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Combining formulation and process aspects for optimizing the high-shear wet granulation of common drugs

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ABSTRACT

The purpose of this research was to determine the effects of some important drug properties (such as particle size distribution, hygroscopicity and solubility) and process variables on the granule growth behaviour and final drug distribution in high shear wet granulation. Results have been analyzed in the light of widely accepted theories and some recently developed approaches.

A mixture composed of drug, some excipients and a dry binder was processed using a lab-scale high-shear mixer. Three common active pharmaceutical ingredients (paracetamol, caffeine and acetylsalicylic acid) were used within the initial formulation. Drug load was 50% (on weight basis).

Influences of drug particle properties (e.g. particle size and shape, hygroscopicity) on the granule growth behaviour were evaluated. Particle size distribution (PSD) and granule morphology were monitored during the entire process through sieve analysis and scanning electron microscope (SEM) image analysis. Resistance of the wet mass to mixing was furthermore measured using the impeller torque monitoring technique. The observed differences in the granule growth behaviour as well as the discrepancies between the actual and the ideal drug content in the final granules have been interpreted in terms of dimensionless quantity (spray flux number, bed penetration time) and related to torque measurements. Analysis highlighted the role of liquid distribution on the process. It was demonstrated that where the liquid penetration time was higher (e.g. paracetamol-based formulations), the liquid distribution was poorer leading to retarded granule growth and selective agglomeration. On the other hand where penetration time was lower (e.g. acetylsalicylic acid-based formulations), the growth was much faster but uniformity content problem arose because of the onset of crushing and layering phenomena.

1. Introduction

Pharmaceutical industries frequently turn to high shear wet granulation in order to convert fine cohesive powders into dense and round granules. The granules are produced by vigorous mixing of a wet powdered mixture generally composed of drug, some excipients and binder (Litster and Ennis, 2004). The overall purpose of this operation is to obtain a final product with improved characteristics, such as better flowability and compressibility. Other benefits can be obtained using high shear wet granulation: for example, the distribution of the drug in the final product as well as the dissolution properties of tablets can be improved (Gokhale et al., 2006).

Most of high shear mixers consist of a stainless steel vessel, a three-bladed impeller and a chopper. Typically, high shear wet granulation is performed as a batch operation. Firstly, dry powders are mixed together by the impeller blade which rotates through the powder bed. Secondly, liquid binder is added while the impeller ensures liquid spreading and the chopper breaks down wet, coarser agglomerates. Finally, densification of granules takes place during wet massing through impeller rotation and without liquid addition (Gokhale et al., 2006).

Besides the description of macroscopic phenomena, some researchers also tried to explain the agglomeration process in a high shear mixer at microscopic level. According to the saturation degree of pore spaces in the granule, Newitt and Conway-Jones (1958) firstly proposed the existence of three saturation states which represent a progressive increase in moisture content: pen-

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dular, funicular and capillary state. Firstly, surface tension at particle–liquid interface and the presence of liquid bridges cause the formation of first agglomerates, thus leading to the pendular state. With increasing the liquid content, a continuous network of liquid can be noted at the funicular state. The capillary state corresponds to the saturation degree at which pore spaces are completely filled. Barlow (1968) also introduced the droplet state, which occurs when liquid completely surrounds the granule.

Many attempts to follow the granule growth have been made by measuring either the power consumption or impeller torque. Leuenberger and co-workers (Leuenberger and Bier, 1979; Bier et al., 1979) compared both of these methods and realized that power consumption and torque noticeably depend on the cohesive force of the wet mass or the tensile strength of the agglomerates. Moreover, they found a reliable relationship between power or torque profiles and the saturation degree of the wet mass (Imanidis, 1986; Leuenberger et al., 1981; Leuenberger, 1982; Leuenberger and Imanidis, 1984). Particularly, a sudden increase of the power/torque value was noted when the pendular state was reached. As more liquid binder was added, torque and power consumption resulted to be relatively constant.

According to these approaches, granule growth behaviour in high shear wet granulation has often been described considering particles as inert material held together by a simple Newtonian liquid added in the liquid phase. However, the reality is frequently more complicated: pharmaceutical formulations are usually composed of powders with different characteristics, which interact with the wetting agent and change their properties. For example, the presence of an amorphous component within the initial powder mixture can have strong effects on the granule growth behaviour. Cavinato et al. (2010) showed that the sudden increase in torque profiles can be correlated with the liquid amount required to attain the dry binder glass transition. In these conditions, dry binder stickiness promotes a faster granule growth.

Palzer (2010a,b) recently proposed a clear classification of pharmaceutical/food powders according to their molecular polarity and their supra-molecular structure, thus giving an effective explanation of the behaviour of the powder particles in different agglomeration processes.

Among all the formulation components, the active substance is usually the most critical ingredient. For example, differences in physical properties between drug and excipients or non-optimal process conditions often lead to selective agglomeration of certain components, causing content uniformity problems. Despite the essential importance of the active substance in pharmaceutical high shear wet granulation, a relatively few works presented a detailed analysis on the role of drug characteristics (such as, for instance, drug type, drug particle size and shape, hygroscopicity) in the granule growth kinetics (Nguyen et al., 2010; Belohlav et al., 2007).

For this reason, the present research is mainly focused on the role of the active ingredient in the agglomeration process. Particularly, the influence of some important drug particle characteristics on granule growth behaviour has been evaluated: different drugs with a different primary particle size and shape were used. Effects of changes in impeller speed or liquid flow rate have been studied as well.

2. Materials and methods

2.1. Materials

Granules containing a common active ingredient were prepared. The active ingredient was either acetylsalicylic acid (Polichimica, Bologna, Italy), or paracetamol (Suzhou Sintofarm Pharmaceutical, Jiangsu, China) or caffeine (Polichimica, Bologna, Italy).

Other ingredients included within the initial formulation were: lactose monohydrate 150 mesh (Lactochem® Regular Powder 150 M, Friesland Foods, Zwolle, The Netherlands), microcrystalline cellulose (MCC) (Pharmacel® 101, DMV International, Veghel, The Netherlands), polyvinylpyrrolidone (PVP) (Kollidon® K30, BASF, Ludwigshafen, Germany) and croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer, Philadelphia, USA).

Deionized water at 20 °C was used as wetting agent.

2.2. Formulation ingredients characterization

A first qualitative analysis of drug particle size and shape was carried out using optical microscopy (Leica DM LM/P®, Leica Microsystem, Wetzlar, Germany). A small sample of each active ingredient was placed on a slide. Particles were dispersed using a small amount of silicone oil before analysis.

A more detailed analysis of the drug PSD was performed using a laser light scattering (LLS) particle size analyzer (Sympatec Helos/KF®, Sympatec, Clausthal-Zellerfeld, Germany). Three different pressures of dispersing air (1, 2, 3 bar) were used in order to identify the possible presence of primary agglomerates and break them. The term "primary" particle or agglomerate is used in this work to identify respectively the drug particle or the agglomerate composed of drug particles. The presence of primary agglomerates in the drug powder bulk is generally due to entanglements, electrostatic and van der Waals forces. Ultimately, three samples for each of the three active ingredients have been analyzed applying the highest pressure (3 bar). Measurement ranges were 0.5–350 μm, 0.5–875 μm and 0.5–1750 μm for paracetamol, caffeine and acetylsalicylic acid, respectively. Sample size was 50–100 mg. The trigger condition for starting the analysis was $C \geq 1\%$, where C is the optical concentration of particles in the measurement chamber. Resulting PSDs were represented by a normalized-sectional frequency distribution (Allen, 1997; Litster and Ennis, 2004) in order to allow a more reliable and reproducible comparison between PSDs.

Water sorption isotherms at 25 °C for active ingredients were determined using a gravimetric analysis system (IGAsorp, Hiden Isochema, Warrington, UK). Samples were kept at different relative humidity grades under nitrogen flow. Accordingly, the weight change of each drug sample during the analysis time was measured. The exposure time of each sample to the different humidity grades corresponded to the time at which the sample weight did not change anymore or otherwise to a maximum of 4 h.

Liquid/powder wettability was also taken into account by measuring the liquid surface tension with the drop pendant method and the liquid–solid contact angle and the drop penetration time with the sessile drop method (Hapgood et al., 2002): magnified movies of binder drops dropping from the tube and lying down on dry formulation were taken using a fast digital camera (FastCam PCI 1000, Photron, UK) at 250 frames per second, and time for complete penetration measured.

2.3. Granules preparation

An experimental plan was designed in order to evaluate the effects of process parameters (impeller speed and liquid flow rate) and formulation variables (type of active ingredient and corresponding size/shape) on the granule growth behaviour and the final product characteristics.

A small scale high shear wet granulator was used (MiPro, 1900 ml vessel volume, ProCepT, Zelzate, Belgium) with a stainless steel vessel, a chopper and a three-bladed impeller. Both impeller

torque and powder temperature were monitored during the experiments. Each experiment was stopped immediately at the end of the liquid addition phase, hence wet massing was not performed. Impeller speed during wetting was set at 500 or 1200 rpm, at a liquid flow rate of 8 or 12 ml/min. At 1200 rpm the "roping regime" was noted. The powder flow regime was determined from the well-known toroidal flow pattern and the powder bed resulted to be more fluidized. At 500 rpm the mixing regime was more likely to be the "bumping regime": powder surface remained horizontal and the bed was raised as the impeller passed underneath (Litster and Ennis, 2004).

The other process variables were kept constant for each granulation experiment: batch size was 40 wt.% compared to the vessel volume (i.e. about 400 g of powder, depending on the formulation bulk density) and the total amount of added water was 25 wt.% compared to the batch size. The formulation (on a weight basis) consisted of approximately: active ingredient (50%), lactose monohydrate 150 mesh (23.5%), micro-crystalline cellulose (20%), PVP (5%) and croscarmellose sodium (1.5%).

In total, 16 experiments were performed: values of process variables are reported in Table 1.

2.4. Granules characterization

Granule samples were taken after the end of the wetting time and dried in an oven at 40 °C until constant weight was achieved. Granules were disposed as a thin layer on the oven plate. Drying procedure was designed in order to avoid noticeable alteration of particle size distribution due to caking and/or attrition phenomena.

Sieve analysis was then performed using a vibrating sieve apparatus (Retsch AS200, Germany) at 5 mm vibration amplitude for 10 min in order to determine PSD of the final product. The sieve apertures were: 45, 90, 125, 180, 250, 355, 500, 710, 850 and 1000 μm. Powder fractions were collected and then weighted. Resulting PSDs were represented by the normalized-sectional frequency distribution (mass-based).

Content uniformity analysis was carried out in order to evaluate the distribution of the active ingredient in different sieve fractions of the final granules. Samples of size fractions corresponding to x_{10}, x_{50} and x_{90} (10th, 50th and 90th percentile, respectively) were chopped and dissolved in suitable solvents: deionized water for caffeine, ethanol for paracetamol and acetylsalicylic acid. Solutions were filtered after 3 min sonication and the drug content was measured using UV/Vis spectrophotometry. Drug-free granules obtained under the same process conditions were chopped and dissolved in order to prepare the blank for the content uniformity analysis.

Several samples of 1 g each were collected during the granulation process at different moisture contents (20, 40, 60, 80, 100% of the total added liquid amount). Magnified images of these samples were taken using a scanning electron microscope (SEM) (Quanta 200 FEG, FEI Company, Czech Republic). Accordingly, images were compared in order to study the growth mechanisms.

Table 1
Experimental plan: values of the process variables.

Experiment number	Active ingredient type	Impeller speed (rpm)	Liquid flow rate (ml/min)
1	Paracetamol	500	8
2		500	12
3		1200	8
4		1200	12
5	Caffeine	500	8
6		500	12
7		1200	8
8		1200	12
9	Acetylsalicylic acid	500	8
10		500	12
11		1200	8
12		1200	12
13	Without drug (lactose 73.5%, w/w)	500	8
14		500	12
15		1200	8
16		1200	12

Table 2
First investigation of active ingredients characteristics through optical microscopy.

	Paracetamol	Caffeine	Acetylsalicylic acid
Particle circularity, φ	0.59 ± 0.21	0.57 ± 0.20	0.62 ± 0.21
Mean particle diameter, d_{10} (μm)	62	113	328
Primary agglomeration	Weak	Very weak	Not present
Primary agglomerate size (μm)	Up to 400	n.a.	n.a.

n.a., not available.

3. Results and discussion

3.1. Results of the formulation ingredients characterization

A first analysis of drug particle size and shape was carried out using an optical microscope. This first investigation also permitted to make observations regarding the presence of primary agglomerates caused by surface forces such as Van der Waals or electrostatic forces.

Figs. 1–3 show the pictures of the three different active ingredients taken using the optical microscope.

Table 2 summarizes the observations derived from the optical microscopy analysis. Mean size is represented by $d_{1,0}$, number length mean:

$$d_{1,0} = \frac{\sum_i x_i y_i}{\sum_i y_i}, \quad (1)$$

where x is the particle size and y is the particles count in the measurement interval i.

Drug primary PSD was then measured with a laser light scattering particle size analyzer. The pressure of the dispersing air has been chosen as such in order to break any agglomerates and to get results that reflect the primary particle size distribution of the product. Fig. 4 shows drug primary PSDs, represented by the cumulative distributions.

As can be observed in Table 2, since the paracetamol particle size is noticeably small, Van der Walls and electrostatic forces are relevant and cause the formation of primary agglomerates. These agglomerates were visually detected using an optical microscope. However, it has been noted that these primary agglomerates are relatively weak: increase in pressure of dispersing air in the LLS particle size analyzer from 1 to 2 bar was sufficient to break them. Accordingly, the paracetamol PSD in Fig. 4 does not show the presence of primary agglomerates.

On the other hand, acetylsalicylic acid particles present the highest mean size. The crystalline habit of the drug particles is clearly columnar and it does not present primary agglomerates. A low percentage of smaller acetylsalicylic acid particles ($d_{10} < 100$ μm) can be identified instead. Caffeine shows a higher mean size compared to paracetamol and a slightly wider PSD.

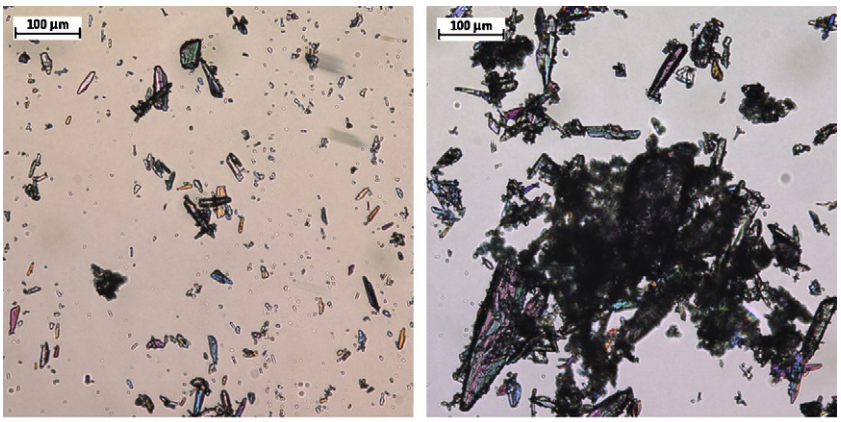

Fig. 1. Pictures of paracetamol taken using an optical microscope: (a) some particles and (b) an agglomerate composed of several paracetamol particles.

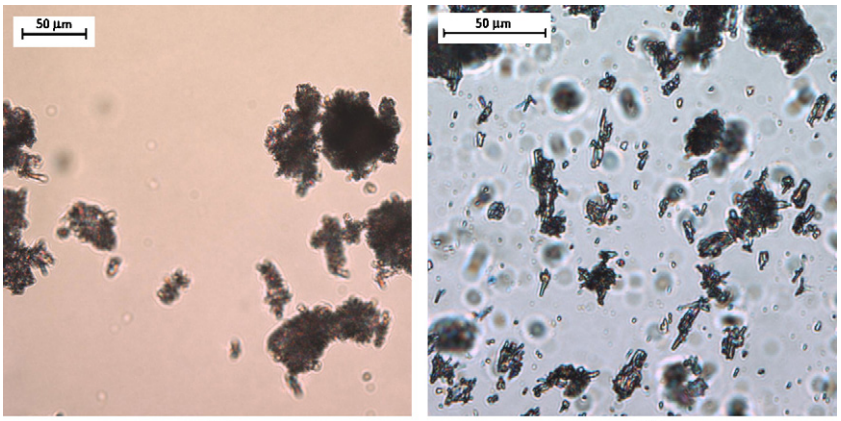

Fig. 2. Pictures of caffeine taken using an optical microscope at different magnifications.

10th, 50th and 90th percentiles (x_{10}, x_{50} and x_{90}) for paracetamol, caffeine and acetylsalicylic acid are summarized in Table 3 and compared with the same percentiles of microcrystalline cellulose and lactose monohydrate. Standard deviation values for the percentiles were all relatively small (between 0.43 and 3.1% on the absolute percentile values).

As can be observed in Table 3, the larger difference between the PSD of paracetamol and caffeine is in the amount of coarse particles, i.e. x_{90}, while the values of x_{10} and x_{50} are comparable. On the other hand, percentile values of acetylsalicylic acid PSD are considerably larger compared to the other active ingredients and the excipients. Lactose monohydrate particles result to be larger than microcrystalline cellulose ones, as can be deducted from the higher x_{10} and x_{50} values, however, presents a narrower PSD than microcrystalline cellulose.

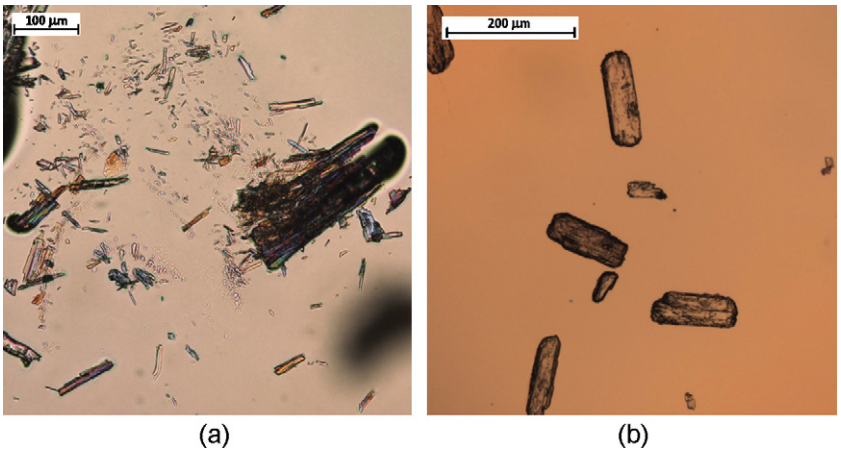

Fig. 3. Pictures of acetylsalicylic acid taken using an optical microscope at different magnifications.

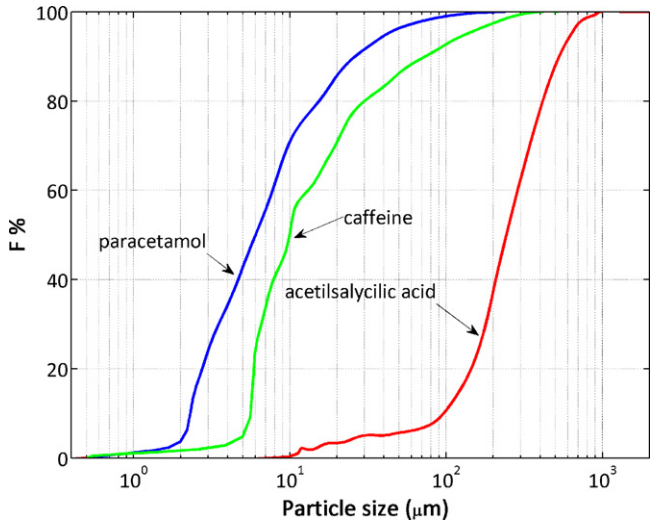

Fig. 4. Primary particle size distributions of the active ingredients measured with laser light scattering.

Table 3
Percentiles (x_{10}, x_{50} and x_{90}) for the three active ingredients (paracetamol, caffeine and acetylsalicylic acid) and the two main excipients (microcrystalline cellulose and lactose monohydrate).

	x_{10} (μm)	x_{50} (μm)	x_{90} (μm)
Paracetamol	2.2	6.0	25.8
Caffeine	5.6	10.0	72.8
Acetylsalicylic acid	92.1	229.1	525.7
Lactose monohydrate	7.6	27.4	88.4
Microcrystalline cellulose	2.3	9.8	105.1

Solubility and hygroscopicity of the active ingredients and excipients are compared in Table 4. Hygroscopicity is here represented by weight variation of powder samples under controlled humidity conditions. Three analysis cycles were performed: firstly, the relative humidity within the instrument chamber was raised from ambient humidity (i.e. about 50%) to 90%, secondly from 90% to dry conditions and finally from dry conditions to 90%. Accordingly, weight variations at the end of the cycles were recorded. The weight variation at the end of the last cycle is here considered as an indication of powder hygroscopicity.

As can be observed from the weight variation values recorded during water sorption analysis and reported in Table 4, caffeine results to be the most hygroscopic active ingredient, since it shows the highest weight increase at the end of the third cycle (i.e. 0 → 90 RH%). On the other hand, acetylsalicylic acid shows the lowest hygroscopicity. Regarding the solubility values reported in Table 4, the active ingredients can be classified in the same order: caffeine is the most soluble active ingredient, paracetamol is less soluble and acetylsalicylic acid is the least soluble.

However, it can be noted that each active ingredient shows relatively low weight variations during water sorption analysis: these weight variations result to be negligible if compared with the most hygroscopic excipient (i.e. microcrystalline cellulose). Solubility values of the active ingredients result to be relatively low as well, if compared with lactose monohydrate solubility, whereas MCC is insoluble in water.

3.2. Results of the torque profile analysis

Formulations (50%, w/w) of paracetamol, caffeine and acetylsalicylic acid were granulated by high shear wet granulation. Deionized water was added through a tube with 1 mm diameter. Impeller torque profiles were online monitored during the granulations and recorded.

Torque profiles recorded during the granulation experiments in Table 1 showed similar trends, and a typical impeller torque profile is presented in Fig. 5. Similar results were also obtained in recent research works, with different excipients and dry binder types by Cavinato et al. (2010). An increase in impeller torque value at the beginning of the process has often been recognized, which is probably due to the progressive densification of the wet mass. A decrease in the profile slope is then observed, thus suggesting a lubrication of the wet mass and consequently the stress on the impeller decreases. After this initial phase, impeller torque profiles show a sudden increase. Betz et al. (2004) also reported similar results: they noted a sudden increase in the power consumption profile during the high shear wet granulation of a drug-free formulation composed of lactose monohydrate 200 mesh (86%), corn starch (10%) and PVP (4%). They explained this phenomenon by considering the initial formation of liquid bridges between particles after a first water uptake phase, thus leading to the achievement of the pendular state.

As can be seen in Fig. 5, the liquid amount required to cause the sudden increase in torque value can be easily identified as a minimum in first derivative profile. Such a critical point can be used as a reference point in order to describe the first stage of the agglomeration process and the achievement of the pendular state.

The inflection point in impeller power profile has been considered as a reliable reference point also in a recent work presented by Campbell et al. (2010). Their results showed that granulation process can be scaled up using a linear relationship between the amount of liquid binder required to obtain the inflection point and Froude number.

Torque curves recorded during experiments in Table 1 have shown that the three different drugs present different liquid requirements corresponding to the sudden increase in torque profiles. Liquid amounts (%w/w on the initial batch size) corresponding to the inflection point in torque profiles (i.e. minimum in first derivative profiles) can be compared in Fig. 6. Experiments with drug-free formulation were run in triplicate in order to test repeatability and reliability of the results: small error bars related to these points demonstrate the satisfactory reproducibility of the experi-

Table 4
Solubility and hygroscopicity of the active ingredients.

	Solubility[a] (g/100 ml H_2O)	Water sorption (weight variation %)[b]		
		50 → 90 RH%	90 → 0 RH%	0 → 90 RH%
Paracetamol	1.43	0.11	−0.01	0.12
Caffeine	1.67	0.17	−0.04	0.19
Acetylsalicylic acid	0.33	0.06	−0.03	0.05
Lactose monohydrate	15	0.21	0.01	0.25
Microcrystalline cellulose	–	11.2	−0.02	11.3

[a] Solubility in water.
[b] Weight variations for the analysis cycles 50 → 90 RH%, 90 → dry RH% and dry → 90 RH%.

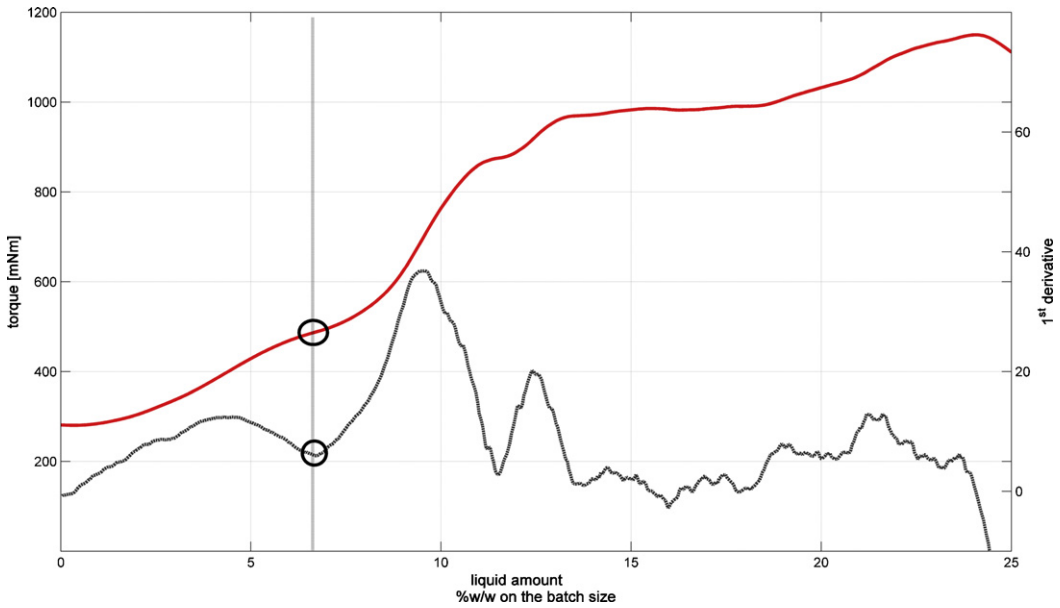

Fig. 5. Impeller torque values (continuous line) and corresponding first derivative profile (dotted line) obtained during the high shear wet granulation of a drug-free formulation (dry binder PVP 5%, w/w): determination of the minimum in the first derivative profile.

mental method. As can be seen in Fig. 6, the inflection point position clearly differs from the three different active ingredients.

Fig. 6 clearly shows that the liquid amount required to strongly increase the impeller torque (i.e. inflection point in Fig. 5) depends on the formulation composition. This means that different formulations, with or without active ingredient, markedly require different amounts of liquid to trigger the actual granule growth, in accordance with the interpretation proposed by Cavinato et al. (2010). According to the characterization of the active ingredients (see Tables 2–4), the differences in drug particle morphology, drug solubility and hygroscopicity are not relevant enough to be considered the main cause of the variation in the liquid amount required to increase the impeller torque. As an example, paracetamol and caffeine present very similar properties in terms of particle shape, solubility and hygroscopicity, but clearly different requirements of liquid to start the actual granule growth. Among the drug particle properties evaluated in the present work, the difference in the primary PSD is likely to be considered the main cause for a different torque inflection point. Particularly, the higher the mean size of the drug particles, the lower is the liquid amount corresponding to the inflection point in torque profiles and required to start most of the granule growth. For example, inflection points for paracetamol occurred after approx. 10% water was added, whereas for acetylsalicylic acid about 5% water was required. The reason for such a different behaviour is likely to be the lower specific surface area and therefore the lower amount of wetting agent required to wet the drug particles and to achieve the pendular state.

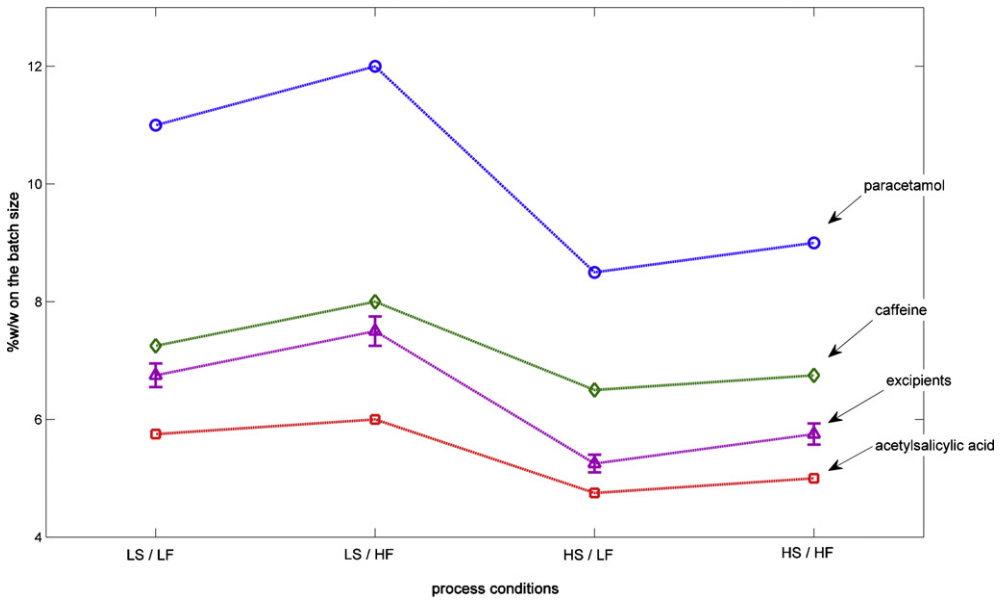

Fig. 6. Liquid amount (%w/w on the batch size) required to determine sudden increase in the torque profiles during granulation experiments with different active ingredients and different process conditions: LS, lower impeller speed (500 rpm); HS, higher impeller speed (1200 rpm); LF, lower liquid flow rate (8 ml/min) and HF, higher liquid flow rate (12 ml/min).

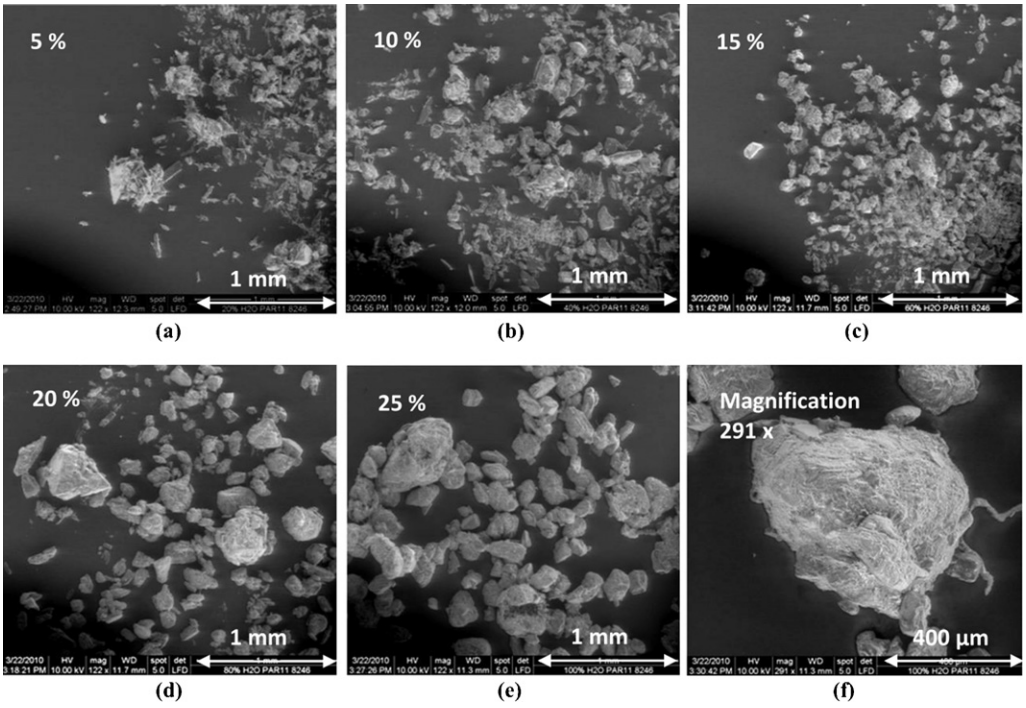

Fig. 7. Granulation samples collected during high shear wet granulation of paracetamol – experiment 3 in Table 1 – at different moisture contents (%w/w on the batch size): (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% at 122× magnification and (f) granule at 25% moisture content and 291× magnification.

This explanation is also supported by the results of Belohlav et al. (2007). Their results demonstrated that granulations with the same active substance and different PSDs required different amounts of wetting agent to perform the optimal granulation process. Particularly, the finer the initial drug PSD, the higher the specific surface area and the higher the amount of wetting agent required to determine the inflection point in the impeller power consumption profile (i.e. start of substantial granule growth).

Also process conditions make important differences in liquid amounts required to get torque profile inflection. As can be seen in Fig. 6, the finer is the primary PSD the larger are the differences between inflection points obtained at low and high rotational speed. This is illustrated for paracetamol, where higher liquid amounts are necessary when impeller speed is lower. Moreover, the highest liquid flow rate gives higher liquid amount percentages.

Summarizing, finer primary PSD, lower impeller speed and higher liquid flow rate seem to cause a higher demand of liquid for the torque inflection point. According to the theory proposed by Leuenberger and co-workers (Leuenberger, 1982; Leuenberger and Bier, 1979; Leuenberger and Imanidis, 1984), a higher liquid amount required for the torque inflection point means that a higher liquid content is required to reach the pendular state and start the liquid bridges formation. According to Cavinato et al. (2010), the start of substantial granule growth might also occur after the addition of higher liquid amount.

3.3. Results of the SEM analysis: granule growth behaviour

In order to validate the different approaches, images of granulation samples collected during granulation experiments at different moisture contents were used for comparison with results of torque profile analysis. Hence, granule size evolution during the agglomeration of paracetamol, caffeine and acetylsalicylic acid is qualitatively described by Figs. 7–9.

Images of granulation samples were taken at the same magnification (i.e. 122×) in order to facilitate the comparison between the effect of different moisture contents or active substances. Larger magnifications of granules at 25% moisture content (i.e. at the end of the granulation process) are furthermore reported.

As can be seen in Fig. 7, for the paracetamol granulate some big agglomerates can be noted at 20% moisture content (see Fig. 7d), whereas pictures at 5, 10, 15% moisture content primarily show non-granulated product.

On the other hand, first granules with caffeine can be located already at 15% moisture content (see Fig. 8c).

Granulations with acetylsalicylic acid in Fig. 9 show some agglomerates at 10% moisture content (see Fig. 9b) and at 15% moisture content only big granules are shown.

Table 5 compares the results of torque profile analysis with those obtained for the SEM analysis of the samples in Figs. 7–9.

The comparison of the moisture contents corresponding to the torque inflection points (i.e. granule growth start) with those related to the images with the first clearly visible agglomerates (i.e. ongoing growth) suggests a similar growth trend. Granule growth seems to occur at lower moisture contents for acetylsalicylic acid, whereas higher moisture contents are required when paracetamol or caffeine is used.

Regarding the effects of primary PSD on the initial nucleation and granule growth phase, similar results were obtained from Realpe and Velázquez (2008). As demonstrated by their results, formulations with relatively coarse size powders and bimodal PSD showed a faster growth rate at the beginning of the process and then a slower growth rate. On the other hand, the formulation with finer primary PSD showed a negligible growth at low moisture content and then a stage with faster growth rate after a certain amount of water was added. They explained this phenomenon by considering the higher cohesive force of small particles produced by larger contact surface which led to stronger, poor deformable granules. Thus, poor deformability caused a lower growth rate at low moisture content and then a “ball growth” after a critical amount of water was added.

According to the approach proposed by Realpe and Velázquez (2008) and the results reported in the present research (see Table 5), it is therefore suggested that the bigger specific surface area, due to

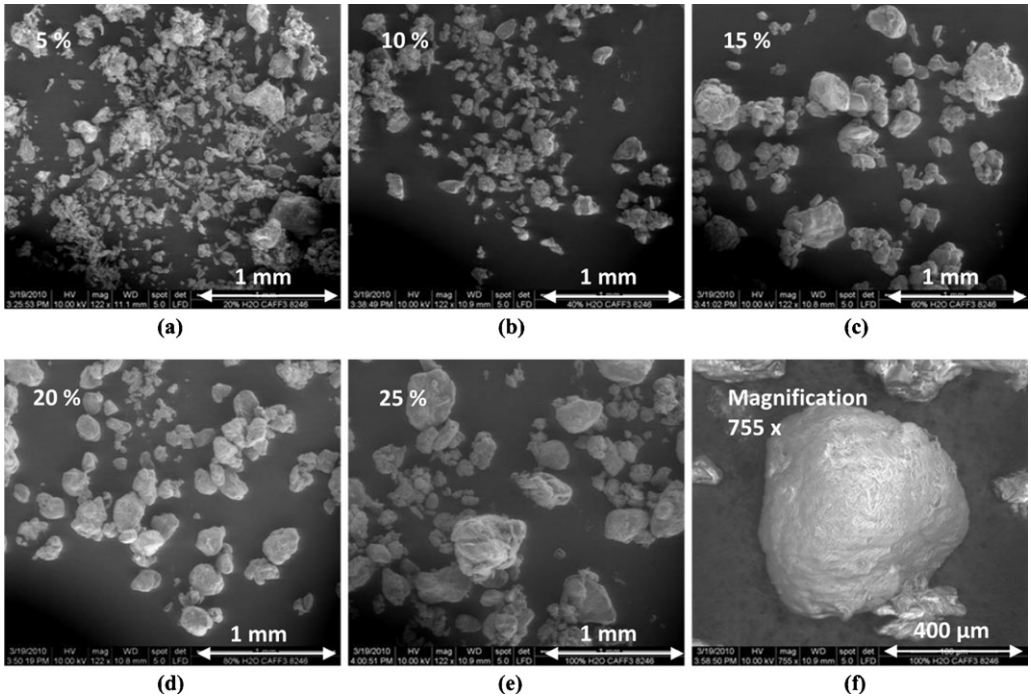

Fig. 8. Granulation samples collected during high shear wet granulation of caffeine – experiment 7 in Table 1 – at different moisture contents (%w/w on the batch size): (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% at 122× magnification and (f) granule at 25% moisture content and 755× magnification.

the smaller x_{10} value, of paracetamol particles compared to caffeine and acetylsalicylic acid particles can be considered as a predominant cause of the higher moisture content required to start the growth.

SEM images in Figs. 7f, 8f and 9f also give some information about the growth mechanism types. It is interesting to see that granules with acetylsalicylic acid at 25% moisture content result to be less spherical than those composed of caffeine and paracetamol. This might be explained by considering the coarse primary PSD of acetylsalicylic acid. In particular, granules with acetylsalicylic acid tend to be composed of a bigger, columnar-shaped drug particle as a core and several smaller particles adhered on the core surface as a layer. The amorphous solid binder is supposed to play an important role in this case, promoting the layering mechanism (see for example results presented by Palzer, 2009). Other researchers (Capes and Danckwerts, 1965; Mackaplow et al.,

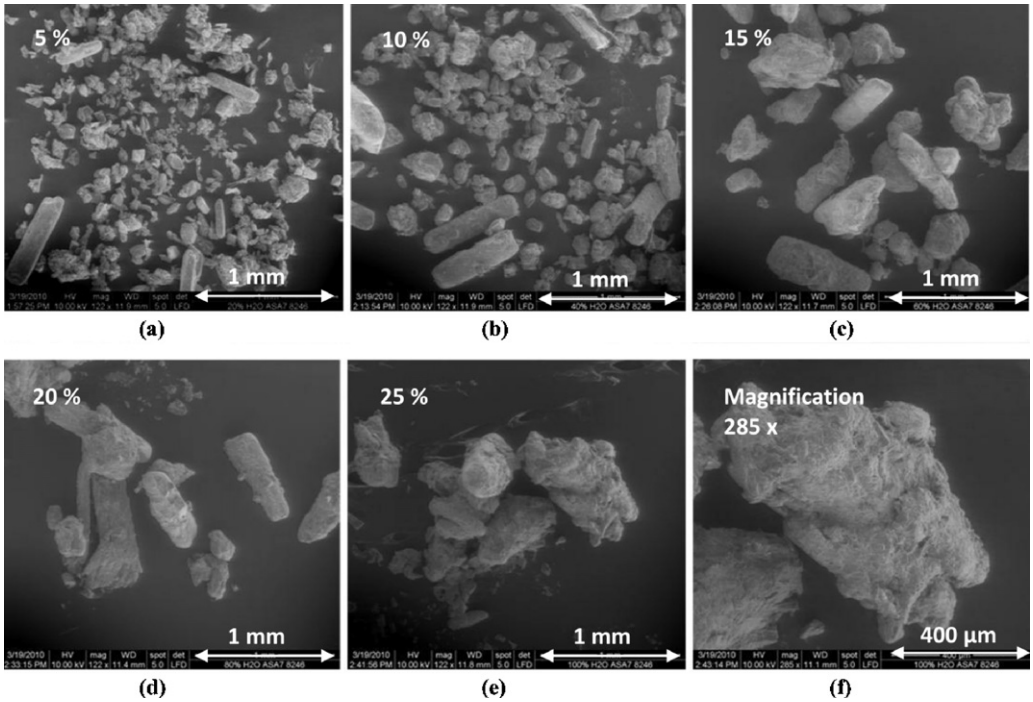

Fig. 9. Granulation samples collected during high shear wet granulation of acetylsalicylic acid – experiment 11 in Table 1 – at different moisture contents (%w/w on the batch size): (a) 5%, (b) 10%, (c) 15%, (d) 20%, (e) 25% at 122× magnification and (f) granule at 25% moisture content and 285× magnification.

Table 5
Start of the actual granule growth: comparison between the results of torque profile analysis (i.e. granule growth start) and the results of SEM analysis (i.e. ongoing growth).

	Moisture content %	
	Torque inflection → growth start	Image analysis → visible agglomerates
Paracetamol	9–12%	20%
Caffeine	7–8%	15%
Acetylsalicylic acid	5–6%	10–15%

2000) studied the effects of primary PSD on the growth mechanism and noted that as primary particle size increased, growth was more likely to occur via a crushing and layering mechanism.

On the other hand, spherical shape of paracetamol and caffeine-based granules can be explained by considering the lower granule deformability which leads to a slower action of shear forces on growing agglomerates.

3.4. Sieve analysis results

Final granules size was furthermore measured by sieve analysis. Fig. 10 shows final granules size represented by the normalized-sectional frequency distribution. The primary PSD of each active ingredient is represented as well.

As can be seen in Fig. 10, the PSDs of the granules containing paracetamol present a larger amount of small particles/agglomerates ($d_{10} < 100\,\mu m$) and a smaller amount of larger agglomerates ($d_{10} > 300\,\mu m$) compared to granules containing caffeine. This fact can be easily explained by considering the relatively smaller amount of coarse particles in the paracetamol primary PSD, i.e. lower x_{90} value.

It can be furthermore noted that difference between drug primary PSD and final PSDs of granules with acetylsalicylic acid is less than for paracetamol and caffeine.

Interestingly, there are no noticeable differences between granules obtained at different process conditions in the case of granulation with caffeine or acetylsalicylic acid. Prominent differences between PSDs of paracetamol-based granules can be noted instead (see Fig. 10a). In particular, granules obtained using the lowest impeller speed and highest liquid flow rate result to be much smaller than the others. In this case, non-granulated powder was found on the bottom sieve. This observation was partly anticipated by torque inflection point analysis, since discrepancies between inflection points at different process conditions were more relevant for paracetamol (see Fig. 9).

3.5. Drug uniformity content in the final granule

The last analysis involved the measurement of drug distribution in different size fractions of final granules. Size fractions corresponding to the 10th, 50th and 90th percentile for each granulation experiment were analyzed. Results of content uniformity measurements and corresponding error bars are shown in Fig. 11. The broken line indicates the ideal condition of 50% (w/w) drug content in the final granule, according to the initial active ingredient load.

Discrepancies between actual and ideal drug content might be due to selective agglomeration of certain components during the process. For example, for a mixture of hydrophobic and hydrophilic primary particles, granule growth of hydrophilic materials tends to take place selectively, as described by Belohlav et al. (2007). Hydrophilic powders tend to be covered by the wetting agent and to absorb it more quickly, becoming more deformable and/or sticky. Increases in deformability increase the bonding or contact area thereby dissipating and resisting breakup forces (Gokhale et al., 2006).

As a matter of fact, each active ingredient used in the present research showed poor hygroscopicity and poor solubility compared to the two main excipients. These differences can be therefore considered as a potential cause of selective agglomeration.

It can be noted in Fig. 11 that most of content uniformity problems occurred with paracetamol, especially at lower impeller speed. Paracetamol-based granules obtained using the lowest impeller speed and highest liquid flow rate showed the highest discrepancies: higher drug content in the biggest granules and very low drug content in the x_{50} size fraction. Caffeine-based granules obtained with the lowest impeller speed also showed content uniformity problems and lower drug concentration in the x_{90} size fraction. On the other hand, granules with acetylsalicylic acid showed the highest gap at both a high impeller speed and a liquid flow rate. In this case, drug content was highest in fines and non-granulated product.

3.6. Discussion of the results

From the above analysis, among the drug particle properties evaluated in this work, the drug primary PSD can be considered as one of the main factors influencing granule nucleation and growth. However, the specificities in the granule growth behaviour as well as the discrepancies between the actual and the ideal drug content in the final granule are more likely to be determined by a combination of different factors (e.g. mean size, PSD width, particle shape, porosity and specific surface area).

The approach developed by Litster, Hapgood and co-workers (Hapgood et al., 2002, 2003; Litster et al., 2001) can be considered in order to best explain these aspects.

The dimensionless spray flux number is defined as (Litster et al., 2001):

$$\Psi_a = \frac{3\dot{V}}{2\dot{A}d_d}, \tag{2}$$

where $\dot{V}$ is the liquid flow rate, $\dot{A}$ is the powder surface flux which is traversing the wetted area and d_d is the droplet diameter. The powder surface flux is defined by:

$$\dot{A} = \nu W, \tag{3}$$

where ν is the powder surface velocity and W is the width of the powder being wet. The powder surface velocity was approximated to 15% of the impeller tip speed: it has been assumed in this work that the powder velocity does not strongly vary during the granulation process with the liquid binder addition (Litster et al., 2001). In order to describe the drop penetration kinetics, Hapgood et al. (2003) considered the dimensionless drop penetration time:

$$\tau_p = \frac{t_p}{t_c}, \tag{4}$$

where t_p is the penetration time of the liquid drops and t_c is the circulation time, which is the time interval between a packet of powder leaving and re-entering the wetted area. The circulation time t_c was approximated to the ratio between the bowl circumference and the powder surface velocity.

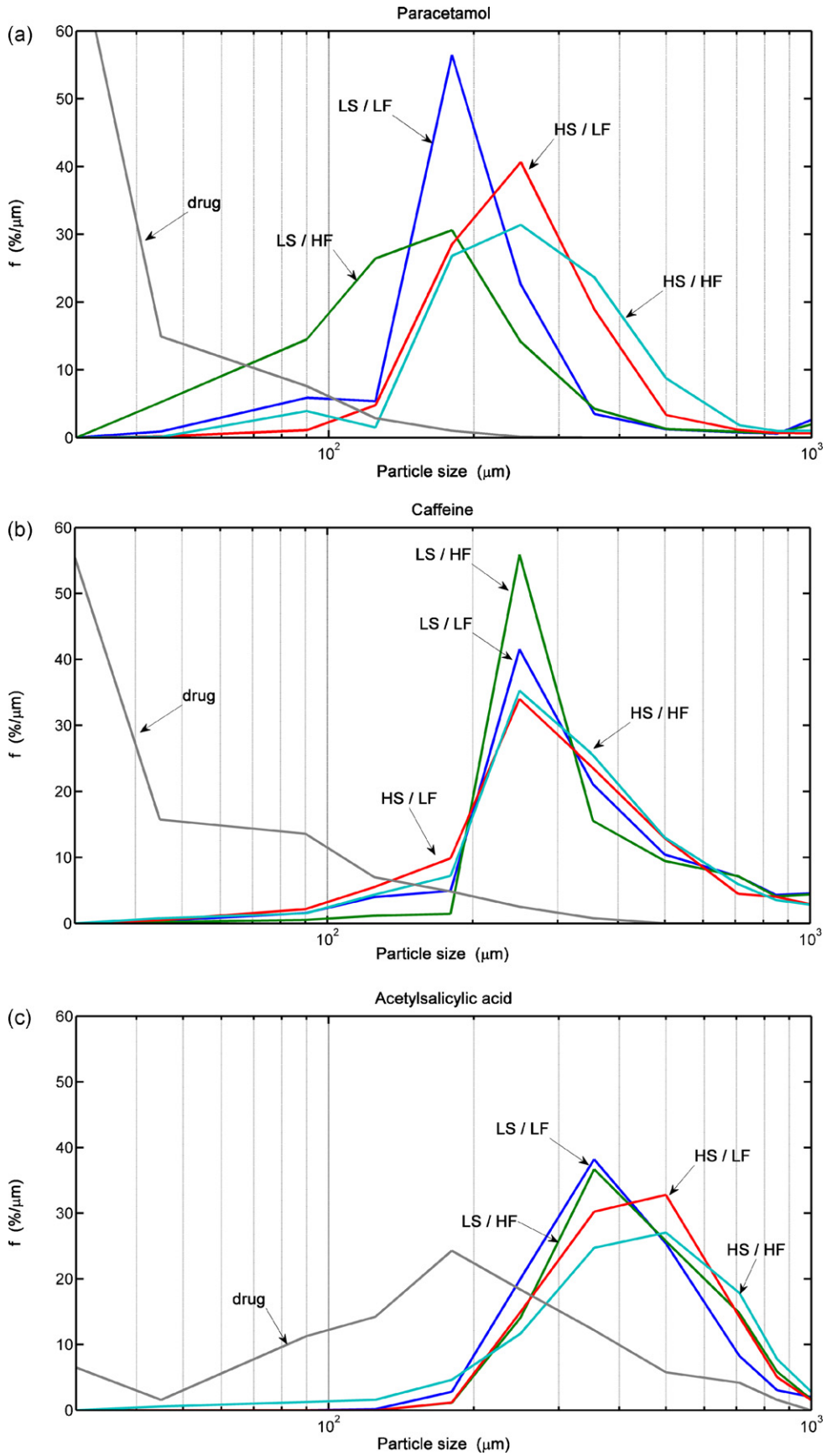

Fig. 10. Particle size distribution measured by sieve analysis of the final granules (25% moisture content) for (a) paracetamol, (b) caffeine and (c) acetylsalicylic acid. Data are represented by the normalized-sectional frequency distributions and compared with the drug primary particle size. Process conditions are: LS, lower impeller speed (500 rpm); HS, higher impeller speed (1200 rpm); LF, lower liquid flow rate (8 ml/min) and HF, higher liquid flow rate (12 ml/min).

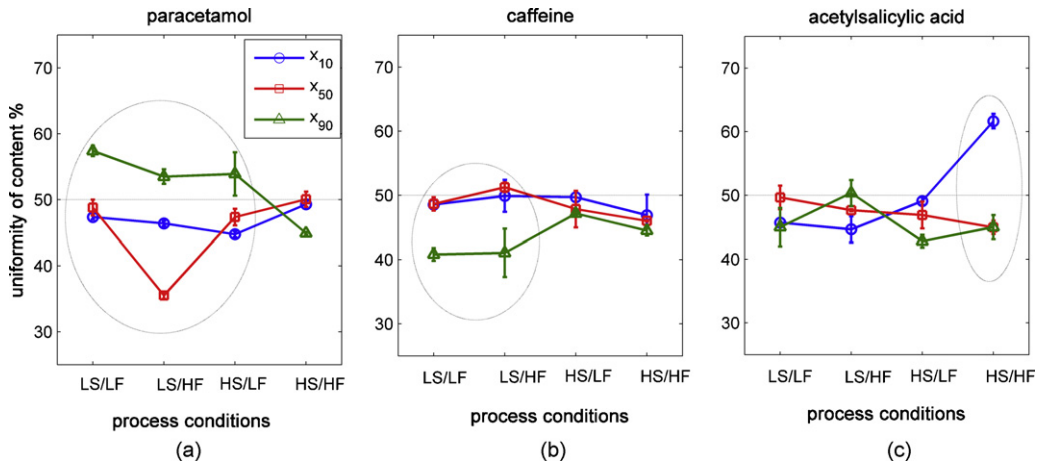

Fig. 11. Content uniformity analysis results: distribution of (a) paracetamol, (b) caffeine and (c) acetylsalicylic acid in the x_{10} (circles), x_{50} (squares) and x_{90} (triangles) size fraction. Process conditions: LS, lower impeller speed (500 rpm); HS, higher impeller speed (1200 rpm); LF, lower liquid flow rate (8 ml/min) and HF, higher liquid flow rate (12 ml/min).

The penetration time t_p can be defined as:

$$t_p = 1.35 \frac{V_d^{2/3}}{\varepsilon_{\text{eff}}^2} \left[\frac{\mu}{R_{\text{eff}} \gamma \cos\theta} \right], \quad (5)$$

where V_d is the drop volume, ε_{eff} is the effective porosity of packing, μ is the liquid viscosity, γ is the liquid surface tension and θ is liquid–solid contact angle.

R_{eff} is the effective pore radius:

$$R_{\text{eff}} = \frac{\varphi d_{32}}{3} \left(\frac{\varepsilon_{\text{eff}}}{1 - \varepsilon_{\text{eff}}} \right), \quad (6)$$

which is a function of the effective porosity of packing, the surface-volume average size d_{32} and the particle shape φ (Hapgood et al., 2003). According to this approach, high values of dimensionless penetration time and dimensionless spray flux lead to a bad liquid distribution. For a given liquid, the penetration time increases with decreasing the particle average size and the effective porosity of packing. The penetration time is therefore a lumped factor which summarizes the effect of some important particle properties. As previously described, t_p was measured experimentally as the time a liquid drop needs in order to be absorbed by the static powder bed composed of the initial formulation.

The liquid amounts required to start the actual granule growth can be related to the values of Ψ_a and τ_p (see Fig. 12).

Table 6 summarizes the values of the penetration time and of the spray flux number as a function of the formulation composition.

Fig. 12 clearly shows that the liquid penetration time is much higher for the drug with the finest primary PSD (i.e. paracetamol), thus the liquid distribution within the wet mass is supposed to be much worse. Moreover, lower impeller speed and higher liquid flow rate determine higher dimensionless spray flux number and consequently a worse liquid distribution. It is therefore suggested that poorer liquid distribution might lead to the presence of lumps and less wet areas, thus worsening the drug distribution as well. Whereas the cause of content uniformity issues for paracetamol and caffeine might be due to unsatisfactory liquid distribution conditions, the high concentration of acetylsalicylic acid in fines can be explained by considering breakage phenomena occurring when impeller speed is higher. These phenomena might be the cause of the layering mechanism detected with SEM image analysis (see Fig. 9). The use of higher liquid flow rate probably led to less homogeneous wetting conditions, thereby promoting the formation of less lubricated areas and leading to more intensive breakage phenomena.

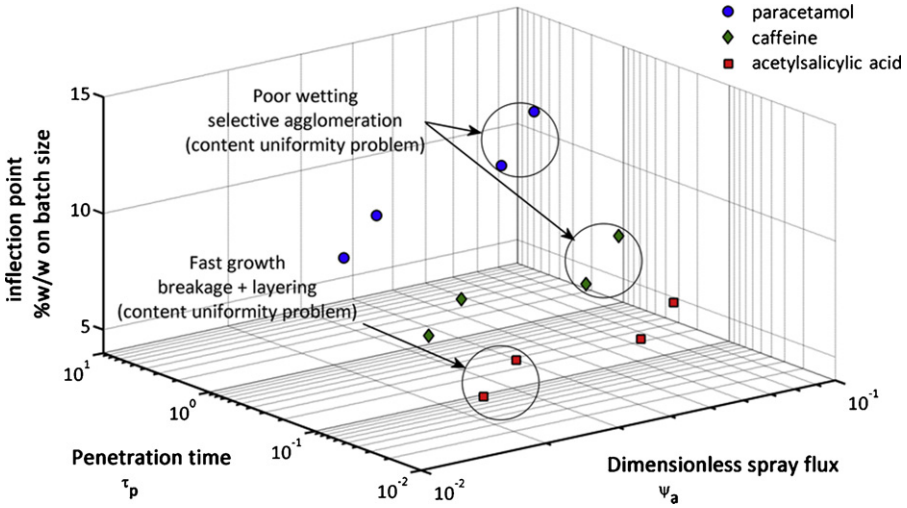

Fig. 12. Liquid amounts required to start the actual granule growth (i.e. inflection point in torque profiles) as a function of the liquid distribution conditions for granulations with different types of active ingredients.

Table 6
Values of the penetration time as a function of the formulation composition and dimensionless spray flux number as a function of process conditions.

	Paracetamol (50%)	Caffeine (50%)	Acetylsalicylic acid (50%)	
Penetration time, t_p (s)	2.43 ± 0.11	0.39 ± 0.03	0.12 ± 0.01	
	LS/LF	LS/HF	HS/LF	HS/HF
Dimensionless spray flux number, ψ_a	0.051	0.076	0.021	0.031

4. Conclusions

The present research was carried out in order to evaluate the influences of some important drug properties (i.e. primary particle size, hygroscopicity and solubility) and process parameters on the granule growth behaviour in high shear wet granulation. Effects on drug distribution in final granules were evaluated as well. Formulations (50%, w/w) of three common drugs (paracetamol, caffeine and acetylsalicylic acid) were granulated.

Inflection point in torque profile was therefore considered as reference point to best quantify the differences between different active ingredients, since this point can be correlated with the start of substantial granule growth. Accordingly, it can be noted that a larger liquid amount is required to allow the start of substantial granule growth during the granulation of paracetamol, which is the drug with the finest PSD. This observation is supported by the comparison between the torque inflection points.

Process conditions resulted to affect the inflection point position especially in the case of granulation with paracetamol. In particular, using lower impeller speed and higher liquid flow rate resulted in a higher liquid amount needed for the inflection point. Since torque inflection point has often been correlated with the start of formation of liquid bridges between primary particles and, thus, the achievement of pendular state, images of granulation samples at different moisture contents were taken with scanning electron microscope (SEM) in order to describe granule growth kinetics. In accordance with torque profile analysis, SEM images showed that the granule growth was slower with decreasing the primary drug size. In fact, a smaller amount of liquid binder was necessary to form first agglomerates containing the drug with the highest mean size (i.e. acetylsalicylic acid).

It was therefore hypothesized that the presence of finer drug particles within the initial formulation led to stronger, poor deformable granules. Thus, poor deformability caused a lower growth rate at low moisture content and then a "ball growth" after a critical amount of water was added.

Granule growth mechanisms resulted to be dependant on the active ingredient type as well. Granules with paracetamol and caffeine resulted to be more spherical than those containing acetylsalicylic acid. Moreover, granules with acetylsalicylic acid were often composed of a bigger, columnar-shaped drug particle as a core and several smaller particles adhered on the core surface as a layer. In this case, granule growth was more likely to occur via a crushing and layering mechanism.

As resulted from sieve analysis, PSDs of paracetamol-based granules obtained under different process conditions were quite dissimilar in terms of mean size and PSD width. In particular, PSD of granules obtained with the lowest impeller speed and highest liquid flow rate resulted to be wider than the others and presented a much lower mean size. On the other hand, granulations with caffeine or acetylsalicylic acid at different process conditions did not lead to noticeable differences between final PSDs.

Concluding, drug distribution in the final product was measured in order to best describe the growth behaviour of the three different formulations. Since each active ingredient showed negligible hygroscopicity and solubility compared to the two main excipients (i.e. lactose monohydrate and microcrystalline cellulose), the risk of selective agglomeration was considerable.

Paracetamol-based granules obtained with the lowest impeller speed and highest liquid flow rate showed more prominent content uniformity problems. Thus, granule growth of excipients particles and paracetamol particles seemed to occur separately. This phenomenon seems to be caused by a worse liquid distribution, as described by the dimensionless spray flux approach.

Analysis of granulations with acetylsalicylic acid showed a higher concentration of the drug in fines when the highest speed and liquid flow rate were used. This fact might be due to a crushing and layering growth mechanism. It was suggested that the highest liquid flow rate value promoted breakage phenomena, probably because of inhomogeneous wetting conditions and thus the presence of less lubricated areas.

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