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Research paper

Experience with the Diosna mini-granulator and assessment of process scalability

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Abstract

A small-scale appliance for the high-shear granulation of pharmaceutical materials (the Diosna P 1–6) was tested in a study investigating the influence of various granulation parameters and formulations on granule size distribution. Increasing the granulation time, the impeller speed and the amount of binder all resulted in an increase in granule size, whilst high fill ratios resulted in an increased proportion of fines. The speed of the chopper did not affect granule size distribution for the formulations tested.

Granule size distribution was highly reproducible within individual bowl sizes. Scale-up to the P 10 granulator could be accomplished without changing the formulation or the granulation conditions providing that the different bowl sizes of the laboratory-scale equipment yielded granulates with comparable size distributions. Further scale-up to Diosna P 25 and P 100 granulators, which are larger scale machines, resulted in granules which were smaller than those prepared in the laboratory-scale equipment.

The Diosna P 1–6 seems to be a useful tool for experimentation carried out in the early phase of pharmaceutical development work. Granulates can be prepared reproducibly and differences in granule size distribution due to machine scale can be assessed.

Keywords: High-shear granulator; Diosna P 1–6 Laboratory Pharma Mixer; Diosna P 10–P 100 Pharma Mixer; Scalability

1. Introduction

In recent years, the use of small-scale equipment for pharmaceutical development work has become increasingly popular [1]. As drug substances are usually in short supply in the initial stages of development, formulation and process development work should be performed in small-scale equipment.

There are a number of companies which manufacture laboratory-scale equipment and they suggest that scale-up operations can be accomplished more easily and more rapidly if the equipment used in the early stages of development and the equipment subsequently used in production comes from the same manufacturer and operates on similar principles.

When a drug or drug-excipient mixture is not suitable for tabletting by direct compression, granulation is often used to prepare an intermediate which is more amenable to tabletting. One of the methods commonly employed for the preparation of such intermediates is wet granulation in a high-shear mixer [2]. Mini-granulators operating on this principle are supplied by a number of companies such as Diosna, Bohle and Zanchetta. They are used for monitoring the granulation process and characterizing material flow properties before, during and after the process and, on account of their size and design, they enable the scale of granulation to be increased easily, thus facilitating uncomplicated transfer of the process to granulators of larger sizes. A variety of different approaches have been adopted for the scale-up of high-shear mixer granulation [1,3–5].

This article describes experience gained with the laboratory-scale equipment manufactured by Diosna. The Diosna mini-granulator allows bowls of different capacities in the range 1–6 l to be easily interchanged, which means that different batch sizes can be manufactured using the same basic equipment. In this study the P 1, P 2 and P 4 bowls were compared with respect to granule size reproducibility and the effect of various process parameters such as impeller and chopper speed.

The aims of the study were, firstly, to confirm that the small-scale equipment is comparable with the well-estab-

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lished larger-scale equivalents and, secondly, to investigate whether scale-up from the small-scale equipment to larger size equipment (Diosna P 10, P 25 and P 100) can be accomplished if the same impeller tip speed, granulation times and fill ratio (the fraction of bowl capacity occupied by the dry powder mixture) as well as the same formulations are used. Particle size distribution was used as a sensitive indicator of changes in the granulate produced.

2. Materials and methods

2.1. Materials

All materials used were of pharmaceutical grade. Water was of demineralized quality. Copovidone (Kollidon VA 64) was purchased from BASF (Ludwigshafen, Germany), lactose (Granulac 200) from Meggle (Wasserburg am Inn, Germany), microcrystalline cellulose (Avicel PH 101) from FMC International (Little Island, Cork, Ireland) and anhydrous calcium hydrogen phosphate from Chemische Fabrik Budenheim (Budenheim, Germany).

2.2. Methods

2.2.1. Granulation process

The powders were weighed, filled into the bowls and premixed using the same impeller and chopper speeds which were employed in the subsequent granulation process. The binder was dissolved in the appropriate amount of water and added to the powder mix while the impeller and chopper were running. The mass was then granulated for the specified time. Adhesion of granulate to the bowl surfaces was variable owing to differences between the bowl sizes in respect of surface/volume ratio. Following granulation, the wet mass was passed through a 1.6-mm mesh screen (FGS, Erweka GmbH, Heusenstamm, Germany) in order to destroy agglomerates and ensure homogeneity. Agglomerates occurred mostly when using the smaller bowl sizes. Prior to sieve analysis, the screened wet mass was dried at 50°C in a tray dryer until a loss on drying value of about 3% was obtained. In most cases, the experiments were performed in duplicate in order to assess the reproducibility of the results.

2.2.2. Sample preparation and sieve analysis

After drying, the granulates were divided using a cone sample divider (Laborette 27 Rotary Sample Divider, Fritsch, Idar-Oberstein, Germany) to give sample sizes of approximately 20 g. Sieve analysis was carried out using a sieve shaker (AS 200 control, Retsch, Haan, Germany); the sieving time was 10 min and the vibration amplitude was 2 mm. The sieves were weighed before and after the shaking process and the cumulative undersize distributions were calculated.

To assess the reproducibility of the sampling and sieve analysis procedures, three different granulates were investigated. Five samples of each granulate were taken and analyzed. The difference between the maximum and minimum values for a single sieve fraction of each granulate was well below 1% of the total sample weight. As sampling and sieve analysis were highly reproducible, only one sample of each granulate was investigated in the subsequent experiments.

2.3. Experimental design

2.3.1. Influence of impeller and chopper speeds on granule size

The experiments were performed in the P 1 bowl using various combinations of impeller and chopper speeds. The same formulation and the same granulation time were used in all experiments (Table 1). The granulates were prepared in duplicate. The granulation process was interrupted every 30 s so that the bowls could be scraped to remove material adhering to the inner surfaces. In contrast to other experiments discussed in this paper, an additional sieving step, employing a 0.8-mm mesh screen, was performed after the granulate had been dried.

Table 1
Granulate formulation and granulation conditions used in tests to determine influence of impeller and chopper speeds on granule size distribution

Formulation	
Anhydrous calcium hydrogen phosphate	85 g
Microcrystalline cellulose	85 g
Lactose	85 g
Copovidone	2.55 g
Water	92.45 g
Granulation conditions	
Pre-mixing time	1 min
Impeller speed	300, 600 and 900 rpm
Chopper speed	1000 and 2000 rpm
Addition of granulating liquid	0.5 min
Granulation time	1.5 min
Impeller speed	300, 600 and 900 rpm
Chopper speed	1000 and 2000 rpm

Table 2
Granulate formulations and granulation conditions used in tests to determine influence of granulation time on granule size distribution

Formulations	
Anhydrous calcium hydrogen phosphate	80 g
Microcrystalline cellulose	80 g
Lactose	80 g
Copovidone	5 or 10 g
Water	79.17 g
Granulation conditions	
Pre-mixing time	1 min
Impeller speed	300 rpm
Chopper speed	1000 rpm
Addition of granulating liquid	0.5 min
Granulation time	1.5 min–5 min
Impeller speed	300 rpm
Chopper speed	1000 rpm

Table 3
Granulate formulations and granulation conditions used in tests to determine influence of amount of binder on granule size distribution

Formulations	
Anhydrous calcium hydrogen phosphate	80 g
Microcrystalline cellulose	80 g
Lactose	80 g
Copovidone	2.43, 5 or 10g
Water	79.17 g
Granulation conditions	
Pre-mixing time	1 min
Impeller speed	300 rpm
Chopper speed	1000 rpm
Addition of granulating liquid	0.5 min
Granulation time	5 min
Impeller speed	300 rpm
Chopper speed	1000 rpm

2.3.2. *Influence of granulation time on granule size*

The experiments were performed in the P 1 bowl. Details of the formulations and granulation conditions used are given in Table 2. Two different formulations were prepared, one containing 2% copovidone and the other 4% (both figures calculated with reference to the dry mass). The granulation conditions were kept constant, except for the granulation time, which was varied between 1.5 and 5 min. The granulation process was interrupted after 30 seconds so that the bowls could be scraped to remove material adhering to the inner surfaces. In addition, scraping was performed after 1.5 min for the granulation time of 3 min and 2.5 min for granulation times of 4 and 5 min.

2.3.3. *Influence of amount of binder on granule size*

Details of the formulations and granulation conditions used are shown in Table 3. The experiments were performed in the P 1 bowl. The granulation time was 5 min in each case. The granulation process was interrupted after 30 and 90 s so that the bowls could be scraped to remove material adhering to the inner surfaces.

Table 5
Granulate formulation and granulation conditions used in the first series of scalability trials

Formulation	
Anhydrous calcium hydrogen phosphate	1 part
Microcrystalline cellulose	1 part
Lactose	1 part
Copovidone	2% of dry mass
Water	33% of dry mass
Granulation conditions	
Pre-mixing time	1 min
Impeller tip speed	3.8 and 7.5 m/s
Chopper speed	P1–P25: 2000 rpm / P100: 1420 rpm
Addition of granulating liquid	0.5 min
Granulation time	1 min
Impeller tip speed	3.8 and 7.5 m/s
Chopper speed	P1–P25: 2000 rpm / P100: 1420 rpm

2.3.4. *Influence of fill ratio on granule size*

The effect of fill ratio (defined as the fraction of bowl capacity occupied by the dry powder mixture and calculated using the dry powder mixture bulk density) was investigated in the P 1 bowl. The capacity of the P 1 bowl used in these experiments was approximately 1.2 l. Details of the formulations and granulation parameters used are given in Table 4.

2.3.5. *Scalability of the granulation process*

Three different formulations were tested to assess scalability between the different bowl sizes. Details of the formulation and the granulation parameters used for the first series of scalability trials are given in Table 5. The experiments carried out prior to these trials showed that granule size distribution is affected by impeller speed, so the impeller tip speeds were kept constant regardless of bowl size during scalability testing. The impeller speeds used in the scalability trials are shown in Table 6. They were calculated from the impeller tip speeds of the larger

Table 4
Granulate formulations and granulation conditions used in tests to determine influence of fill ratio on granule size distribution

Formulations/Fill ratio	10%	20%	40%	50%	60%	70%
Anhydrous calcium hydrogen phosphate	22.08 g	44.17 g	88.33 g	110.42 g	132.5 g	154.74 g
Microcrystalline cellulose	22.08 g	44.17 g	88.33 g	110.42 g	132.5 g	154.74 g
Lactose	22.08 g	44.17 g	88.33 g	110.42 g	132.5 g	154.74 g
Copovidone	0.67 g	1.34 g	2.68 g	3.35 g	4.02 g	4.68 g
Water	24.01 g	48.03 g	96.06 g	120.08 g	144.09 g	168.11 g
Granulation conditions						
Pre-mixing time	1 min					
Impeller speed	600 rpm					
Chopper speed	1000 rpm					
Addition of granulating liquid	0.5 min					
Granulation time	1.5 min					
Impeller speed	600 rpm					
Chopper speed	1000 rpm					

Table 6
Calculation of impeller speeds for different bowl sizes

Bowl size	Bowl capacity [1]	Impeller speed corresponding to impeller tip speed of 3.8 m/s	Impeller speed corresponding to impeller tip speed of 7.5 m/s
P 1	1.23	500 rpm	1000 rpm
P 2	2.09	430 rpm	860 rpm
P 4	4.07	330 rpm	660 rpm
P 10	Appr. 10	Adjusted by supplier to reach relevant tip speeds	
P 25	Appr. 25		
P 100	Appr. 100		

scale equipment (3.8 m/s and 7.5 m/s) and the diameters of the impellers used in the various bowls of the laboratory equipment. The Diosna P 10, P 25 and P 100 were operated at the impeller speeds pre-set by the supplier. A uniform fill ratio of 37% was used to avoid effects due to differences in fill ratios. The experiments were performed in duplicate.

Details of the formulation and the granulation parameters used for the second series of scalability trials are given in Table 7. This formulation did not include anhydrous calcium hydrogen phosphate. A fill ratio of 32.2% was used.

In the third series of trials, anhydrous calcium hydrogen phosphate was included again, the concentration of binder was decreased and the proportion of granulating liquid was adjusted. A fill ratio of 46% was used. The preparation and granulation conditions (see Table 8) were identical to those employed in the second series of trials.

3. Results and discussion

All granulation runs carried out resulted in particle size enlargement of the powder mixture. The granulates were free-flowing in contrast to the original powder mixtures.

3.1. Influence of impeller and chopper speeds on granule size

The particle sizes were influenced by the impeller speed but not by the chopper speed. Increasing the impeller speed made the granules coarser and reduced the proportion of fines. The influence of the different impeller speeds on the size of the granules was more pronounced between 300 and 600 rpm than between 600 and 900 rpm (Fig. 1). The fact that the chopper speed did not influence the size of the granules might be due to the relatively small scale of the chopper blades. Unlike all the other parts of the Diosna P 1–P 4, the chopper blades were not scaled down proportionally from the production equipment.

3.2. Influence of granulation time on granule size

As the runs carried out using the 2 and 4% copovidone formulations gave comparable results with regard to the influence of the granulation time on particle size distribution, only the results for granulates containing 4% copovidone are shown in Fig. 2. Increasing the granulation time resulted in a shift in the particle size distribution towards coarser particles. This was attributed to improved wetting of the wet mass during the granulation process [6,7].

3.3. Influence of amount of binder on granule size

As Fig. 3 shows, increasing the amount of binder resulted in a shift in particle size distribution towards coarser particles and a reduction in the proportion of fines. Similar find-

Table 7
Granulate formulation and granulation conditions used in the second series of scalability trials

Formulation	
Microcrystalline cellulose	1 part
Lactose	5.1 parts
Copovidone	3.5% of dry mass
Water	22% of dry mass
Granulation conditions	
Pre-mixing time	3 min
Impeller tip speed	3.8 and 7.5 m/s
Chopper speed	P1–P25: 2000 rpm / P100: 1420 rpm
Addition of granulating liquid	20 s
Granulation time	100 s
Impeller tip speed	3.8 and 7.5 m/s
Chopper speed	P1–P25: 2000 rpm / P100: 1420 rpm

Table 8
Granulate formulation and granulation conditions used in the third series of scalability trials

Formulation	
Anhydrous calcium hydrogen phosphate	3.3 parts
Microcrystalline cellulose	1 part
Lactose	5.1 parts
Copovidone	1.7% of dry mass
Water	18.4% of dry mass
Granulation conditions	
Pre-mixing time	3 min
Impeller tip speed	3.8 and 7.5 m/s
Chopper speed	P1–P25: 2000 rpm / P100: 1420 rpm
Addition of granulating liquid	20 s
Granulation time	100 s
Impeller tip speed	3.8 and 7.5 m/s
Chopper speed	P1–P25: 2000 rpm / P100: 1420 rpm

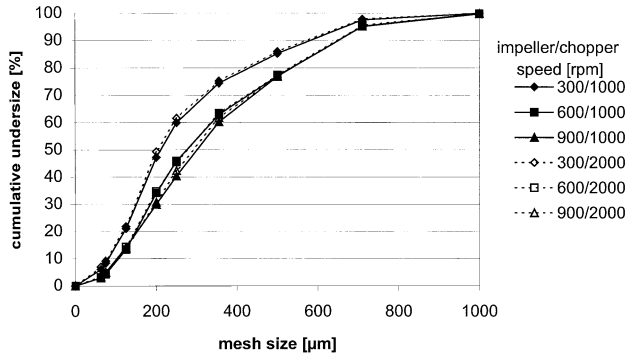

Fig. 1. Influence of the impeller and chopper speed on the size distribution of the granules.

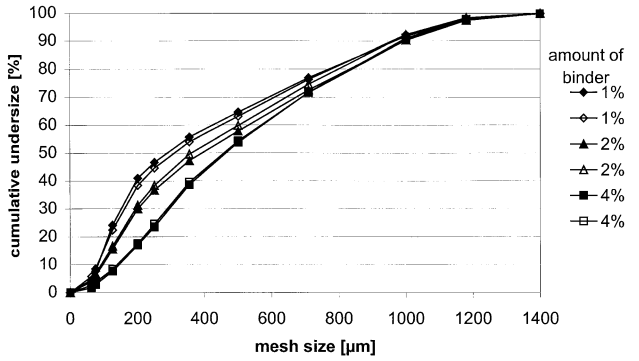

Fig. 3. Influence of the amount of binder on the size distribution of the granules for two repeated experiments.

ings were obtained when granulation times of 2, 3 and 4 min were used. These results are consistent with data reported by other authors [6].

In the above experiments, the relationships which are observed to exist between various parameters during granulation in high-shear mixers were reproduced in the small-scale Diosna P 1. Increasing the impeller speed and the granulation time induces a densification of the wet mass which will result in higher liquid saturation for a given amount of granulating liquid. Higher liquid saturation favors granule growth [7]. It is important to determine the influence of impeller speed, granulation time and amount of binder in order that differences which may occur on scale-up can be assessed in appropriate experiments. It cannot be taken for granted that similar particle size distributions will be obtained in experiments carried out in different sizes of bowl.

3.4. Influence of fill ratio on granule size

Scraping of the inner surface of the bowl during the granulation process was necessary in all experiments, especially at higher fill ratios. For example, when a fill ratio of 70% was used, most of the wet material adhered to the bowl surface, and mixing and granulation could only be performed with scraping after 15, 45 and 75 s of the granulation time. When the fill ratio was 80%, it was impossible to obtain a processed batch. In all other experiments adhering granules were scraped from the bowl walls after 30 s. For fill ratios larger then 20% an additional scraping was performed after 1 min.

The size distributions obtained at a fill ratio of 10% were comparable with those obtained at a fill ratio of 20%. The size distributions obtained at fill ratios of 50–70% were comparable with one another, but there was a shift towards finer particles compared to the size distributions obtained at lower fill ratios (Fig. 4). It appeared that, at lower fill ratios, more efficient wetting of the granulate occurred if the granulation conditions were not changed. In these experiments carried out in the P 1 bowl, the fill ratio had a very marked effect on the size distribution. In the subsequent scalability trials, therefore, the fill ratio was specified for each series of trials and kept constant within that series.

3.5. Scalability of the granulation process

The results obtained with Formulation 1 are shown in Fig. 5 for duplicate experiments each bowl size. In the P1 bowl the granulation process was interrupted after 30 s so that the bowls could be scraped to remove material adhering to the inner surfaces.

The results show that granule size distribution was reproducible within individual bowl sizes but differed markedly

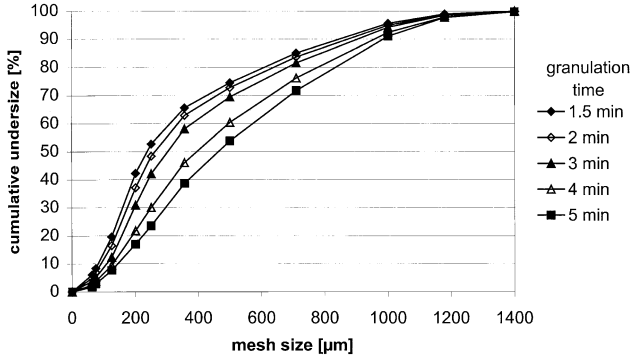

Fig. 2. Influence of the granulation time on the size distribution of the granules.

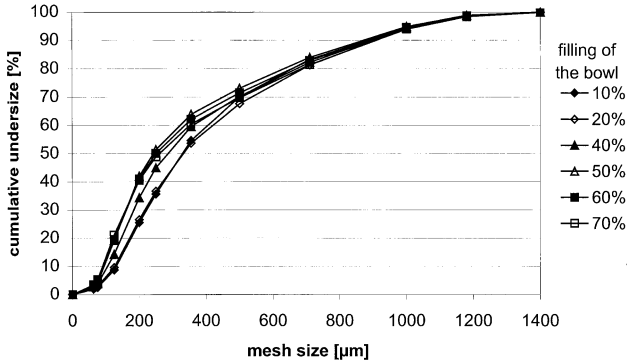

Fig. 4. Influence of fill ratio in the P1 bowl on granule size distribution.

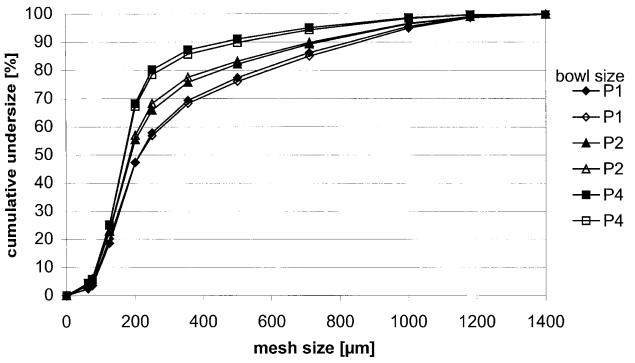

Fig. 5. Influence of the bowl sizes used for the granulation on the size distribution of the granules (formulation 1).

between bowl sizes. Increasing the bowl size increased the proportion of fines and shifted the size distribution towards smaller granules. Hence, the granulation process was more effective in the smaller bowls. Although the granulation time was only 1 min, which was short compared to previous experiments, the granulating liquid must have been evenly distributed as the granule size distribution was reproducible within each bowl size. However, as the size distribution differed even between the three small-scale bowls, no additional trials were performed in larger-scale equipment using the formulation and granulation parameters described.

The results obtained for Formulation 2 at the two impeller tip speeds specified are shown in Figs. 6 and 7. For the P1 bowl the granulation process was interrupted after 45 and 75 s so that the bowls could be scraped to remove material adhering to the inner surfaces. Two batches were manufactured in each bowl size, data are given as mean values and minimum and maximum value as well. In all cases, the granules were free-flowing and relatively small in size. As with Formulation 1, granule size distribution was reproducible within individual bowl sizes. In contrast to Formulation 1, however, granule size distribution was also comparable between the different bowl sizes available

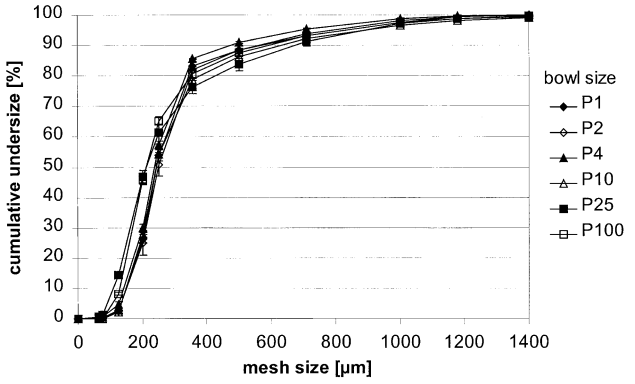

Fig. 6. Influence of the bowl sizes used for the granulation on the size distribution of the granules (formulation 2, impeller tip speed 3.8 m/s) for two repeated experiments in all bowl sizes (given are the mean values and the minimum and maximum values).

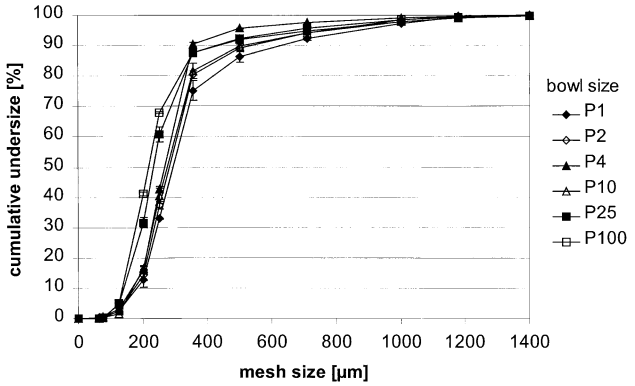

Fig. 7. Influence of the bowl sizes used for the granulation on the size distribution of the granules (formulation 2, impeller tip speed 7.5 m/s) for two repeated experiments in all bowl sizes (given are the mean values and the minimum and maximum values).

with the P 1–P 4 equipment. Scalability was thus demonstrated for the P 1–P 4 bowl sizes.

When an impeller tip speed of 7.5 m/s was used (Fig. 7), slightly finer granules were obtained in the P 4 bowl than in the other bowl sizes. This was attributed to the fact that, after the granulating liquid had been added, the impeller speed fell because the impeller motor was not sufficiently powerful to effect the required speed adjustment. The decrease in impeller tip speed resulted in a reduction in granule size and an increase in the proportion of fines. After this series of tests, the electronic device controlling the impeller speed was adjusted so that, in the subsequent experiments, the impeller speed remained constant even when granulation was carried out in the P 4 bowl.

The size distributions of granules prepared in the Diosna P 10 were comparable to those prepared in the laboratory-scale granulators. Hence, the process used for this formulation in the Diosna P 1–P 4 was fully scalable to the larger Diosna P 10.

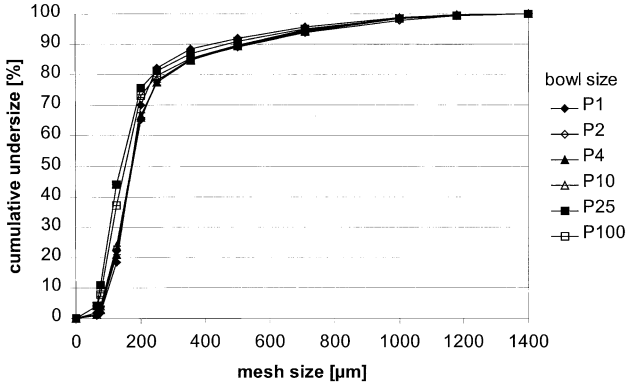

Fig. 8. Influence of the bowl sizes used for the granulation on the size distribution of the granules (formulation 3, impeller tip speed 3.8 m/s) (single experiments in the P1–4 and two repeated experiments in the P10–P100, given are the mean values and the minimum and maximum values).

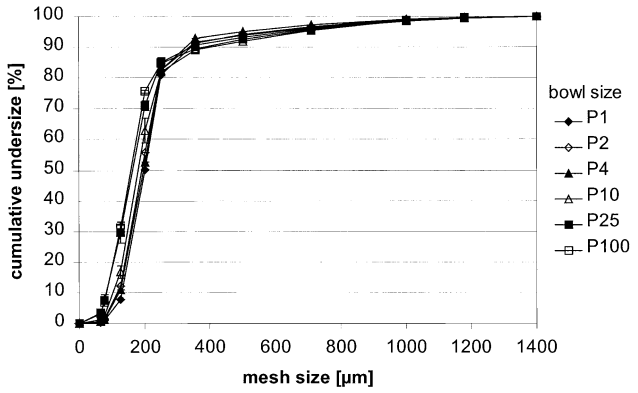

Fig. 9. Influence of the bowl sizes used for the granulation on the size distribution of the granules (formulation 3, impeller tip speed 7.5 m/s) (single experiments in the P1–4 and two repeated experiments in the P10–P100, given are the mean values and the minimum and maximum values).

The P 25 and P 100 machines produced granules with similar size distributions and the results were highly reproducible within an individual machine. However, the size distributions obtained with these larger scale machines differed from those obtained with the smaller-scale equipment (P 1–P 10). The granules produced by the P 25 and the P 100 were smaller although the same formulation and the same granulation conditions had been employed. The differences in granule size were more pronounced at higher impeller tip speeds.

One possible reason for these differences might simply be the increase in the scale. However, it must be borne in mind that, although transferring the process from the P 25 to the P 100 involved a four-fold increase in batch size, the granule size distributions obtained with these two machines were very similar. Hence, the decrease in granule size between the small scale and the production scale can hardly be due to an increase in batch size alone since the scale-up factors in all the other experiments were less than four.

A more likely reason is that the P 25 and P 100 used in these experiments represent older versions of their respective types. In the intervening period, Diosna has changed the geometry of the impeller blades on these machines and the blades are now at a higher angle. The P 1–P 4 and P 10 mixer-granulators used in our experiments have impeller blade geometries which are similar to those of the newer P 25 and P 100 machines but differ from those of the older versions. This might at least partially explain why the results obtained are highly reproducible within a single series of machines (P 1–P 10 on the one hand and P 25–P 100 on the other) but are less comparable as between the two series.

The results obtained for Formulation 3 at the two impeller tip speeds specified are shown in Figs. 8 and 9. No scraping of the bowls had to be performed in this test series. Two batches were manufactured in each bowl size of the Diosna P10, P25 and P100, in the P1–4 only one batch was manufactured in each bowl size. The results show that granule size distribution was again reproducible within individual bowl sizes. As with Formulation 2, the results were comparable within the P 1–P 10 series of machines and within the P 25–P 100 series. Again, however, there was a shift towards finer particle sizes in the granules produced using the P 25 and P 100.

4. Conclusions

The granulation process as run in the laboratory-scale equipment was influenced by the granulation time, the amount of binder, the impeller speed and the fill ratio (the fraction of bowl capacity occupied by the dry powder mixture).

In general, the results were highly reproducible within individual bowl sizes. If the results were comparable across the different bowl sizes of the laboratory-scale granulator, the process could be scaled up to the P 10 granulator without changing the formulation or the granulation conditions, whereas in the larger equipment a tendency to slightly smaller particles sizes was observed.

The Diosna P 1–P 4 seems to be a useful tool for experimentation carried out in the early phase of pharmaceutical development work. Granulates can be prepared reproducibly and differences in granule size distribution due to machine scale can be assessed.

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