, which was especially important for costly materials. No manual sampling was needed, greatly reducing operator exposure to potentially harmful materials. On the other hand, sterile products could be protected from the external environment. Product information was collected from the entire run, allowing greater process understanding.

The in-line sizing system also provided information on the duration required for the process to stabilize from start-up, allowing real-time decision when steady-state was reached. This facilitated the collection of products only during stable spray dryer operation, if required. For the pilot-scale spray dryer used in this case, the unstable state lasted for about 2 min after starting a run (Fig. 3). With in-line information, the potentially out-of-specification initial products could be discarded and proper collection performed only when steady-state was established. This would also help to minimize wastage due to over-estimation of process start-up time as operators would be able to tell exactly when the process stabilized from the particle size charts.

However, when atomizing wheel speed was lowered from 27,500 to 23,000 rpm during the run, the change in median particle size was marginal from the time history window, as the difference was only a few microns. As a result, the measured median size values seemed to fall within the usual variations of multiple replicated particle size measurements. Only upon detailed post-acquisition data analysis were the differences in product particle size values apparent. Changes in the time history graph for median particle size would have been more evident if the particle size range produced was larger. However, this did not imply that the measurement technique was insensitive to changes in particle size, as, if it was the case, these differences would not be elucidated during post-acquisition data analysis. It was more likely to be due to the limited ability to visualize small changes in real-time, especially with compounding factors such as concurrent incidences of particle agglomeration. The apparent limited sensitivity to detect changes in median particle size was also seen in another study involving the use of the Insitec in-line sizing system with a classifier mill (24). Changing the grinding classifier rotor speed did not give rise to a noticeable change in Dv(50) in the time history graph. Instead, there was an obvious rise in the Dv(90) line as rotor speed was decreased. In our study, this effect on Dv(90) was also not apparent.

Although there was no necessity for post-production sampling plans and sample collection and preparation, careful pre-commissioning planning and design were required before installation of the in- or on-line measurement system. Especially for on-line systems, they had to be positioned at locations of uniform product flow to ensure representative sample extraction (7). Any factors, such as vibrations, leaks or elbows in the delivery pipes that could affect product flow had to be considered. Sampling probes would have to be located at a reasonable distance away from these sources. The measurement system itself should also be fixed such that the original product flow remained unaffected (24). As the in-line set-up was used in this study, no sample extraction was performed and product flow effects on particle size were expected to be less than those encountered in on-line systems. Nevertheless, care was taken to position the sizer as far as away from the elbows in the delivery pipe as possible. In addition, the vast amount of information generated with the use of PAT in industrial settings requires specialized data management systems and judicious interpretation of data for reliable results to be obtained.

At-Line Laser Diffraction

At-line instruments are useful for their mobility and flexibility while satisfying PAT requirements. The at-line set-up was hence employed with the same laser diffraction equipment but positioning it adjacent to the spray dryer. As sample feed rates and eductor air flow rates could affect particle size results, these parameters had to be optimized before actual runs were conducted. The sample feed rates used included those that
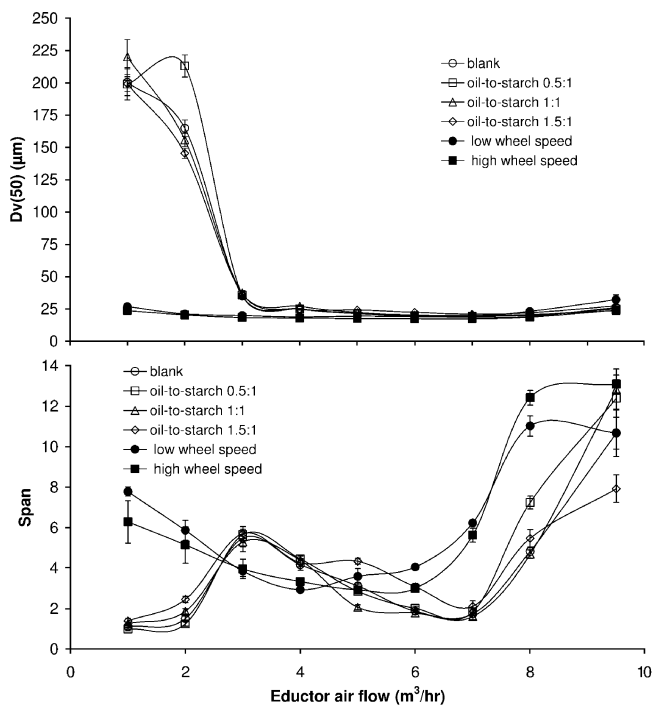

Fig. 4. Effect of eductor air flow on Dv(50) and Span for at-line sizing (*open symbols*, microspheres produced using modified starch as wall material; *filled symbols*, microspheres produced using maltodextrin as wall material)

Table II. Dv(50) Measured by At-line Laser Diffraction at Different Sample Feed Rates (Mean±S.D., n=3)

Feed Rate (g/h)	Dv(50; μm)					
	Blank[a]	Oil/wall 0.5:1[a]	Oil/wall 1:1[a]	Oil/wall 1.5:1[a]	Low Wheel Speed[b]	High Wheel Speed[b]
400	16.6±0.2	21.0±0.1	20.7±0.1	21.6±0.3	19.5±0.4	17.3±0.1
450	16.5±0.1	21.3±0.1	20.8±0.2	21.6±0.3	19.6±0.4	17.4±0.2
500	16.5±0.1	21.1±0.2	20.8±0.1	21.5±0.4	19.6±0.5	17.3±0.2
550	16.7±0.2	21.1±0.1	20.6±0.1	21.5±0.4	19.3±0.4	17.3±0.1
600	16.7±0.2	21.3±0.1	20.8±0.2	21.4±0.5	19.2±0.3	17.5±0.1

[a] Microspheres made of modified starch as wall material
[b] Microspheres made of maltodextrin as wall material

gave the microsphere concentration expected to be encountered in-line in this study (400–600 g/h).

Generally, median particle size started to decrease as eductor air flow increased (Fig. 4). However, as the eductor air flow increased further, there was an unexpected rise in median particle size. Besides aiding agglomerate dispersion, the eductor air flow also served to accelerate the particles towards the measurement zone. The increase in median particle size at this time was probably due to the agglomerated particles reaching the measurement zone before they had time to be sufficiently dispersed. This also showed that the individual microspheres were strong enough to withstand the impact of the purge air forces used such that they were not broken down, which would have resulted in a sudden decrease in particle size instead. Span values showed largely similar trends (Fig. 4). For microspheres of modified starch, however, there was an additional increase in span as eductor air flow was increased from 1 to 3 m³/h.

The optimal eductor air flow required was material specific. Minimum particle size was achieved at different eductor air flow rates for the different types of microspheres studied. For maltodextrin microspheres, it was found that an eductor air flow of 5 m³/h was sufficient to break up the agglomerates to achieve a minimum span value. For blank and oil-loaded microspheres of modified starch, however, a higher eductor air flow of 7 m³/h was needed. This was likely because the presence of surface oil on the oil-loaded microspheres made them adhere to each other more strongly, requiring greater energy for dispersion. It could also be due to the inherent poorer flowability of the wall material itself, as blank microspheres of modified starch behaved similarly to oil-loaded ones in this aspect. These results implied that experimental conditions had to be tailored to the type of material sized. More cohesive materials would possibly require higher eductor air flow rates for sufficient agglomerate dispersal. Particle size results were not significantly affected by the feed rates used in this study (Table II).

Figure 5 shows the typical size distribution curves obtained using the at-line laser diffraction system. For all the different types of microspheres studied, the second mode was barely noticeable and appeared more like an extended tail of the size distribution curve. This implied that although most of the agglomerates were broken up by the eductor air flow, there was still a small percentage of them remaining. This could also suggest that some agglomerates were formed during the spray drying process before microspheres were completely dried, resulting in fused microspheres. This was especially prominent for blank microspheres made of modified starch, although the reason is not immediately clear. A closer look at the Dv(50) values showed significant differences between in-
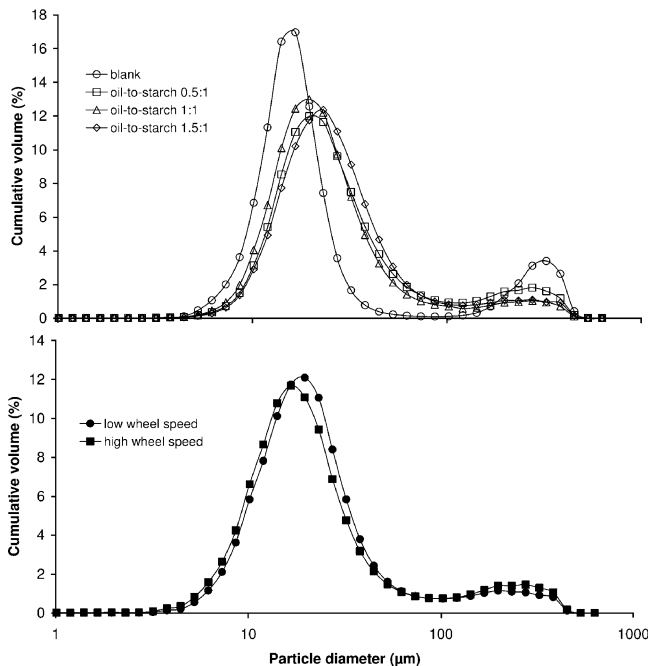

Fig. 5. Representative particle size distribution curves for microspheres obtained from at-line laser diffraction (*open symbols*, microspheres produced using modified starch as wall material; *filled symbols*, microspheres produced using maltodextrin as wall material)
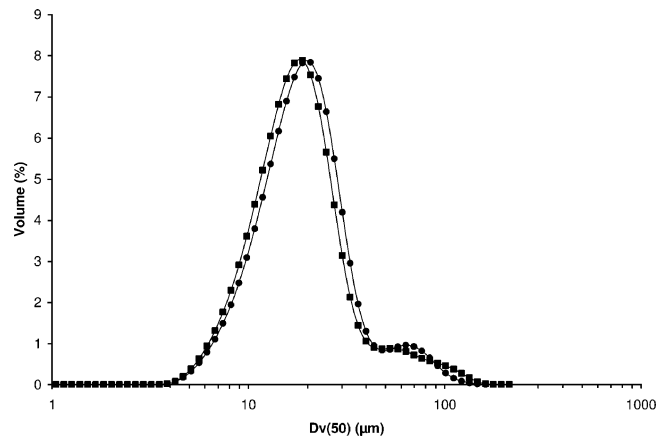

Fig. 6. Size distribution curves obtained by off-line laser diffraction for maltodextrin microspheres produced at *filled circle*, low and *filled square*, high wheel speed

line and at-line sizing, especially for microspheres made of modified starch as wall material. Standard deviation values were also much lower with the at-line sizer.

Some of the advantages of having an at-line set-up as opposed to one in-line are greater flexibility and cost-effectiveness. Instead of having one in-or on-line instrument dedicated to each process line, a single particle sizer could be used for many different lines, or moved to different sampling points in the same process line. Due to its close proximity to the process equipment, rapid sampling, analysis and process modifications may also be achieved. As shown in this study, the at-line set-up was especially useful for determining the unit particle size of materials prone to agglomeration as it allowed adequate sample dispersion. The at-line system could also be attached in- or on-line if needed. However, at-line process analysis is a destructive process and sample recovery is not possible unlike the in- and on-line set-ups. In addition, manual sampling is required.

Off-Line Laser Diffraction

Dv(50) values obtained off-line were similar to those determined at-line and bimodal size distributions were also observed (Fig. 6). This indicated that some agglomerates were still present. However, the second mode was lower (60–70 μm) for off-line laser diffraction than that of in-line measurements (80–400 μm). This could be attributed to some degree of aggregate breakdown during post-production handling and transit within the conveying conduit of the off-line sizer during size measurement. However, these forces were not sufficient for complete agglomerate dispersal and thus would still be unsuitable for very cohesive powders.

Light Microscopy

Light microscopy allowed differentiation between individual microspheres and agglomerates. Only discrete microspheres were sized, giving the lowest median size values. The difference in Dv(50) values was also due to the fact that the laser diffraction measurements produced volume-weighted values unlike measurements performed using the microscope which gave rise to number-weighted values. Volume-weighted values were always higher than number-weighted ones. For oil-loaded microspheres, the disparities between size data obtained with the in-line laser diffraction sizer and light microscopy/image analysis were greater at higher oil loadings, due to higher tendencies of the microspheres adhering to one another in the presence of surface oil. The microscopic method was manual and tedious as clumps or agglomerates had to be visually discerned. Images of microspheres to be sized were taken and their outlines demarcated before size measurements were made. For a statistically valid measurement, a large number of microspheres had to be measured and it was time consuming. Thus, this was significantly less efficient than the laser diffraction method used. The relative proportion of product analyzed was also much lower for the microscopic method as compared to laser diffraction. Besides requiring lengthy analyses, it is potentially affected by operator biasness and sampling errors. Moreover, it has been found to be less useful for powders with broad size distributions (27). As with at-line and off-line laser diffraction methods, particle sizing results would only be meaningful if samples remained unchanged after production.

However, light microscopy, when used with image analysis, allows the measurement of various dimensional parameters of particles such as sphericity, perimeters and areas. Direct observation of particle morphology is also possible. This would be useful for non-spherical, unknown or new materials especially during the research and development phase. In addition, faster alternative image-based techniques like digital surface imaging (28) and dynamic image analysis (29) are available. Laser diffraction instruments, on the other hand, generally do not distinguish well between particle shapes and mainly rely on spherical models in the computation of particle sizes (21), although techniques are available to size non-spherical particles by laser diffraction (25,26). In this study, this was not a major problem as the spray dried particles produced were generally spherical, except for the agglomerates present.

CONCLUSION

A feasibility study on the use of PAT for microsphere sizing during spray drying was conducted. It was found to be a rapid and convenient method which provided instantaneous information about the particle size distribution of the microspheres as they were made. The at-line set-up appeared to be superior to the in-line set-up in this particular application. Judicious data management and interpretation of results from PAT-enabled instruments are essential to allow valid conclusions to be made.

REFERENCES

1. Process Analytical Technology (PAT) Initiative. The U.S. Food and Drug Administration Website. Available at: http://www.fda.gov/cder/OPS/PAT.htm. Accessed December 7, 2005.
2. M. L. Balboni. Process analytical technology: Concepts and principles. *Pharm. Technol.* **27**(254):54–66 (2003).
3. H. G. Brittain. *Physical characterization of pharmaceutical solids*, Marcel Dekker, Inc., New York, 1995.
4. M. Alderliesten. Mean particle diameters. Part IV: Empirical selection of the proper type of mean particle diameter describing a product or material property. *Part. Part. Syst. Charact.* **21**:179–196 (2004).
5. T. Allen. *Particle size measurement. Volume I. Powder sampling and particle size measurement*5Chapman & Hall, London, UK, 1997.
6. C. Washington. *Particle size analysis in pharmaceutics and other industries–theory and practice*, Ellis Horwood Ltd, West Sussex, UK, 1992.
7. G. M. Crawley. Particle sizing online. *Powder Metall.* **44**:304–306 (2001).
8. M. Birch, S. J. Fussell, P. D. Higginson, N. McDowell, and I. Marziano. Towards a PAT-based strategy for crystallization development. *Org. Process Res. Dev.* **9**:360–364 (2005).
9. S. Brenek, D. EndeamP. Rose. *The application of high shear wet milling to achieve particle size with in-situ monitoring via FBRM*, Mettler Toledo Real Time Analytics Users' Forum, London, UK, 2004.
10. L. X. Yu, R. A. Lionberger, A. S. Raw, R. D'Costa, H. Wu, and A. S. Hussain. Applications of process analytical technology to crystallization processes. *Adv. Drug Delivery Rev.* **56**:349–369 (2004).
11. J. Q. Zhang and Y. Yan. On-line continuous measurement of particle size using electrostatic sensors. *Powder Technol.* **135–136**:164–168 (2003).
12. R. M. Carter, Y. Yan, and S. D. Cameron. On-line measurement of particle size distribution and mass flow rate of particles in a pneumatic suspension using combined imaging and electrostatic sensors. *Flow Meas Instrum.* **16**:309–314 (2005).
13. On-line particle size distribution analysis using a novel technology. The Department of Trade and Industry Basic Technologies

Programme Website. Available at: http://www.basictechnologies.gov.uk/site/projects/BTIASPRINGPS6Feb04.doc. Accessed December 8, 2005.

14. K. Masters. *Spray drying handbook*5John Wiley & Sons, New York, 1991.

15. J. Broadhead, S. K. E. Rouan, and C. T. Rhodes. The spray drying of pharmaceuticals. *Drug Dev. Ind. Pharm.* **18**:1169–1206 (1992).

16. R. O. Cook, R. K. Pannu, and I. W. Kellaway. Novel sustained release microspheres for pulmonary drug delivery. *J. Contr. Rel.* **104**:79–90 (2005).

17. A. Picot and C. Lacroix. Encapsulation of bifidobacteria in whey protein-based microcapsules and survival in simulated gastrointestinal conditions and in yoghurt. *Int. Dairy J.* **14**:505–515 (2004).

18. G. Coppi, V. Iannuccelli, M. T. Bernabei, and R. Cameroni. Alginate microparticles for enzyme peroral administration. *Int. J. Pharm.* **242**:263–266 (2002).

19. M. I. Ré. Microencapsulation by spray drying. *Drying Technol.* **16**:1195–1236 (1998).

20. L. H. Tan, L. W. Chan, and P. W. S. Heng. Effect of oil loading on microspheres produced by spray drying. *J. Microencap.* **22**:253–259 (2005).

21. D. L. Black, M. Q. McQuay, and M. P. Bonin. Laser based techniques for particle size measurement: a review of sizing methods and their industrial applications. *Prog. Energy Combust. Sci.* **22**:267–306 (1996).

22. R. Xu. *Particle characterization: light scattering methods*, Kluwer Academic Publishers, Dordrecht, The Netherlands, 2000.

23. T. L. Harvill, J. H. Hoog, and D. J. Holve. In-process particle size distribution measurements and control. *Part Part Syst Charact.* **12**:309–313 (1995).

24. J. Crosley, C. Mann, J. Scotland. Advantages of the use of in-line particle size analysis in a contract processing facility. PARTEC2001, International congress of particle technology. Nuremberg, Germany, 2001.

25. T. Matsuyama and H. Yamamoto. Particle shape and laser diffraction: A discussion of the particle shape problem. *J. Disper. Sci. Technol.* **25**:409–416 (2004).

26. Z. Ma, H. G. Merkus, J. G. A. E. de Smet, C. Heffels, B. Scarlett. New developments in particle characterization by laser diffraction: size and shape. Powder Technol. 111:66–78 (2000).

27. C. Andrès, P. Bracconi, P. Régianult, P. Blouquin, M. H. Rochat, and Y. Pourcelot. Assessing the particle size of a broadly dispersed powder by complementary techniques. *Int. J. Pharm.* **167**:129–138 (1998).

28. N. Laitinen, O. Antikainen, and J. Yliruusi. Characterization of particle sizes in bulk pharmaceutical solids using digital image information. *AAPS PharmSciTech.* **4**:383–391 (2003).

29. R. Xu and O. Andreina Di Guida. Comparison of sizing small particles using different technologies. *Powder Technol.* **132**:145–153 (2003).