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Influence of granulation and compaction on the particle size of ibuprofen—Development of a size analysis method

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Abstract

The aim of this work was to study the impact of the process on drug particle size. We chose ibuprofen, practically insoluble in water, as granulometry greatly influences its dissolution rate. We developed an original method using a laser granulometer to assess the size of ibuprofen within a blend before and after granulation and then compression. Wet granulation was performed with a Lodige and a Diosna granulator. The granules were then compressed. The evolution of ibuprofen particle size after these operations was checked. Two grades of ibuprofen differing in size were studied: ibuprofen 25 and ibuprofen 50.

After the wet granulation of ibuprofen 50 with a Lodige or a Diosna granulator, a decrease in size was observed. This could be caused by shocks occurring in the granulator. On the other hand, after compression of the granules, ibuprofen particle size increased and was greater than that measured before granulation. Compression could induce some fragmentation of ibuprofen associated with the plastic deformation and then, under pressure, a closeness of the fragments or deformed particles which could bind or associate with one another because the melting point of ibuprofen is not very high.

In the case of ibuprofen 25, the same phenomena were observed after compression. But, after granulation, particle size was not modified. There was little breaking of ibuprofen particles in the granulator because they are much smaller than those of ibuprofen 50.

This work shows the impact of the process on drug particle size when producing tablets. The method developed made it possible to differentiate and measure the size of ibuprofen particles in a blend.

Keywords: Size analysis; Ibuprofen; Granulation; Compression; Process impact

1. Introduction

When a drug is administered orally in its solid form as a tablet, the absorption rate is controlled by the speed at which the drug dissolves in the fluids at the absorption site. The general relationship describing the dissolution process was given by Noyes and Whitney stating that

$$dC/dt = KS(C_s - C)$$

where dC/dt is the rate of dissolution, K a constant, S the surface area of the dissolving solid, C_s may be considered as the solubility of the drug in the solvent, and C is the concentration of drug in solvent at time t. The expression $(C_s - C)$ represents the concentration gradient between the diffusion layer and the bulk solution. Where absorption is limited by dissolution rate, C will always be negligible compared to C_s (Gibaldi, 1970).

According to the Noyes–Whitney equation, dissolution rate is directly proportional to the effective surface area of the drug, i.e. the surface area of drug accessible to dissolution fluids. Therefore, the particle size of a drug may affect dissolution rate and influence drug absorption. This is of particular consequence when slowly dissolving, poorly soluble drugs are considered.

Ibuprofen, which is practically insoluble in water, is proposed in different sizes with different dissolution rates (Pereira de Almeida et al., 1995). When this drug is formulated, dissolution rates can be compared to select size specifications for the drug. Another important factor to be considered is the difference between the specific surface area and the effective surface area of the drug, that is the area of the drug in a dosage form as "seen" by the gastrointestinal fluids, in particular after disintegration.

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The choice of the drug based on its dissolution rate does not take into consideration the impact of the process on drug particle size. Indeed, during the different stages of tablet manufacturing, drug particles are submitted to high levels of stress that lead to material transformations. This concerns for example fragmentation (brittle materials), deformation (ductile materials), fusion and recrystallization (materials with low melting point) (Khan and Rhodes, 1975).

The aim of this work was to study the impact of the manufacturing process on the particle size of ibuprofen. Two grades of ibuprofen were used. Granules were obtained by wet granulation with two types of granulators and then compressed. The evolution in ibuprofen particle size was estimated after these operations. To do this, we developed an original method using a laser granulometer to assess the size of ibuprofen before and after granulation and then compression. This method made it possible to differentiate and to measure ibuprofen size within a blend.

2. Materials and methods

2.1. Materials

Ibuprofen was obtained from BASF (Ludwigshafen, Deutschland). Two grades of ibuprofen with different particle size were used in the reported experiments: ibuprofen 25 and ibuprofen 50 (BASF nomenclature).

Corn starch, Lycatab PGS (pregelatinized starch) (Roquette, Lestrem, France), aerosil 200 (Degussa, Frankfurt, Deutschland), stearic acid were used as excipients included in the formulation of granules.

2.2. Methods

2.2.1. Preparation of granules

Granules containing 67% ibuprofen were prepared. Granulating was performed in a Diosna high shear mixer (10 L bowl) (Diosna, Osnabrueck, Germany) and in a Lodige mixer (Laboratory mixer, 5 L) (Lodige, Paderborn, Germany) using a 1 kg batch and water as the wetting liquid.

2.2.1.1. Granulation in the Diosna mixer. Ibuprofen and aerosil were mixed for 5 min at 1400 rpm impeller speed and 1400 rpm chopper speed. Starches were added and the blend was mixed for 5 min.

Then water was continuously added over a period of 10 min using a peristaltic pump, in quantity sufficient to achieve a satisfactory wet mass. During the wetting, the chopper speed was increased to 2800 rpm. The wet mass was then passed through the 1.20 mm diameter sieve of a Frewitt oscillating granulator (Frewitt, Fribourg, Switzerland). The passing granules were dried in a drying oven, at 50 °C for 5 h and calibrated through the 1.20 mm diameter sieves of the Frewitt oscillating granulator.

2.2.1.2. Granulation in the Lodige mixer. Ibuprofen and aerosil were mixed for 5 min at 312 rpm. Starches were added and the blend was mixed for 5 min. Then water was added over a period of 10 min, with the speed at 239 rpm. The wet mass was submitted to the same operations as those obtained with the Diosna granulator.

2.2.2. Tabletting

The granules were blended with 4% corn starch and 0.5% (w/w) stearic acid in a Turbula mixer (Bachofen, Basel, Switzerland) for 5 min at 42 rpm. Tablets containing 200 mg of ibuprofen were prepared using a Frogerais MR 15 rotary tablet machine (Frogerais OA, Vitry/Seine, France) equipped with curved punches of 11 mm diameter and 10 mm curvature radius. Tablets with mechanical strength of 40 and 80 N were produced. Mechanical strength was measured with a Schleuniger tablet tester (IMA France, Rueil Malmaison, France) on 10 tablets.

2.2.3. Dissolution test

In vitro drug release from the tablets was studied in pH 6.8 phosphate buffer (USP XXVIII) with 0.01% polysorbate 20 using the paddle apparatus (USP XXVIII, Sotax, Basel, Switzerland) (900 mL, 37 °C, 75 rpm, $n = 6$). At predetermined time intervals, 3 mL samples were withdrawn and analysed UV-spectrophotomtrically ($\lambda = 223$ nm, Anthelie Advanced, Secoman, Domont, France).

For the initial ibuprofen, the assay was made on 200 mg powder using a flow-through cell and a 5 mL/min flow.

2.2.4. Granulometric analysis of ibuprofen

2.2.4.1. After granulation and compression. The granulometric analysis of ibuprofen in the blend was carried out after granulation and compression by laser diffractometry with a Malvern Mastersizer X laser size analyser and the small volume sample dispersion unit (Malvern, Orsay, France) on liquid dispersions. The Mie theory is used for the determination of particle size.

During granulometric measurement by laser diffractometry, there were parasitic signals in the sample diffusion image because of impurities present in the dispersing liquid. To remove them, a background measurement was made; this measures diffusion when no sample is in the laser beam. This background measurement is then subtracted from the sample diffusion image so as to obtain only the signal from the sample particles.

The principle of our method is to measure the background on the blend after dispersion of the granules or the tablet in the dispersion medium and after elimination of ibuprofen (that is to say on the excipients). Then, the sample measure is made on the whole blend, that is to say excipients and ibuprofen. After subtracting the background, only the information concerning ibuprofen remains. The signal obtained for ibuprofen is sufficiently significant with regard to the background because the blend contains 67% ibuprofen.

This principle supposes that:

- ibuprofen particles are completely individualized and dispersed;
- the method does not modify particle size;
- dispersion is homogeneous.

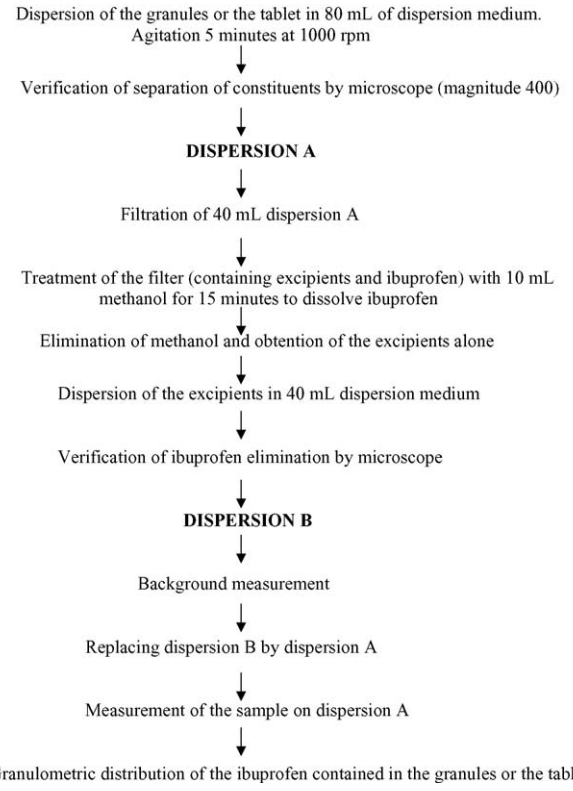

Fig. 1. Treatment procedure of granules or tablets for the granulometric analysis of ibuprofen by diffractometry laser.

The dispersion medium was a saturated aqueous solution of ibuprofen with 0.01% polysorbate 20. The temperature of the dispersion medium was controlled and kept constant ($25 \pm 0.5\,^{\circ}C$) using a water bath. Tablets and granules were dispersed using a Rayneri agitator ($v = 1000$ rpm). We checked that the dispersion method does not modify the particle size by analysing the particles with a microscope. Fig. 1 presents the treatment of the granules or the tablet for the granulometric analysis of the ibuprofen contained.

We checked that methanol had no influence on the remainder excipients by comparing their size after dispersion in methanol and after dispersion in a saturated aqueous solution of ibuprofen with 0.01% polysorbate 20.

2.2.4.2. Analysis of the initial ibuprofen. The granulometric analysis of ibuprofen before granulation and compression was carried out by laser diffractometry with a Malvern Mastersizer X laser size analyser on liquid dispersions. The Mie theory is used for the determination of particle size. The dispersion medium was a saturated aqueous solution of ibuprofen with 0.01% polysorbate 20 (temperature: $25 \pm 0.5\,^{\circ}C$).

To compare the granulometric distributions of ibuprofen before and after granulation and compression, the analysis of the initial ibuprofen was carried out using the same background as after granulation, that is to say dispersion B (Fig. 1). The background is made on the dispersion B (dispersion of the excipients without ibuprofen). Then the initial ibuprofen (grade 25 or 50) was added to this dispersion B and the sample measurement was realised. After subtracting the background (signal from dispersion B), only the information concerning the initial ibuprofen remains.

For each measurement, we present the mean diameter, the median diameter ($d_{50\%}$), the diameters under which 10% particles ($d_{10\%}$) and 90% particles ($d_{90\%}$) are to be found, respectively. Each result is the mean of three assays.

2.2.4.3. Repeatability of the measurement. According to the ISO 13320 norm, the repeatability of characteristics particle sizes should be as follow: for the median size ($d_{50\%}$), the coefficient of variation should be smaller than 3%. Values at the sides of the distribution, e.g. $d_{10\%}$ and $d_{90\%}$ should have a coefficient of variation not exceeding 5%.

The granulometric analysis of ibuprofen after granulation were realised 5 times and the coefficients of variation were determined for the $d_{50\%}$, $d_{10\%}$ and $d_{90\%}$. They were 1.40%, 3.02% and 3.26%, respectively, and confirm the repeatability of the method.

2.2.5. Validation of the granulometric analysis

To establish if our method could assess the correct size distribution of one component in a blend, we compared particle size determined on one hand with the classical method of granulometric analysis by laser diffractometry and, on the other hand, with the method we proposed. This comparison is realised for two types of materials: for calibrated glass beads (Glass Microspheres Malvern, 15–120 μm) as well as for an excipient (microcrystalline cellulose, Vivacel 102, Rettenmaier and Söhn, Ellwangen-Holzmühle, Deutschland).

The classical method of granulometric analysis by laser diffractometry is made on aqueous dispersions. The background is measured on water alone, and then particles to be measured are dispersed in water and the sample measurement is made on these particles (glass beads or cellulose).

The measurement realised according to our method is as follows: Latex beads (Sigma latex beads -6.4 ± 1.9 μm) are dispersed in water and the background is measured on this dispersion. Then, the calibrated glass microspheres are added to this dispersion and the sample measure is made. After substracting the background (corresponding to the latex beads), only the information concerning the glass microspheres remains. The result is compared to the one obtained with the classical method of granulometric analysis by laser diffractometry. A concordance between the results obtained by the two methods will make it possible to validate our method.

The same experiment is realised with the microcristaline cellulose (Vivacel 102) instead of the glass microspheres.

A statistical test of mean comparison is used (test of $u -$ table $P(u)$).

3. Results and discussion

The granulometric characteristics of the glass microspheres and of the microcrystalline cellulose particles (Vivacel 102) were determined on one hand by the classical method of granulometric analysis by laser diffractometry, and on the other hand by

Table 1
Granulometric analysis of different materials for the validation of the method developed (mean ± S.D.)

	Mean diameter (μm)	$d_{50\%}$ (μm)	$d_{10\%}$ (μm)	$d_{90\%}$ (μm)
Glass particles				
Classical method	54.13 (±0.25)	51.28 (±0.1)	29.26 (±0.05)	84.93 (±0.27)
Developed method	52.96 (±0.12)	50.17 (±0.13)	28.08 (±0.13)	83.47 (±0.25)
Vivapur 102				
Classical method	110.42 (±2.3)	97.01 (±2.5)	27.28 (±1.3)	220.49 (±5.1)
Developed method	107.95 (±1.3)	93.38 (±1.5)	25.85 (±0.8)	213.69 (±1.85)

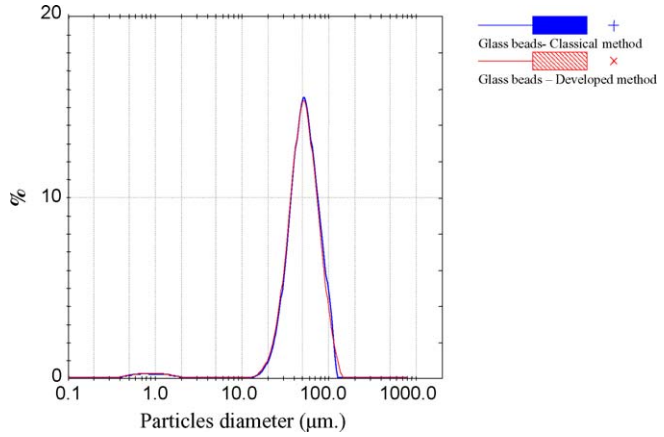

Fig. 2. Granulometric distribution of the glass beads by the two methods of diffractometry laser.

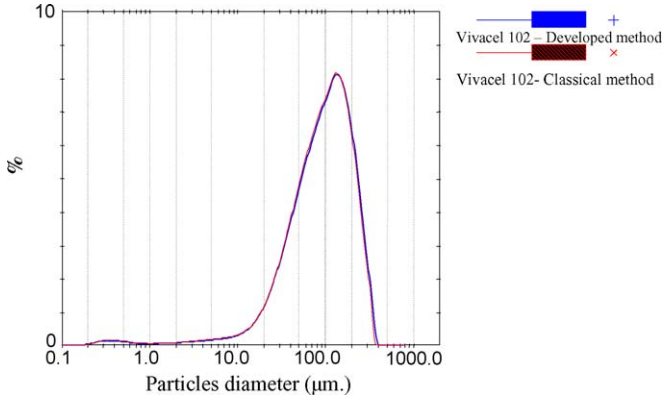

Fig. 3. Granulometric distribution of Vivacel 102 by the two methods of diffractometry laser.

the method we proposed in this work (Table 1). Figs. 2 and 3 present the granulometric distributions obtained for the glass beads and for Vivacel 102, respectively. The comparison of the mean diameters obtained with the two methods shows that they did not differ significantly ($P > 0.01$) and this for the two materials tested. These results validate the method we developed to assess the size of an individual component in a blend. This method provides a correct size analysis.

Table 2 presents the granulometric analysis of ibuprofen 25 and ibuprofen 50 by laser diffractometry before granulation and compression. These results will be used as references. They will make it possible to appraise the size evolution of ibuprofen after the process of granulation or/and compaction.

The different granules were submitted to the method developed to determine the granulometric distribution of ibuprofen within these granules. Results are presented in Table 3.

A comparison of Tables 1 and 3 show that after wet granulation of ibuprofen 50, a decrease in size occurs. The mean diameter of ibuprofen 50 decreases from 95.95 to 64.13 and 74.57 μm after wet granulation with Lodige and Diosna granulators, respectively. This decrease in size could be induced by the abrasion of particles during the mixing and by shocks occurring in the granulator because the ibuprofen 50 particles present needle-shape habit which favours fragmentation. In fact, ibuprofen is not ranged in the brittle products and Marshall et al. (1993) showed that the mechanism of consolidation of ibuprofen after compression was a balance between elastic and plastic deformation. Di Martino et al. (2002) with Heckel's analysis confirmed that ibuprofen is a plastic–elastic material, but during their study, a certain fragmentation propensity has also been pointed out, the extend of which could be affected by the crystal habit.

In the case of ibuprofen 25, particle size is not greatly modified after granulation. The mean diameter of ibuprofen 25 decreases from 56.34 to 48.81 μm after wet granulation in the Diosna granulator. Few particles broke in the granulator because they are much smaller than those of ibuprofen 50.

The different granules were then compressed using a Frogerais MR 15 rotary tablet machine. Our method was again used on the tablets to determine the granulometric distribution of ibuprofen after compression.

Table 4 presents the results obtained in the case of ibuprofen 50.

A comparison of Table 3 and Table 4 shows that after compression of the granules, ibuprofen particle size increases and

Table 2
Granulometric analysis of the two grades of ibuprofen before any operation (mean ± S.D.)

	Mean diameter (μm)	D 50% (μm)	D 10% (μm)	D 90% (μm)
Ibuprofen 25	56.34 (±1.47)	49.92 (±0.52)	20.01 (±0.13)	102.08 (±3.57)
Ibuprofen 50	95.95 (±1.31)	82.50 (±1.97)	37.02 (±1.22)	176.56 (±1.28)

Table 3
Granulometric analysis of ibuprofen in the different granules (mean ± S.D.)

	Mean diameter (μm)	$d_{50\%}$ (μm)	$d_{10\%}$ (μm)	$d_{90\%}$ (μm)
Granules Lodige with ibuprofen 50	64.13 (±1.08)	60.63 (±1.65)	23.10 (±0.98)	110.12 (±1.84)
Granules Diosna with ibuprofen 50	74.57 (±4.81)	69.25 (±1.22)	25.17 (±0.39)	131.29 (±3.07)
Granules Diosna with ibuprofen 25	48.81 (±2.5)	47.42 (±2.5)	13.41 (±1.17)	85.46 (±3.77)

Table 4
Granulometric analysis of ibuprofen 50 after compression (mean ± S.D.)

	Mean diameter (μm)	$d_{50\%}$ (μm)	$d_{10\%}$ (μm)	$d_{90\%}$ (μm)
Tablet with granules Lodige (D = 40 N)	128.74 (±2.36)	121.0 (±2.32)	30.67 (±0.59)	236.02 (±4.45)
Tablet with granules Lodige (D = 80 N)	132.65 (±1.55)	121.57 (±0.38)	29.62 (±0.32)	251.16 (±6.42)
Tablet with granules Diosna (D = 80 N)	152.02 (±0.98)	140.98 (±0.77)	51.65 (±2.56)	271.14 (±1.48)

is higher than that measured before granulation (Table 2). The mean diameter of ibuprofen 50 in the granules obtained with the Lodige granulator was about 64 and about 130 μm after compression, that is to say about the double. The results for tablets with 40 N mechanical strength and those with 80 N are similar. For granules obtained with the Diosna granulator, the mean diameter of ibuprofen 50 was about 75 and 152 μm after compression.

Granules containing ibuprofen 25 were also compressed and submitted to the granulometric analysis (Table 5).

In the case of ibuprofen 25, the same phenomena as for ibuprofen 50 were observed after compression: mean diameters increased from about 49 μm in the granules to 102 and 113 μm in the tablets. Here again, the results for tablets with 40 and 80 N mechanical strength were similar.

Which ever the ibuprofen studied, compression increased particle size. After compression, ibuprofen particle size was twice its previous size in the granules. Actually, compression could induce some fragmentation of ibuprofen associated with the plastic deformation and then, under pressure, a closeness of the fragments or deformed particles that could bind or associate with one another because the melting point of ibuprofen is not very high (75–77 °C (The Merck index)). Moreover, it has been previously reported that the low melting point of ibuprofen can induce partial particle fusion during compression (Di Martino et al., 2002).

Ibuprofen particle size in the 40 N mechanical strength tablets was close to that in the 80 N mechanical strength tablets. Pressures of 600 and 1500 kg/cm^2 were needed to obtain the 40 and 80 N mechanical strength tablets, respectively. This increase in pressure had no effect on the granulometric distribution of ibuprofen in the tablets. Probably ibuprofen fragmentation and deformation reaches its maximum at 600 kg/cm^2 and does not evolve much beyond.

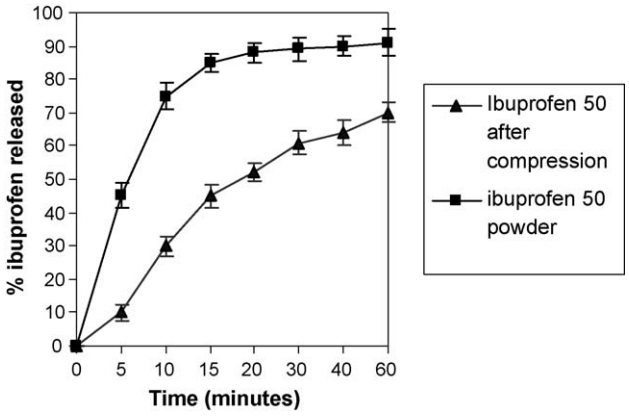

Fig. 4. Dissolution kinetic of ibuprofen 50 before and after compression in pH 6.8 phosphate buffer.

After granulation and compression, ibuprofen particle size is different from its initial size. For a drug like ibuprofen which is practically insoluble in water, this may have important repercussions on the dissolution rate and so on bioavailability.

We therefore compared the dissolution kinetics of the initial ibuprofen 50 and after granulation and compression. The results are presented in Fig. 4. The tablets tested are those obtained after compression of ibuprofen 50 granules in the Lodige mixer, with 80 N mechanical strength.

The dissolution rate of ibuprofen 50 after granulation and compression was delayed. It was not similar to that of ibuprofen 50 before any manufacturing step. This result shows that it is

Table 5
Granulometric analysis of ibuprofen 25 after compression (mean ± S.D.)

	Mean diameter (μm)	$d_{50\%}$ (μm)	$d_{10\%}$ (μm)	$d_{90\%}$ (μm)
Tablet with granules Diosna (D = 40 N)	102.44 (±1.08)	95.47 (±0.89)	23.12 (±0.11)	190.46 (±2.16)
Tablet with granules Diosna (D = 80 N)	113.05 (±5.58)	101.24 (±2.63)	39.01 (±0.90)	218.50 (±3.57)

difficult to specify beforehand the size of a drug without taking into account the manufacturing process.

4. Conclusion

This work shows the impact of the manufacturing process on drug particle size when producing tablets. In the case of ibuprofen, particle size decreases during granulation. This is particularly important when the initial size is bigger. On the other hand, after compression, particle size increases, probably after fusion of the particles that are sufficiently near to each other, and under the effect of pressure. Ibuprofen particle size is twice its previous size in the granules.

The method we have developed makes it possible to differentiate and to measure the ibuprofen particle size in a blend.

When a drug is formulating, it is difficult to specify beforehand the size of a drug without taking into account the manufacturing process.

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