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Research paper

Microscale granulation in a fluid bed powder processor using electrostatic atomisation

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ABSTRACT

The aim of this study was to use the electrostatic atomisation in miniaturised fluid bed granulation process and define the effect of process parameters. The process parameters included in the study were granulation liquid flow rate, atomisation voltage and binder concentration in the granulation liquid. Altogether 22 batches were granulated in Multichamber Microscale Fluid bed powder Processor (MMFP). Granule size distributions were measured with both sieves and image analyses. With these process conditions, the atomisation liquid flow rate had a strong positive correlation with the granule size. Increasing the atomisation voltage increased the granule size, which is contradictory with the expectations. The effect of the binder concentration remained unclear. Although it is challenging to model the fluid bed granulation process in micro-scale, multivariate methods such as principal component analysis (PCA) are helpful in studying the most important phenomena.

1. Introduction

Fluid bed granulation process is widely used in the pharmaceutical industry, as well as in metallurgical, agricultural, petroleum, construction and chemical industries. In the pharmaceutical industry, the main goal is to produce free flowing, fine and homogenous granules of certain particle size and density that possess as good properties (e.g. compressibility) as possible for the final drug product and are easy to handle. To achieve all these objectives, the process parameters related to the fluid bed granulation have been studied extensively during the last four decades [1].

In traditional fluid bed equipment, twenty different process parameters can be obtained. These parameters can be related besides to the actual process (e.g. inlet air temperature), also to the granulator apparatus (e.g. the shape of the chamber) or to the material to be granulated (e.g. solubility) [1]. In production scale, the granulation liquid flow rate, the atomising air pressure and the amount of binder are relevant parameters defining the droplet size. The linear relationship between the droplet size and the granule size in fluid bed granulation has been reported by several authors [2–4]. Increase in the granulation liquid flow rate and in the binder concentration has been found to increase the granule size [2].

It has been stated that the cost to develop a new drug is 900 million US dollars [5]. The development time is nearly a decade, and nine of ten attempts to develop a new product fail. Therefore, it is urgent to develop new methods to speed up the product development in the early phase. Formulation development is not the most expensive part of drug development, but shorter the time the faster the product will be on the market and therefore economical benefit is obvious. Also expensive new materials and strict regulatory requirements [6] have created a need for small and effective tools for formulating procedures. Miniaturisation has been an ongoing trend in pharmaceutical development for several years [7]. One of the main reasons for miniaturisation besides the costs is the limited amount of the active pharmaceutical ingredient (API) in the early stages of formulation development [8]. In EUFEPS project New Safe Medicines faster it is stated that seamless processes and miniaturisation lead to a faster drug development process [9]. A well-known fact in the pharmaceutical development is that better understanding of the processes leads to better products. These miniaturised approaches are needed to increase the understanding of the physical and chemical phenomena that are important in pharmaceutical unit operations [10] .

Even though high throughput screening (HTS) of new molecules is a standard method for most of the companies in identifying and

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characterising the lead molecules [11,12], not many miniaturised devices for the high throughput formulation screening have been introduced. As the micro-scale research of manufacturing processes exceeds further, there will be a high need for analytical methods for the miniaturised samples because the familiar and well-described methods such as sieve analysis may not be suitable for small sample sizes.

In the electrostatic atomisation (or in electrospraying), an electric field is applied at the liquid surface. Electric field induces a high surface charge density on the surface. Since like charges repel each other, the surface experiences an outwards directed coulombic force. When this force exceeds the force caused by the surface tension, the liquid surface disrupts. The size of these droplets can be varied by changing the electric field or the granulation liquid feeding rate. In addition to the relatively uniform size, these droplets also have a uniform charge. Thus, the charge-to-mass ratio (specific charge) is also relatively uniform which enables the trajectories of the droplets to be controlled with an external electric field [13]. This property is extremely useful in our miniaturised device since fine droplets can be directed to the fluidised powder and the attachment of the liquid to the column wall can be reduced. The theories applied in micro-scale fluid bed granulation using electrostatic atomisation and the full operation principles of the electrostatic nozzle are described in detail elsewhere [14]. With electrostatic atomisation it is possible to produce droplets that have a very narrow size distribution [15]. Since there is a linear relationship between droplet size and granule size in theory, it should be possible to produce granules with very narrow size distribution using electrostatic atomisation in fluidised bed.

When the atomisation potential is applied to the pipe containing the granulation liquid, the liquid surface at the capillary tip disrupts. As a result, small highly charged droplets are emitted. When these droplets leave the nozzle, they encounter various forces: gravitational force, air drag force caused by the upwards moving air, electrostatic force caused by the induced image charge at the earthed shield and the repulsive space charge force caused by the droplets themselves. The repulsive space charge force tends to expand the spray towards the chamber walls, because the direction of the emitted droplets has a small radial component [14].

Multichamber Microscale Fluid bed powder Processor (MMFP) has been developed for fast characterisation of pharmaceutical materials. The device consists of five conical fluid bed glass chambers, which are individually controllable. Compared to other miniaturised fluid bed devices such as MP-Micro™ (batch size from 20 to 100 g), Mini Airpro fluid bed (batch size from 200 to 300 g) or GA 22 fluid bed (batch size from 50 to 300 g), in MMFP the batch size for the granulation can be relatively small (from 20 to 50 g). So far, MMFP has been used for studying solid-state transitions during fluidisation [10], dehydration process parameters [16], drying of pharmaceutical materials [17], fluidisation behaviour of different materials [18] and pellet tackiness determination [19]. Due to the differences the in operating principle compared to the production scale equipments, MMFP is more suitable for early phase formulation screening studies than for scale-up purposes. The use of pneumatic nozzle is not possible in MMFP, since the air flow would seriously be disturbed. Compared to production scale fluid bed devices, the dimensions of granulation chamber in MMFP are different. Due to precisely controlled air flow, no separate filter bags are needed in the device.

This is the first time, when granulation liquid droplets are generated via electrostatic atomisation in fluid bed granulation in this scale. Since this small scale is challenging, the purpose of this study was to evaluate the effects of granulation liquid flow rate, binder concentration in the granulation liquid and the voltage applied to the granulation liquid on the granule size.

2. Materials and methods

2.1. Materials

A common tablet filler α-lactose monohydrate [20] (Pharmatose 80 M, DMV International, Netherlands) was granulated in MMFP. Less than 20% of the particles were reported to be smaller than 100 μm, 70–90% of the particles were reported to be smaller than 250 μm and 95% of the particles were reported to be smaller than 315 μm [21]. Three different concentrations (6%, 8% and 10% w/w) of polyvinylpyrrolidone (PVP, Kollidon K-25, BASF, Germany) and ion-exchanged water were used as granulation liquid. This relatively coarse α-lactose monohydrate was chosen for the remarkably good fluidisation and granulation properties in the MMFP [14].

2.2. Experimental set-up

2.2.1. Multichamber Microscale Fluid bed powder Processor (MMFP)

Multichamber Microscale Fluid bed powder Processor (Ariacon Oy, Turku, Finland) is presented in Fig. 1a and a more simplified version in Fig. 1b. The device uses a conical fluidisation chamber made from glass. The inner diameter of the lower part of the granulation chamber is 20 mm, and the diameter of the upper part is 100 mm. Fluidisation occurs in the lower part of the chamber, and the upper part acts as an aerodynamic brake decreasing the fluidising air velocity. The air distributor consists of circular fine mesh (aperture 50 μm) which is connected to the chamber with an o-ring. The air flow rate and the temperature of the inlet air are controllable. Automation, instrumentation, and process data management of the MMFP was designed using the outlines described in the article by Räsänen et al. [18].

The MMFP module was connected to a process air control unit (Ilmasäätö Oy) for controlling the moisture content of the inlet air. Relative humidities and temperatures of the inlet and outlet air were measured using Humicap 233 sensors (Vaisala Oyj, Vantaa, Finland). The inlet air of the fluidisation unit in use was heated to the desired temperature (60 °C) using both process air control unit and a resistor-type heating element. A temperature controller and a Pt-100 type sensor (Mikor, Turku, Finland) controlled the temperature of the inlet air.

2.2.2. Electrostatic nozzle

A schematic diagram of the granulation set-up and the nozzle is presented in Fig. 2. The nozzle consists of earthed shield, polytetrafluoroethylene (PTFE) insulation and metal capillary connected to a DC high voltage power supply (Spellman, High Voltage Corporation, USA). The outer diameter of capillary was 0.5 mm and the axial distance from the tip to the shield was adjusted to 4 mm. The nozzle was placed into the granulation chamber made of glass, 10 cm above the powder bed. The granulation liquid was pumped through the capillary using a syringe pump (Model NE-1000, New Era Pump Systems, Inc., USA).

2.3. Process conditions

2.3.1. Granulation

In the beginning of the granulation experiments, 25 g of lactose monohydrate was poured into the chamber and the air flow rate was adjusted to 200 ml/s. The batch size was the smallest possible but large enough to ensure enough granules for further analysis. The relative humidity of the inlet air was kept at 0% in this study. As the air flow rate in the powder bed reached the rate of 100 ml/s, the high voltage supply was switched on to apply a negative atomisation potential to the capillary, and after that the pumping of the granulation liquid was started. It was crucial to start the pump after the voltage supply to avoid the possibility of big non-atomised droplets to reach the bed.

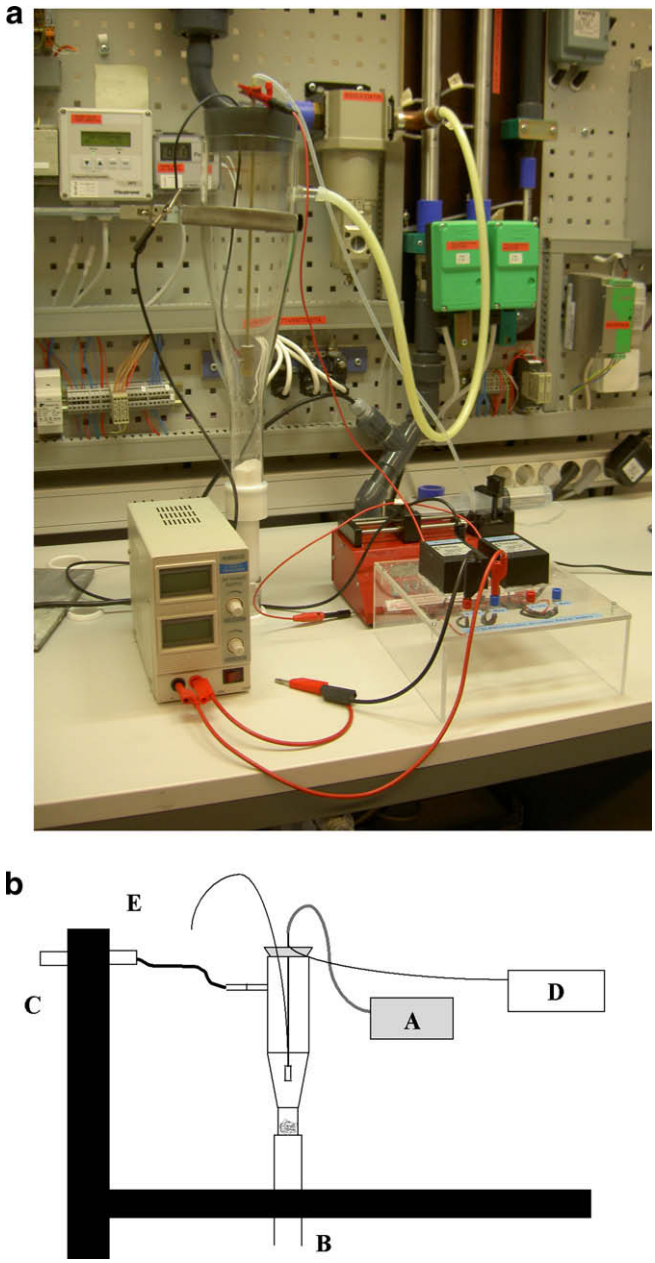

Fig. 1. (a and b) The photo of MMFP granulating chamber and simplified schematic diagram of MMFP chamber and the granulation set-up. A, syringe pump; B, Inlet air pipe from the process air control unit; C, outlet air pipe; D, high voltage supply; E, ground wire.

As the bed weight increased due to the spraying of the granulation liquid, the air flow rate was raised to 800 ml/s stepwise manually. After the granulation liquid addition, the granules were dried for 6 min with an air flow rate of 300 ml/s at 60 °C. Since the target mean particle size for tabletting is usually 300–600 μm (depending on the formulation), after the drying the batch was poured through 2 mm sieve to exclude possible larger aggregates. Sieving the oversize fraction – which is defined by the final formulation – is a standard operating procedure in the fluid bed granulation in the industry. To avoid granule breakage due to excess moisture, the granules were kept in a tray dryer (60 °C) for 2 h.

Although all the process parameter combinations for a full set of experiments were tested before carrying out the experiments, all the experiments did not succeed. The design of successful (defined by yield) experiments (n = 22) is presented in Table 1. All process

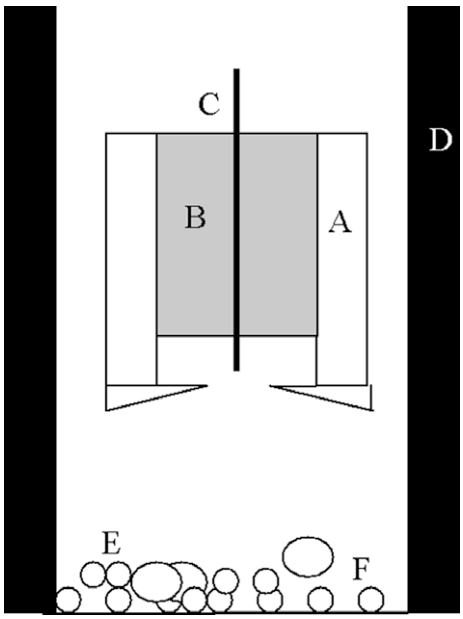

Fig. 2. The schematic diagram of the experimental set-up (not in scale) A, earthed shield; B, insulator; C, metal capillary; D, fluidisation chamber; E, powder bed; F, metallic air distributor (modified from [15]).

parameters were varied in low (−), medium (0) and high (+) levels. Further in the figure legends the process conditions are denoted with these symbols in following order: granulation liquid flow rate, atomisation voltage and PVP concentration in the granulation liquid. All other process parameters not mentioned in Table 1 were kept as constant during all the experiments. In subset A the volume of added granulation liquid was 1 ml and in subset B 3 ml. The granulation liquid was added at 3 min time in each experiment. Since the material was sticking often to the column walls, only batches with a yield of 70% or more after granulation were included in the final data analysis (Table 1). The densities of the granulation liquid concentrations were taken into account in the granulation liquid flow rate.

2.4. Particle size determination

2.4.1. Sieve analysis (SA)

After the photographing for the image analysis, the batches were analysed with sieve analysis with miniaturised sieve stack (Fritsch GmbH, Germany) with apertures of 45 (S8), 65 (S7), 125 (S6), 250 (S5), 355 (S4), 500 (S3), 710 (S2), and 1000 μm (S1). The amplitude of the sieve shaker was 4 mm and the sieve stack was kept in a shaker for 4 min. The representative particle diameters for the granules, $D10$, $D50$ and $D90$, were obtained from the sieve analysis results using the method of Meshali [22]

$$d_m = \frac{1}{\sum \frac{x_i}{d_i}} \quad (1)$$

where x_i is the relative weight of the given fraction with a geometrical mean diameter (d_i) equal to

$$d_i = \sqrt{d_1 \cdot d_2} \quad (2)$$

Because of the small batch size, it was not possible to do the sieve analysis in triplicate to evaluate the standard deviation. The diameter of the sieves was 10 cm, which according to the manufacturer allows sieving of amounts of approximately 10 g. The actual measured samples varied from 9.5 to 15.2 g as the amount of oversize granules varied from batch to batch (from 0.2 to 10.6 g).

Table 1
Process parameters and amount of analysed particles by IA of granulated batches

Batch	Flow rate (ml/h)	Voltage (kV)	PVP (%, w/w)	Process conditions	Yield AG (%)	IA (*n*)
SUBSET A						
1	16	3.8	6	− + −	82	799
2	32	3.8	6	+ − −	73.2	*
3	16	4.8	6	− + −	96.4	504
4	32	4.8	6	+ + −	73.6	480
5	18	3.8	10	− − +	84.8	*
6	36	3.8	10	+ − +	72	315
7	18	4.8	10	− + +	79.2	*
8	36	4.8	10	+ + +	76.8	297
9	18	4.3	8	− 0 0	75.6	*
10	34	4.3	8	+ 0 0	77.2	*
11	30	3.8	8	+ − 0	74.8	*
SUBSET B						
12	44	3.8	6	− − −	86.8	334
13	48	3.8	10	− − +	83.2	*
14	96	3.8	10	+ − +	78.8	432
15	48	4.8	10	− + +	68.8	292
16	96	4.8	10	+ + +	74.4	385
17	94	4.3	8	+ 0 0	70.2	*
18	66	3.8	8	0 − 0	70	*
19	68	4.3	10	0 0 +	77.2	*
20	66	4.3	8	0 0 0	72	*
21	66	4.3	10	0 0 0	74.8	*
22	66	4.3	10	0 0 0	77.2	*

*, not analysed; AG, after granulation.

2.4.2. Image analysis (IA)

For the image analysis, four samples (0.5 g) of each batch were randomly collected from the storage jar and poured into a petri dish with grid lines. Five of the checks in the petri dish had a blackened background, and only particles on those grids were analysed. An optical microscope (Leica MZ6, Leica Mikroskopie und Systeme Gmbh, Bensheim, Germany) was used to take images of the particles. The microscope was used in a dark room with the absence of any background illumination. Altogether 20 figures per each batch were taken. Image Analysis Software (Leica Qwin, Leica Imaging Systems Ltd., Cambridge, England) was used to determine the size of the granules.

2.4.3. Multivariate visualisation

To better differentiate between the batches, a multivariate analysis method, principal component analysis (PCA), was applied to the sieve data set (SIMCA P v. 10.5, Umetrics AB, Sweden). PCA is a multivariate projection method, which is often used in the early stage of data analysis in qualitative investigations to classify between the results, detect different trends, define outliers or to just have an overview of the data [23]. PCA extracts and displays systematic variations in data matrix, which is in this case formed by the sieve results of different batches. Similarities and differences between the observations (masses of sieve fractions) are explained by the score values that summarize the information from the original variables. The origin of the differences or similarities is explained by the loadings, which also describe how the variable influences the principal components (PC). Each PC consists of a score vector and a loading vector and they are organized so that PC1 explains the most of the variation and the PC2 the second most [24].

3. Results and discussion

3.1. Particle size analysis

3.1.1. Sieve analysis

The representative particle diameters *D*10, *D*50 and *D*90 for all the 22 batches are presented in Fig. 3. The smallest and largest

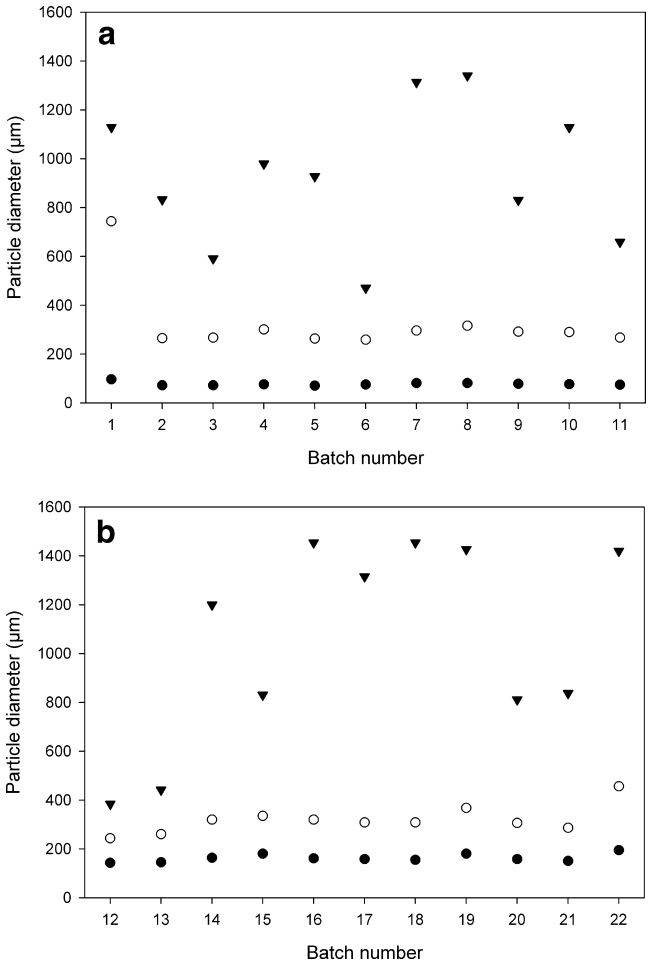

Fig. 3. (a and b) *D*10, *D*50 and *D*90 values of batches in the subset A (a) and subset B (b).

granules of subsets A and B are presented in Fig. 4. Granule sizes are fairly similar despite the different quantity of granulation liquid in subsets. Based only on these sieving results it is questionable to draw conclusions about the process parameters and granule size. Although low granulation liquid flow rate and low atomisation voltage seemed to produce smaller granules.

Increase in PVP concentration resulted as an increase in larger granules, as expected (Fig. 8). This effect was clearer within the subset B due to the higher volume of the granulation liquid.

Based on theoretical assumptions about the process parameters in fluid bed granulation, and electrostatic atomisation and process variable effects on granule size in ordinary fluid bed equipment, batch 3 was estimated to produce smallest and batch 14 the largest granules [2,14]. The sieve analysis results (Fig. 5) indicated that the granules in batch 14 were larger than those in batch 3, but there was yet larger difference among the *D*10, *D*50 and *D*90 values in other batches (batches 12 and 22).

3.1.2. Image analysis (IA)

D_p-values for the granules (projected area diameter, i.e. the diameter of a circle having the same area as the projected area of the particle) were obtained by optical microscopy and IA. As can be seen from Fig. 6 , the amount of larger granules (>1000 µm) increased clearly when the atomisation voltage was increased. This result deviates from the expectation derived from the theory of atomisation, which states that higher voltages would produce smaller droplets and hence produce smaller granules. The reason

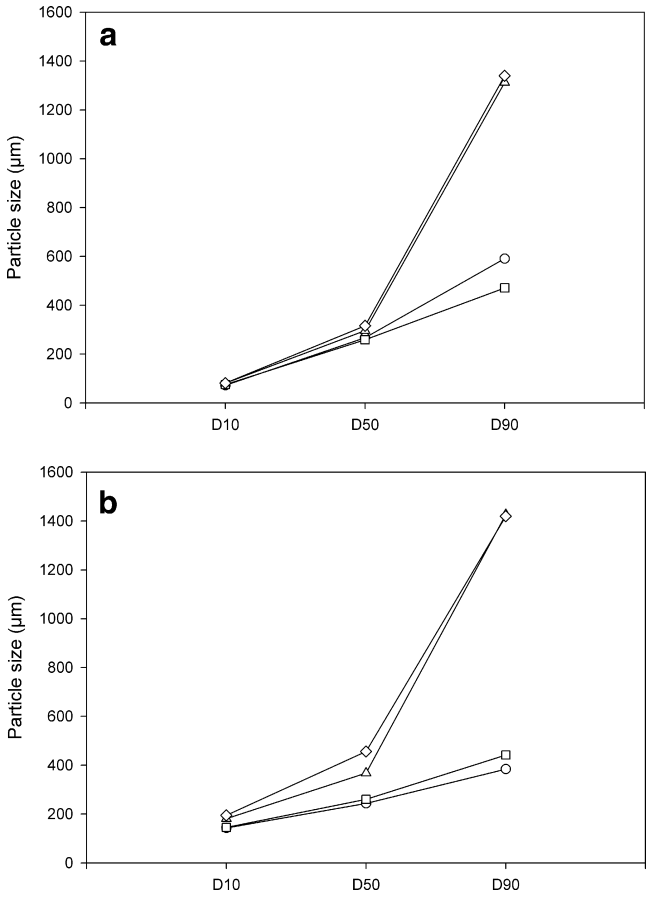

Fig. 4. (a and b) The smallest granules were produced in batch 3 (○) and batch 6 (□) in subset A (a) and in batch 12 (○) and batch 13 (□) in subset B (b). The largest granules were produced in batch 7 (Δ) and batch 8 (◇) in subset A (a) and in batch 19 (Δ) and batch 22 (◇) in subset B (b).

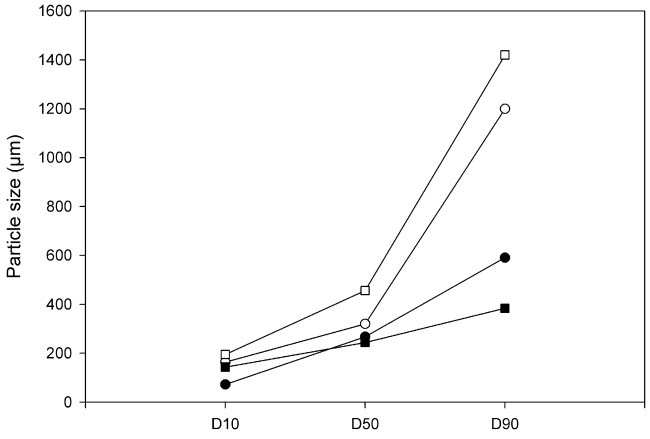

Fig. 5. Process conditions that produce smallest and largest granules by theory: batch 3 (●), batch 14 (○) and the smallest and largest granules of all the produced batches: batch 12 (■) and batch 22 (□).

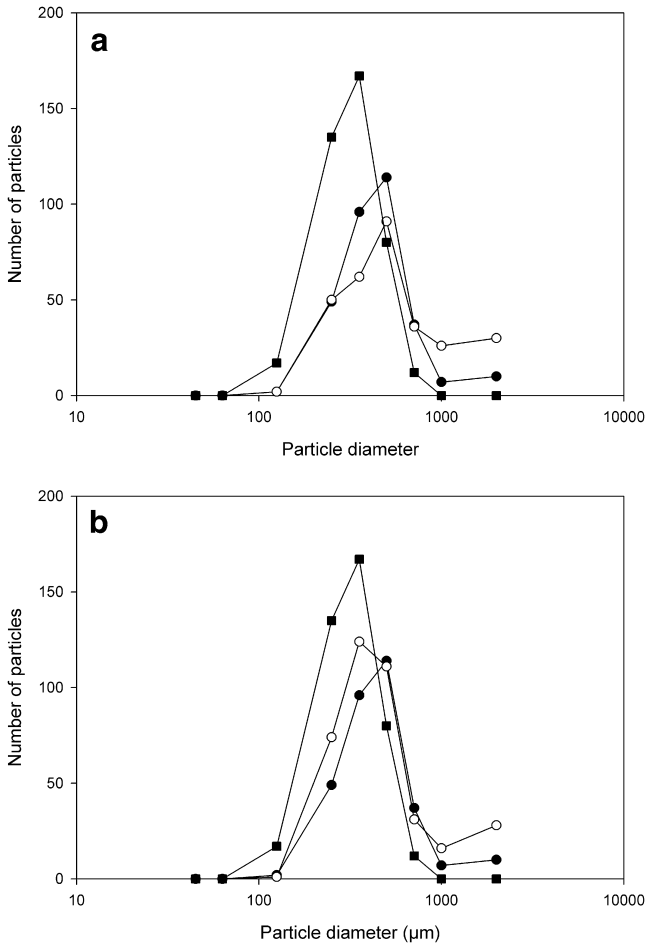

Fig. 6. (a and b) Particle size distributions obtained by IA. Process conditions + – + (●) and + + + (○) versus ungranulated lactose monohydrate (■) in subsets A (batches 6 and 8, a) and B (batches 14 and 16, b).

may be that very fine droplets do not reach the powder bed, but spray-dry in the high inlet air flow. The solubility of α-lactose monohydrate is high in the granulation liquid, which results in larger and strong granules [25]. These results may be different if the granulated materials possessed dissimilar solubility properties. Typical granules from different batches are presented in Fig. 7.

The bimodal shape of particle size distribution is characteristic for α-lactose monohydrate in ordinary fluid bed granulation at the end of granulation liquid spraying [26]. The bimodality of the final particle size distribution (Fig. 6) caused high standard deviation (SD), as the number of particles calculated from different batches varied a lot (Table 1) High SD ruled out the batch analysis i.e. *t*-test assuming unequal variances to differentiate between different process parameter combinations.

3.2. Visualisation of the granule size data

Fig. 9 shows how the *D*10, *D*50 and *D*90 values of the batches are placed in the 3D-plot. Granulation liquid flow rate has a significant effect on the granule size when the rate exceeds the critical value of 36 g/h. Flow rates above the critical value increase the relative humidity in the process and thus influence the mixing behaviour, as stated previously [27]. It was not possible to cluster the data based on atomisation voltage or PVP concentration.

In PCA of all the batches, batch 12 was found to be an outlier and was removed from the model. After the removal, two principal components were needed to explain about 70% of the variation in the data (Fig. 10 a and b). The Q^2-value, which describes how well the model predicts the variation in the data, was 23.6%. The first component explained 51% and the second component 19% of the variation. For the first PC, the differences can be explained by the particle size. The further on the left the scores are in the plot, more dominating is the granule mass fraction on the sieves S5–S8, i.e. the amount of bigger granules is higher in the batch. Similarly, the further on the right the scores are, more dominating is the

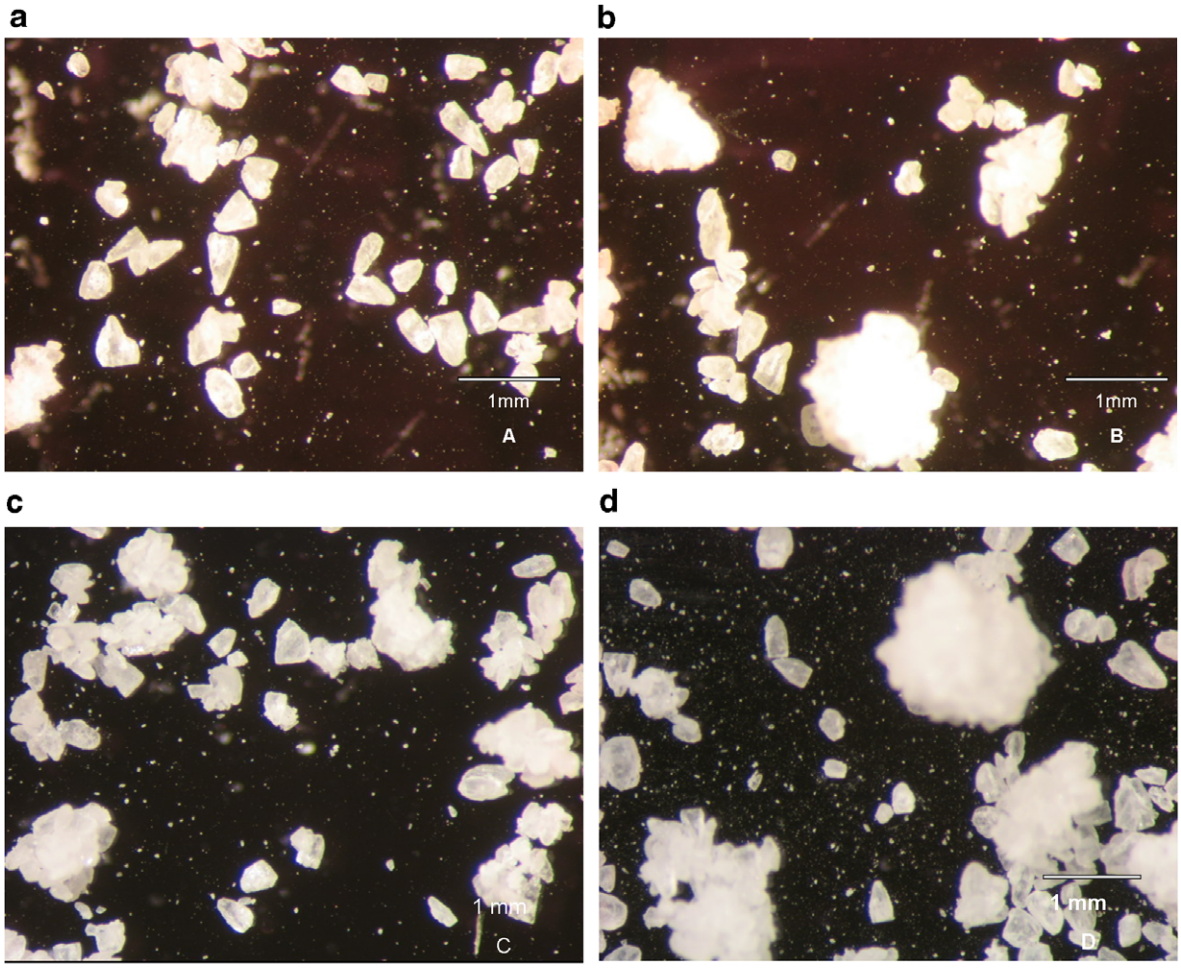

Fig. 7. (a–d) Typical samples of granules. A: batch 5, subset A (– – +); B: batch 8, subset A (+ + +); C: batch 12, subset B (– – –) and D: batch 16, subset B (+ + +).

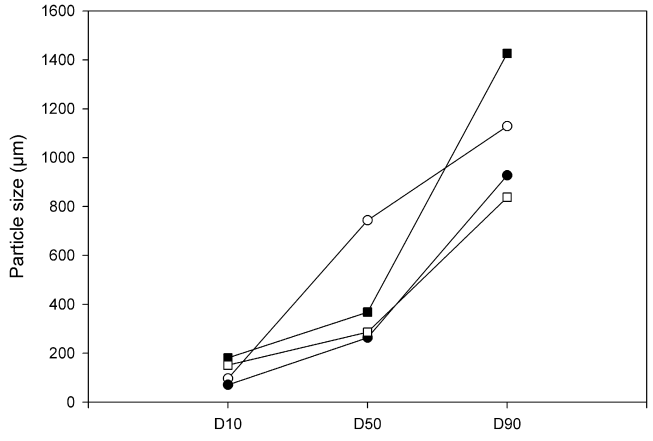

Fig. 8. Effect of PVP on the granule size distribution, subset A: batch 1 (– + –, ○), batch 7 (– + + , ●), Subset B: batch 21 (0 0 0, □), batch 19 (0 0 +, ■).

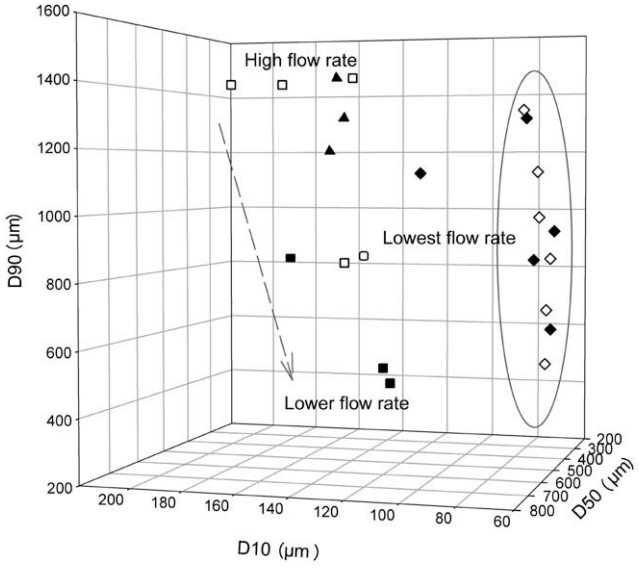

Fig. 9. Interpretation of the effect of the granulation liquid flow rate by visualisation of *D*10, *D*50 and *D*90 values of the granulated batches ♦ flow rate 16–18 g/h, ◇ flow rate 30–36 g/h, ■ flow rate 48 g/h, □ flow rate 66–68 g/h, ▲ flow rate 94–96 g/h.

granule mass fraction on sieves S1–S4, i.e. the amount of small granules is high in the batch. The explanation for variation in PC2 remains unclear so far. Large parallel and simultaneous changes in atomisation voltage and PVP concentration can be distinguished, as the scores plot can be divided in sections by these. The loadings plot (Fig. 10b.) showed how the measured sieve fractions contributed to the separation of the batches. For instance, in batch 16 the amount of particles on 710 µm sieve (S2) is high. Batches that were far apart form each other in PCA plot also differed largely also according to the sieve analysis data.

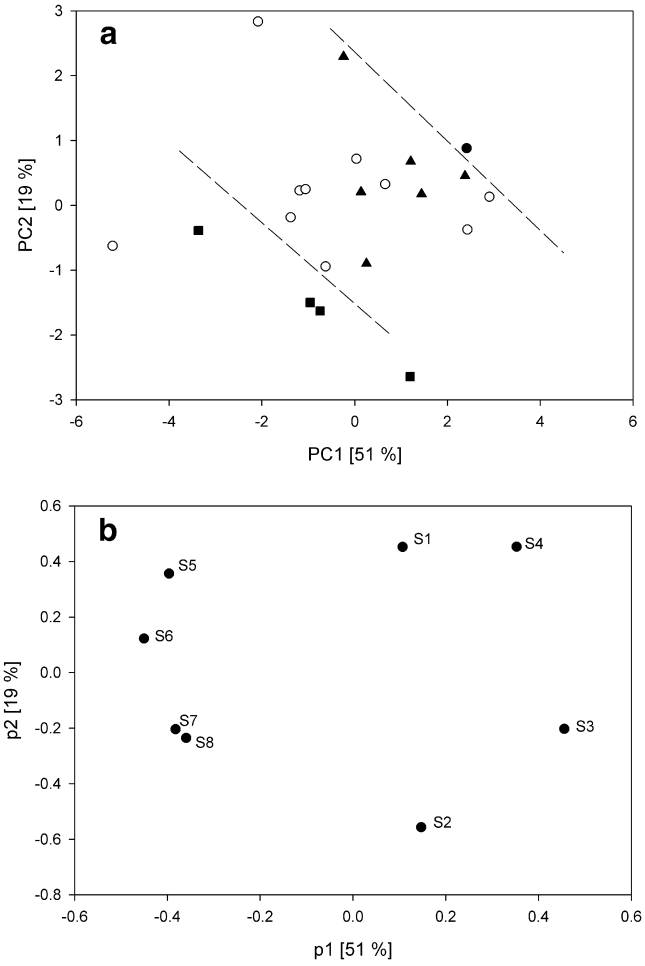

Fig. 10. (a and b) Scores (a) and loadings (b) plot of all batches ($n = 21$) for process conditions (x + +, ■), (x 0 0, ▲) and (x − −, ●), where x is any condition (low, medium or high) of the granulation liquid flow rate. Other process conditions are marked with ○.

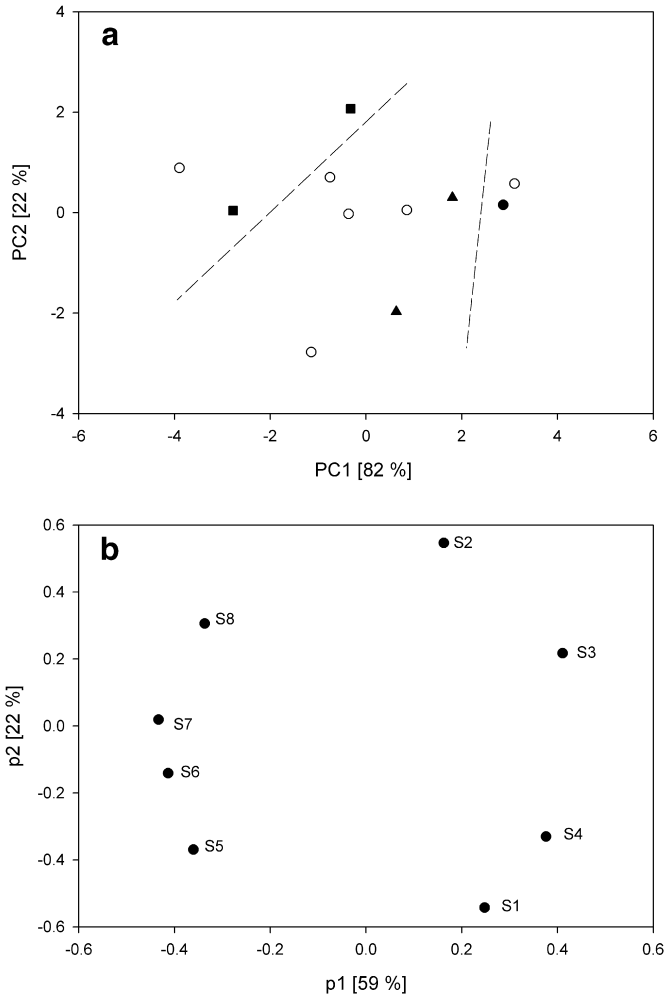

Fig. 11. (a and b) Scores (a) and loadings (b) plot of all batches of subset A for process conditions (x + +, ■), (x 0 0, ▲) and (x − −, ●), where x is any condition (low, medium or high) of the granulation liquid flow rate. Other process conditions are marked with ○.

To outline the differences between the batches further, the sieve analysis data of subsets A and B were processed separately with PCA. Two principal components were needed to explain 82% of the variation in the data of subset A (Fig. 11a and b). Q^2-value for this model was 51%. First component explained 59% and second component 22% of the variation. As in the previous PCA of the whole data set, it was also possible to differentiate the batches based on the changes in atomisation voltage and granulation liquid flow rate. Also in this PCA, the first component could be related to mass fractions on different sieves similarly as in the previous PCA for all the batches. PCA of subset B resulted in high negative Q^2-values for both the principal components and was regarded as not valid model.

4. Conclusions

MMFP is a handy micro-scale process tool for studying the granulation properties of materials with relatively small sample size. Within these process conditions and device, granulation liquid flow rate had the largest positive effect on the granule size. The conclusion that the particle size decreases when atomisation voltage increases has to be so far considered as strongly related to the conditions of this experimental set-up. The specific effect of the binder concentration in the granulation liquid on the granule size remained unclear, but the effects of binder concentration and the atomisation voltage seemed to be proportional on the granule size.

It is crucial to investigate more pharmaceutical materials of different particle sizes and solubilities, since in this study it was not possible to produce any truly narrow granule size distributions.

To confirm applicability of the well-known correlation between the droplet size and the particle size in micro-scale fluid bed process using electrostatic atomisation, the droplet size of the produced spray has to be studied separately.

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