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Laser diffraction and image analysis as a supportive analytical tool in the pharmaceutical development of immediate release direct compression formulations

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Abstract

Immediate release direct compression tablet formulations require a strict control of the particle characteristics (i.e. particle size (distribution) and shape) of both the active pharmaceutical ingredient (API) and the excipients. In this publication, the development of a dry dispersion laser diffraction (LD) method has been outlined. With this method, the chemical development of an API meant for the manufacturing of an immediate release direct compression tablet formulation can be supported. Comparison with static image analysis (SIA) and scanning electron microscopy (SEM) data often shows laser diffraction to generate different size data. However, since LD is fast and frequently shows an adequate precision over a wide particle size range, the technique is still considered as a valuable analytical tool in the screening of the particle size distribution of API batches. In the future, automated (static) image analysis and dynamic image analysis are believed to become more and more important, since these techniques will allow the fast analysis of large amounts of particles with a minimum intervention of the operator.

Keywords: Laser diffraction; Static image analysis; Scanning electron microscopy; Particle size distribution; Direct compression

1. Introduction

A major part of pharmaceutical industry is involved in the development of new drugs with high(er) therapeutic activity, and less side effects. Thereby, one of the current trends is to develop drugs that can be administered at a low(er) dosage level. For practical reasons, the API is never administered as such, rather by means of a dosage form, which should guarantee the dosing to the patient of a constant and defined amount of API. In case of a so-called direct release solid dosage form (i.e. tablets and capsules), the formulation intends to be nothing more, than a simple carrier of the API. The development of a sustained release formulation may be the next phase in the life cycle of a drug, since this prevents the multiple administration of the drug.

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Though a direct release formulation seems to be nothing more than a simple dosing device, it may seriously affect the pharmaceutical activity of the drug in terms of the dissolution and absorption rate (Jounela et al., 1975; Ridolfo et al., 1979) of the API. As a result, both the API and the dosage form should be fully characterized, such that a constant quality of the product can be guaranteed. During the development of a new drug, characterization of the API, the excipients and the drug product is of major importance in the optimisation of both the formulation characteristics and the manufacturing process. The manufacturing of direct release tablets may occur on the basis of wet granulation of the API. However, wet granulation is sometimes considered to be a time consuming process, whereas the drying of the granules may lead to degradation effects. As a result, in pharmaceutical industry, so-called direct compression is considered as a serious alternative for the manufacturing of direct release tablets.

In general, the particle size (distribution) and shape of the API can significantly influence the manufacturability (e.g. content uniformity), the stability and the bioavailability of an immediate release direct compression tablet. With regard to the manufacturability, a good flowability of the blend, i.e. the dry mixture of excipients and API, is critical for the compression of the tablets in terms of dissolution and content uniformity (Zhang and Johnson, 1997; Yalkowsky and Bolton, 1990). In order to guarantee good flowability of the blend, particle morphology and more important particle size (distribution) should be aligned with the particle characteristics of the excipients. A proper selection of the particle characteristics of the various ingredients should avoid segregation of the blend, and 'air bubble' formation during the process of direct compression (Johanson, 1996).

As a general approach in the development of a new immediate release direct compression tablet formulation, initially different API batches with differences in particle size (distribution) and shape are produced in order to determine the optimal particle characteristics of the API. These different API batches result in different blends, of which the flowability characteristics can be determined and ranked. In addition to this, different tablet batches are produced with the aforementioned blends, and of which the content uniformity, dissolution and stability profiles are determined. Typical stability studies could be short-term stressed open dish studies, in which both the chemical and physical–chemical characteristics of the tablets are monitored. Eventually, this will lead to the selection of the desired particle size characteristics of the API.

It is obvious that precise and accurate analytical methodologies should be in place to support the abovementioned process. In an early phase of the development process where the selection of the particle characteristics of the API is made, emphasis is laid on research and development related methodologies, enabling the characterization of the morphology and the particle size (distribution) of the API. In a later stage, often a more ready to use analytical methodology is preferred for the Quality Control (QC) of the product, and meant to monitor the consistent quality of the API production batches with regard to the particle size (distribution). Finally, a clear correlation between the initial R&D data and the final QC methodology should be established in order to be able to define and justify the release specifications of the API production batches (Johnson and Swindell, 1996).

More than for wet granulation, direct compression formulations require a strict control of the particle characteristics, i.e. particle size (distribution) and shape, of both the API and the excipients. As a result, for the development of an immediate release direct compression tablet formulation the particle characterization of the API is of utmost importance. For the characterization of small particles, a large number of techniques is available, of which laser diffraction (LD) appears to be most regularly applied (van de Hulst, 1981; Black et al., 1996; ISO 13320-1, 1999). An explanation for the wide use of LD, is the fact that the technique is mentioned in the various pharmacopoeias, since it is considered to be a universal approach in the characterization of both dry powders, suspensions and sprays.

Though LD has the clear advantage of being a fast and user-friendly technique, which generates size distribution profiles based on the analysis of a huge amount of particles, for the past few years a limited applicability of LD has been claimed (Etzler and Deanne, 1997). As an important argument, LD is considered merely as a relative technique for the mapping of size distribution patterns, since it assumes particles to be spherical, which in practice they almost never are. Furthermore, experimental results on LD may differ from one supplier to the other, and sometimes even from one instrument model to the other. This should primarily be

explained by the efforts of suppliers to maximize the size range of their instruments, either by the development of unique and sometimes proprietary hardware, or by the development of unique software (i.e. deconvolution algorithms). In addition, LD data may differ as a result of the effort of the manufacturers to maximize the application range of the instrument by the development of dedicated and supplier specific sample handling modules for the dispersion of the particles. Though the technological development of laser diffraction is still going on, the technique is not yet able to generate information on the shape of the particles (Ma et al., 2000). Because of this reason, one should be careful using LD as the one and only source of particle characterization equipment. In practice, static image analysis (SIA) based on optical microscopy (ISO 13322-1, 2002) and scanning electron microscopy (SEM) have shown to be very useful for the further characterization of particles. However, both techniques have so far shown serious limitations with regard to the cycle times for analysis and the number of particles counted. This explains that LD is still considered as an important tool for the characterization of pharmaceutical substances.

The degree of correlation between LD and SIA highly depends on the shape of the particles. While for SIA the particles orient themselves with their largest projected area in the *x*-, *y*-plane of the microscope slide, the LD diffraction pattern results from the random orientation of the particles. Thereby, the scattering pattern is the accumulatively average of all orientations, but weighted heavily by the longest dimension of each particle (Xu and Di-Guida, 2003). As a result, in LD the detected signal is weighted to some extent towards the perpendicular orientations as observed for SIA. This has been confirmed in literature, where for spherical and platelike particles the size distribution data obtained with LD appear to show a good agreement with the area-based data as obtained with SIA (Brewer and Ramsland, 1995).

Within this paper, the development of a robust, precise and accurate LD method is outlined. The different stages of this development process are discussed based on a real life example, and the following steps will be discussed in more detail: (a) SEM characterization of the different API batches, (b) SIA characterization of the different API batches to generate a better understanding of the absolute particle size distribution, (c) selection of an LD methodology (i.e. wet dispersion versus dry dispersion), (d) screening and optimisation of the different parameters of the LD method, and (e) evaluation of the precision of the LD method.

2. Experimental

2.1. Chemicals

Various API batches of the same API, but with differences in size and shape were from Johnson & Johnson Pharmaceutical Research and Development (Beerse, Belgium).

2.2. Instrumentation

2.2.1. Dry dispersion laser diffraction system

Dry dispersion laser diffraction measurements were performed with a Malvern Instruments model Mastersizer 2000 instrument (Malvern, UK). The instrument was equipped with a Scirocco 2000 dry powder dispenser, which was operated at various inlet pressures. The Fraunhofer model was used for the deconvolution of the diffraction pattern. Based on application of the general purpose model, the volume-weighted size distribution was determined together with the d10, d50, and d90 cumulative undersize.

2.2.2. Wet dispersion laser diffraction system

Wet dispersion laser diffraction measurements were performed with a Coulter model LS 130 instrument (Fullerton, CA, USA). The instrument was equipped with a Small Volume Module (SVM) wet dispersion module, which was operated at a stirring speed setting of 6. The Fraunhofer model was used for deconvolution of the diffraction pattern. The volume-weighted size distribution was determined together with d10, d50, and d90 cumulative undersize.

2.2.3. Static image analysis system

Static image analysis measurements were performed with a Meiji Techno model ML2000 optical microscope (Saitama, Japan) equipped with a Sony model xc-75CE B/W CCD camera (Tokyo, Japan) and Image Pro version 4.5.0.29 image analysis software from Media Cybernetics (Carlsbad, CA, USA). Based

on the particle areas of ca. 10.000 particles, the volume-weighted size distributions and the d10, d50, and d90 cumulative undersize were reported.

2.3. Sample preparation

2.3.1. Laser diffraction analysis (dry dispersion)

For dry dispersion of the API, a sample amount of approximately 5 g was introduced into the dry powder disperser.

2.3.2. Laser diffraction analysis (wet dispersion)

For wet dispersion of the API, a sample amount of approximately 200 mg was predispersed in 15 ml of the dispersant. Then the predispersion was introduced in the wet dispersion module until an adequate obscuration level was obtained.

2.3.3. Static image analysis (dry dispersion)

For the preparation of microscopy slides, a small amount of API was dispersed in air using a homemade dry powder disperser at a vacuum pressure of <0.05 bar.

2.3.4. Static image analysis (wet dispersion)

A small amount of API has been dispersed in silicon oil, prior to the preparation of a microscopy slide.

3. Results and discussion

3.1. SEM characterization of the different API batches

Prior to the development of a laser diffraction method, details should be known on the morphology of the primary particles. For this purpose, SEM images of typical fine and coarse API batches are presented in Figs. 1 and 2, respectively. These images clearly demonstrate that during the development trajectory of an API the morphology of the various development batches may significantly differ. For the API batches that are used within this study, the morphology appears to vary from small irregular shaped flakes (i.e. thin, flat particles of approximate similar length and width) to large regular shaped plates (i.e. flat particles of approximate similar length and width, but with a greater thickness than flakes). Additionally, these API batches have a rather broad size distribution, with an estimated longest dimension of the largest particles of ca. 100–200 μm for the flakes, and of ca. 800 μm for the plates. This clearly illustrates that the use of LD in the chemical development of a new API should be robust with respect to the size range of the method.

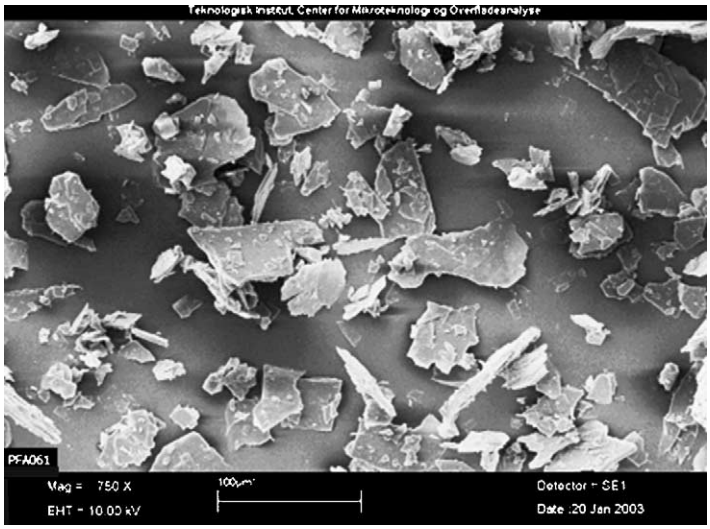

Fig. 1. Representative SEM image of API consisting of fine particles (the unit scale corresponds to 100 μm).

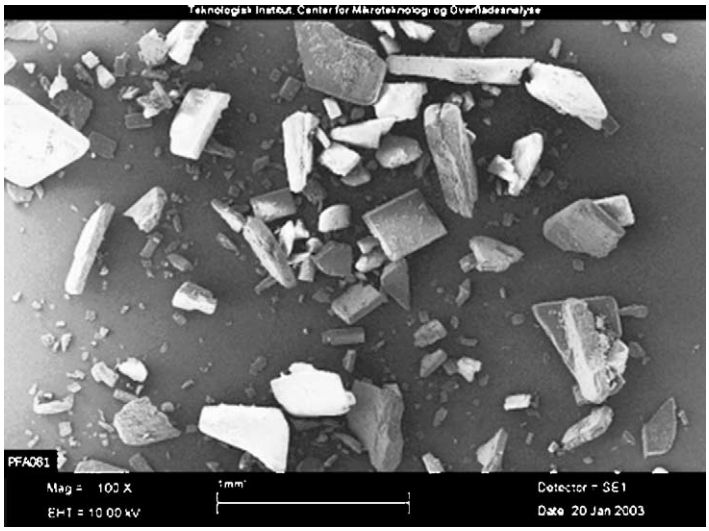

Fig. 2. Representative SEM image of API consisting of coarse particles (the unit scale corresponds to 1 mm).

3.2. SIA characterization of the different API batches

In addition to SEM analysis, various API batches were analysed with SIA to determine the size distribution, and to characterize the API particles in terms of brittleness, and the tendency to agglomerate. All SIA analyses were done using both wet and dry dispersion of the sample material. Based on the measured areas, volume distributions were calculated for correlation with the LD data. In Table 1, the d10, d50 and d90 cumulative undersize are presented for various API batches. It appears from these data that for each API batch the size distribution data as obtained with either wet and dry dispersion are quite comparable. For the dry dispersion data, the somewhat lower d10 cumulative undersize for the coarse API batches might be explained by a slight degree of breaking of the brittle plates. Additionally, for the fine(r) batches, the somewhat higher d50 and d90 cumulative undersize for the dry dispersion measurements could be explained by a certain degree of agglomeration, and the difficulty of having these particles dispersed by dry dispersion without breaking them. This leads to a rather general

Table 1
Size distributions obtained with SIA for various batches of API

Batch	Morphology	Dispersion[a]	d10[b]	d50[b]	d90[b]	*N*[c]
Batch A	Flakes	Wet	32	72	155	10109
		Dry	32	120	241	13013
Batch B	Plates	Wet	224	485	858	10801
		Dry	134	430	745	12105
Batch C	Plates	Wet	254	493	769	10654
		Dry	191	412	751	10365
Batch D	Flakes	Wet	70	131	280	10855
		Dry	67	153	295	10043

[a] Wet, wet dispersion; dry, dry dispersion.
[b] d10, d50 and d90 cumulative undersize (μm).
[c] Number of particles counted.

conclusion, that the API crystals and especially the big plates are relatively brittle, while the small flakes have a serious tendency to agglomerate. Especially for a dry dispersion LD method, these features put some severe restrictions to the analytical conditions, since the dispersion energy should not be too high in order to prevent the breaking of particles. Furthermore, the dispersion energy should not be too low, in order to prevent that the diffraction pattern is measured for agglomerates, and not for isolated and well dispersed particles.

3.3. Selection of an LD methodology

If a LD method needs to be developed for the size distribution analysis of API batches with a large variety in shape and size, regularly wet dispersion of the sample is the first choice to explore. In general, for a wide series of product qualities the use of a suitable dispersion liquid more readily leads to robust dispersion conditions. For this purpose, the API particles should show a good wetability and poor solubility characteristics. Once the suitable dispersion liquid is known, the stirring speed may need to be optimised in order to obtain a stable signal for both small and large particles, such that any agglomerates will be broken apart, but without any breaking of the primary particles. Though in many cases, a suitable dispersion liquid can be found, occasionally the dispersion liquid may show some difficulties, and dry dispersion of the API is then to be preferred over wet dispersion.

Initially, with the wet dispersion LD method applying diethylether as the most suitable dispersant, reproducible results were obtained for API batches consisting of relatively small particles with a size less than 100 μm. In addition to this, sufficient correlation was demonstrated comparing those results with the results as obtained for the in-line monitoring of the API crystallization process using so-called Focussed Beam Reflectance Measurement (FBRM) (Müller et al., 1998). However, during the development trajectory of the immediate release direct compression tablet formulation, a larger particle size of the API appeared necessary. In Table 2, typical results are presented on the wet dispersion LD analysis of the API in diethylether. These results clearly demonstrate that for the API particle size going up, the precision of the method is going down. Based on these observations, it was concluded that the wet dispersion laser diffraction method was not suitable for the LD analysis of the various API development batches.

Table 2
Typical wet dispersion laser diffraction results as obtained in diethylether for API consisting of larger particles

	d10 (μm)	d50 (μm)	d90 (μm)
Mean	20	145	428
Standard deviation	15	96	176
R.S.D. (%)	77	66	41

In order to improve the performance of the LD method for API batches with a larger particle size, a dry dispersion LD method was developed. The initial method required the use of ca. 5 g of API at a 2 bar pressure setting of the dry dispersion module. In Table 3, typical results are presented for the dry dispersion LD analysis of the API. These results clearly demonstrate, that for API with a larger particle size, changing from wet dispersion to dry dispersion improves the precision of the method significantly. However, a serious shift of the *d*-values appeared to occur, and the in-line FBRM measurements did not show a correlation anymore. In addition to this, comparison with image analysis data did not lead to a consistent data set. Therefore, it had to be concluded that with the precision going up, the accuracy of the method had gone down, resulting in a method with limited capabilities for monitoring the particle characteristics of API development batches.

The necessity for having a robust LD method with adequate precision and accuracy was demonstrated soon afterwards, as certain batches of the directly compressed tablets appeared to show a tendency to burst when stored at high relative humidity. This phenomenon seemed to be more pronounced for API batches consisting of larger particles. As a result, the dry dispersion LD method had to be improved especially with regard to its accuracy.

Table 3
Typical dry dispersion laser diffraction results as obtained at a pressure setting of 2 bar for API consisting of larger particles

	d10	d50	d90
Mean	3.9	22	112
Standard deviation	0.2	1	6
R.S.D. (%)	4	5	5

3.4. Screening and optimisation of the different parameters of the dry dispersion LD method

For dry dispersion LD measurements, pressure setting, feedrate, and measuring time may in general have serious effects on the measured particle size distribution. For this purpose, an experimental design study was initiated taking into account these critical parameters, as well as the different product qualities (i.e. coarse and fine material). As a starting point for the development of the LD method, several response curves were determined by means of varying one parameter at the time. For the API, the d10, d50 and d90 cumulative undersize were monitored, and initial optima were found at a measuring time of 7.5 s, a feedrate of 60%, and a vacuum pressure of 0.1 bar, the latter actually being the lowest possible pressure setting of the instrument. The experimental data as shown above clearly demonstrate that for this product the vacuum pressure has the most pronounced effect on the measured particle size distribution. In Fig. 3, the d50 cumulative undersize of three batches, each with a different average particle size, is plotted as a function of the vacuum pressure. From these data, the brittleness of the API is once again clearly demonstrated, and it can be clearly observed that this phenomenon appears to be more or less identical for both the fine and coarse material.

After these initial experiments, the optima for the measuring time, feedrate and vacuum pressure were used as a basis for the further definition of the experimental design, i.e. the factors and levels (see Table 4). For this purpose, it was decided to keep the measuring time constant at 7.5 s. The experimental design was set up as a two-level full-factorial design with two centre points per categoric level, and the runs were randomised prior to analysis. The experimental design was evaluated based on the dl0, d50, and d90 cumulative undersize of the various size distributions, and a model

Table 4
The various factors and levels as defined for the experimental design study

Factor	Low	High
Instrument		
Vacuum pressure (bar)	0.10	0.30
Feedrate (%)	40	80
Product		
Particle size	Fine	Coarse

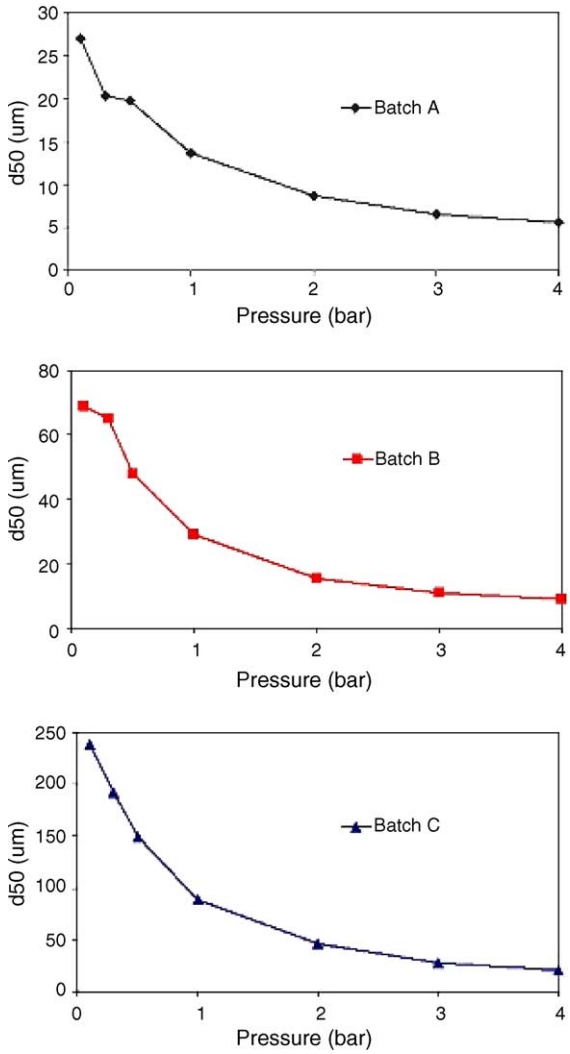

Fig. 3. For three API batches with a different particle size, the d50 cumulative undersize has been plotted as a function of the vacuum pressure.

was fitted with main-effects and two-way interactions. Figs. 4 and 5 present the surface response plots for both fine and coarse material. Based on these results, one can conclude that in all cases the particle size is decreasing at a higher vacuum pressure, and that this effect is most clearly to be observed for the coarse particles. The latter can be readily understood since the breaking of large particles generally leads to a more pronounced change in particle size distribution compared to small particles. Furthermore, a clear effect of

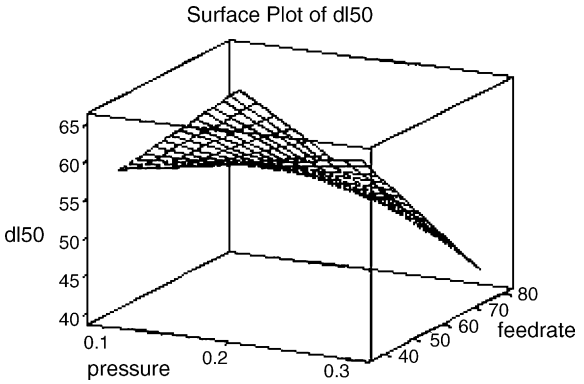

Fig. 4. A typical d50 surface response plot for fine, flake-shaped API material.

the feedrate was observed, which tends to be more pronounced at a higher vacuum pressure of 0.3 bar. Taking all this into account, maximum robustness of the dry dispersion LD method is expected for the various API batches at a vacuum pressure of 0.1 bar. At this low-pressure setting, the feedrate was finally set at 80%.

Having the nominal conditions defined, the next step concerned the comparison of the LD method with SIA and SEM results, in order to verify the degree of correlation between the various techniques. In Tables 5 and 6, comparison of the LD data with the SIA data is presented for both fine and coarse API material. It appears that the estimated longest dimensions as determined with SEM are quite close to the d90 cumulative undersize as obtained with SIA. However, if the LD data are compared with the SIA data, only a limited correlation is observed. Especially for the fine API batches the differences appear to be more pronounced. Based on these observations, one should conclude that if one needs to know the true dimensions of certain particles, SIA and SEM are definitely to be preferred over LD. Nevertheless, LD is fast, and it, therefore, allows a rapid screening of new batches of API. Furthermore, a robust performance of the LD method can be realised over a wide particle size range. As a result, the technique is suitable to detect batch-to-batch variations and to monitor trends in the size distribution and average particle size.

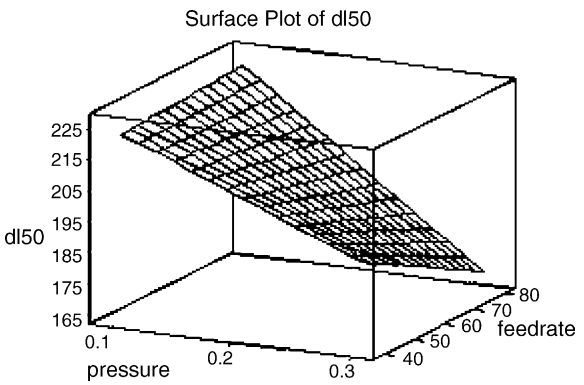

Fig. 5. A typical d50 surface response plot for coarse, plate-shaped API material.

Table 5
Comparison of the LD and SIA volume weighed size distribution data for a API batch consisting of fine particles

Test	Dispersion	d10	d50	d90
LD	Dry	12	52	514
SIA	Dry	32	120	241
	Wet	32	72	155

3.5. Evaluation of the precision of the dispersion LD method

Finally, the precision of the method was evaluated by means of analysing different API batches on the same instrument by two analysts, each analysing the API samples on a different day. Table 7 demonstrates adequate precision of the dry dispersion LD method, except for the d90 cumulative undersize of one of the API batches. The rather high R.S.D. for the d90 cumulative undersize of Batch C apparently relates to the larger particle size, and probably illustrates insufficient homogeneity of the sample, which emphasizes the necessity for thorough mixing and splitting of the sample prior to analysis. Finally, adequate precision and robustness was demonstrated for the dry dispersion LD method, since the R.S.D. for the series of d50

Table 6
Comparison of the LD and SIA volume weighed size distribution data for a API batch consisting of coarse particles

Test	Dispersion	d10	d50	d90
LD	Dry	85	351	747
SIA	Dry	134	430	745
	Wet	224	485	858

Table 7
Precision evaluation of the dry dispersion laser diffraction method by means of the multiple analysis by two analysts of three different API batches using a single instrument

Analyst	d10	d50	d90
Batch A			
1	15	66	173
1	16	66	172
2	16	66	176
2	16	69	192
Mean	16	67	178
Standard deviation	0.4	1	10
R.S.D. (%)	2	2	5
Batch B			
1	17	59	206
1	16	59	201
2	16	58	198
2	17	60	195
Mean	17	59	200
Standard deviation	0.5	0.8	4.7
R.S.D. (%)	3	1	2
Batch C			
1	32	222	439
1	33	224	444
2	33	238	552
2	34	244	547
2	32	224	447
Mean	33	230	486
Standard deviation	1	10	58
R.S.D. (%)	3	4	12

cumulative undersize of Batch D (with a somewhat larger particle size than Batch B) did not exceed the internal requirements of 10% (data not shown here).

4. Conclusions

LD is a fast technique with adequate precision over a wide particle size range. Since it can be sufficiently linked with true and absolute size data obtained with SIA and SEM, LD may be considered as a useful analytical tool for the particle characterization of the API batches that are manufactured during the development trajectory of a new pharmaceutical product. For a proper characterization of particles, LD should certainly not be the only technique used for that purpose. Though SIA is already an important technique for the characterization of small particles, the technique is elaborate, and the expertise of the operator is crucial in the generation of correct data. As a result, automated (static) image analysis and dynamic image analysis are believed to become more and more important, since these techniques will allow the fast analysis of a sufficiently large amount of particles.

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