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The development of a novel formulation map for the optimization of high shear wet granulation

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ABSTRACT

With a view to describing the powder agglomeration process, particles have often been considered as inert material and the solid–liquid interactions have rarely been contemplated.

The present research aims to fill the gap in understanding how the nucleation and the early stage of the granule growth depend on some important formulation properties.

The glass transition concept coupled with on-line impeller torque monitoring and measurements of the time evolution of the particle size distribution was used to give a description of the early stage of the agglomeration process in high shear wet granulation. A mixture of commonly-used pharmaceutical powders, which are amorphous and crystalline in nature, was processed.

Accordingly, a new formulation map is presented which describes the onset of significant granule growth as a function of the key formulation components (i.e. diluent, dry and liquid binder).

From this map, the minimum amount of liquid binder required to induce appreciable granule growth is determined as a function of the type, quantity, hygroscopicity and particle size distribution of the diluent and the solid binder. This map can be obtained from a priori glass transition measurement using a static humidity conditioning system and by fitting the experimentally obtained data using a modified Gordon–Taylor equation.

1. Introduction

The pharmaceutical industry frequently applies high shear wet granulation to a powder mixture in order to improve the particle characteristics, the homogeneity and the flowability properties [1,2]. High shear wet granulation is therefore an example of particle design, since an initial powder mixture composed of a drug and some excipients can be transformed in design structured agglomerates through liquid addition and vigorous mixing [3].

In spite of the importance and the widespread use of this industrial operation, currently it is not completely clear how a change in the process conditions and formulation variables can affect the evolution of the granule properties. Many efforts have been made with a view to engineering the process, splitting up the agglomeration process into different stages, such as the initial granule formation phase or nucleation [4], the granule growth and finally breakage [5]. However, wet granulation has remained in practice more an art than a science, as pointed out by Iveson et al. [6].

Therefore our ability to control the high shear granulation process in order to establish a key factor such as the end-point conditions, for instance, is still an unsolved problem.

Several and varied methods have been explored for this purpose. Briens et al. [7] and Daniher et al. [8] proposed an end-point monitoring technique based on the acoustic emission survey. However, at present, the granulator power consumption and impeller torque monitoring are the most widespread methods to monitor the agglomeration process since they are a direct measurement of the resistance of the wet mass to mixing [9–11]. The power consumption or impeller torque profiles have been traditionally subdivided into different phases, as described by Leuenberger et al. [12]: (1) a first slight increase in the profile, usually related to nuclei formation and moisture sorption, (2) a rapid increase in the profile slope, due to the attainment of the pendular state (formation of liquid bridges), and (3) a plateau phase in the profile which indicates the transition from the pendular to the funicular state. Some authors consider this plateau region as an equilibrium stage between granule growth and breakage, corresponding to optimal granule characteristics [13].

Modern and scientific approaches to granulation understanding aim to split and analyze every single agglomeration phase. In

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Table 1
Formulation composition for the second experimental set.

Experiment	Lactose monohydrate 150 M amount (%, w/w)	Microcrystalline cellulose MCC amount (%, w/w)	Binder type and amount (%, w/w)	Croscarmellose sodium amount (%, w/w)
1	76.0%	20% constant	HPMC, 2.5%	1.5% constant
2	73.5%		HPMC, 5.0%	
3	71.0%		HPMC, 7.5%	
4	68.5%		HPMC, 10.0%	
5	76.0%	20% constant	PVP, 2.5%	1.5% constant
6	73.5%		PVP, 5.0%	
7	71.0%		PVP, 7.5%	
8	68.5%		PVP, 10.0%	

this work we focus on the early stage of the growth phase and on the potential of on-line impeller torque measurements to monitor the granule growth. Whereas most research has been primarily devoted to end-point determination, less effort has been dedicated to the understanding of the granulation onset.

In addition, particles have often been considered inert materials, i.e. interactions between solid particles and liquid have seldom been considered. Notable exceptions are those of a few authors which explained the agglomeration of different powder mixtures as a consequence of increased powder stickiness [14] or a change in the deformability and viscosity of the wet mass [15] when the powder temperature is below the material glass transition temperature.

The aim of this work is to close the gap in understanding how the main formulation properties affect the early stage in the agglomeration of a powder mixture, which is not composed by inert glass beads but by amorphous and crystalline particles. In order to achieve this result, the impeller torque profile analysis has been coupled with the binder glass transition concept. It has been demonstrated that the granulation onset can be identified as an abrupt increase in the impeller torque value when the amount of the added liquid exceeds a critical threshold indicated here as minimum liquid volume (MLV).

The experimental results have been, thus, gathered in a new formulation map which combines the key elements of the powder mixture and gives the minimum liquid volume necessary to start the agglomeration process. It has been also demonstrated how to construct the formulation map using independent measurement of the dry binder glass transition temperature.

2. Materials and methods

Variations of a common, active-free pharmaceutical formulation were considered. The resultant formulations were mixtures of amorphous and crystalline powders.

Lactose monohydrate 150 mesh (Lactochem® Regular Powder 150 M, Friesland Foods, Zwolte, The Netherlands) and microcrystalline cellulose (MCC) (Pharmacel® 101, DMV International, Veghel, The Netherlands) were used as main diluents. Croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer, Philadelphia, USA) was used as disintegrant while the solid binders were hydroxypropylmethylcellulose HPMC (Pharmacoat® 603/Methocel® E5, Shin-Etsu Chemicals, Niigata, Japan) or polyvinylpyrrolidone PVP (Kollidon® K30, BASF, Ludwigshafen, Germany). Excipients were granulated using deionized water at 20 °C.

Experiments were performed in a small scale, top driven granulator (MiPro 1900 ml, ProCepT, Zelzate, Belgium) with a stainless steel vessel, a chopper and a three bladed impeller. Granulator was equipped with a measuring/registering system for impeller torque and powder temperature values during granulation.

The volumetric fill level of the vessel was 40%, for a weight of about 400 g. A premixing stage at 1000 rpm and for 5 min was performed prior each of the granulation experiments. Granulating liquid was added through a tube with a 1 mm diameter by a computer controlled dosimeter.

Two experimental sets were performed. In the first set three granulation experiments were carried out to determine the influence of impeller speed on impeller torque profiles and on particle size distribution of the final granules. At this stage powder mixture composition was held constant and was (on weight basis): lactose monohydrate 150 M (73.5%), microcrystalline cellulose (20%), HPMC (5%) and croscarmellose sodium (1.5%). All the experiments were stopped immediately after liquid addition so that the massing phase was not carried out.

Variable conditions were: the impeller speeds at 500, 850 and 1200 rpm, whereas the total amount of liquid and liquid addition flow rate were always fixed at 100 ml and 10 ml/min, respectively.

A second set of granulation experiments was performed with different formulation compositions under the same process conditions (i.e. impeller speed of 850 rpm, chopper speed of 3000 rpm, total amount of water added of 100 ml and water addition rate of 10 ml/min).

This experimentation was designed to determine the role of the dry binder on the granule growth phase. The changes in the formulation composition involved the binder type (HPMC and PVP) and amount (in the range 2.5–10%, w/w) as shown in Table 1.

Granule samples were taken immediately after the end of the wetting time and dried. Drying was given a special care to preserve as much as possible the granules' size. A first gentle drying was carried out at constant temperature and pressure (20 °C and 1 bar) in a mildly ventilated drying room, and a second drying in an oven for 1 h with a temperature of 50 °C and a pressure of 5 mbar. The wet material was arranged as a thin layer (thickness was about 5 mm). This procedure was followed for minimizing incidental alteration in particle size distribution (PSD) due to the drying method (e.g. attrition in fluid bed dryer, caking in oven at high temperature).

The PSD was characterized by sieve analysis and image analysis. The sieving method consisted on 5 mm of vibration amplitude for a 10 min analysis time. Sieves apertures were: 45, 90, 180, 250, 355, 500, 710, 850 and 1000 μm. Image analysis of granulates was performed using a camera with a 2/3 in. CCD (Jai, CV-300) and interfaced with a Image Tool PC program (ImageTool©, Copyright 2008, Evans Technology, Inc.).

A gravimetric analysis system (IGAsorp, Hiden Isochema, Warrington, UK) was used in order to determine the water sorption isotherm for each formulation component at 25 °C.

Binder samples were kept at different relative humidity grades under nitrogen flow; the weight change of each binder sample during the time course analysis was measured by a hygrometer. The exposure time of each sample to the different humidity grade corresponded to the time at which binder sample weight did not change anymore or otherwise to a maximum time of 12 h.

Curves representing influence of water content on binder glass transition temperature were determined by DSC. HPMC and PVP duplicate samples (about 500 mg) were preconditioned in a atmosphere at given RH%. Samples were weighted and spread as a thin

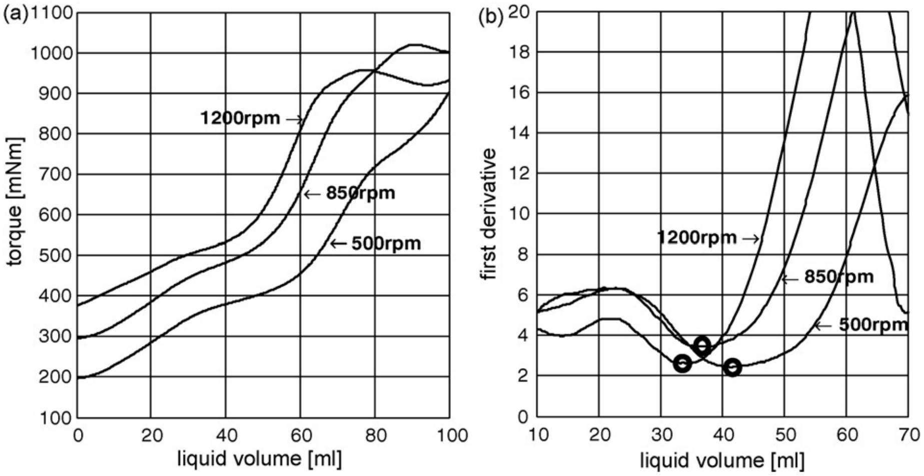

Fig. 1. Results of the first experimental set: (a) impeller torque as a function of the liquid addition at different impeller speed and constant formulation and (b) determination of the points corresponding to the first derivative minimum value (circles).

layer (about 0.5 mm) in a series of 4 hermetic vessels, where the humidity was maintained by saturated salt solutions covering a wide range of relative humidity (11–90% RH). Samples remained in the controlled atmosphere for 7 days. Water content in binder samples was verified using Karl–Fisher titration.

Glass transition temperature for each sample was then measured by temperature modulated differential scanning calorimetry (TMDSC, TA Instruments Q2000, with T_0 technology). TMDSC applied the flowing heating policy: first equilibration stage at 80 °C, then at −50 °C for 5 min (heating rate, respectively 10 and −10 °C/min); then heating up to a maximum temperature of 120 °C (5 °C/min), using a modulation amplitude of ±1 °C every 60 s. Measures were performed using hermetic aluminium pans (T_0 pans), in which 5–10 mg samples were weighted.

3. Results and discussion

The first experimental set was performed to analyze the effect of impeller speed on the shape of torque profiles, at constant formulation.

Fig. 1(a) shows the numerically filtered torque profiles obtained from the first granulation experiments as a function of the added liquid. As can be seen, the shape of the profiles obtained using different impeller speeds is very similar. In accordance with the explanation proposed by Leuenberger et al. [12], the impeller torque profile is a measure of the resistance of the wet mass to mixing and it can be divided into different phases, characterizing different stages during the agglomeration process. Firstly, the torque value increases almost linearly with the water addition, suggesting a progressive densification of the wet mass. A decrease in the slope is then observed, which can be explained by an increased lubrication of the mass which causes a decrease of the stresses on the impeller. A sudden increase in the slope can be noted when the added water volume is larger than a critical value. This abrupt increase in the slope denotes the formation of the liquid bridges and the achievement of the pendular state.

In order to best identify the liquid volume required to obtain the pendular state, the first derivative was calculated and plotted as a function of the added liquid in Fig. 1(b). As can be noticed in Fig. 1(b), the minimum value in the first derivative profile does not strongly depend on the impeller speed, suggesting it may depend mainly on the formulation properties.

In order to monitor the PSD evolution during the agglomeration, image analysis was used to obtain a more accurate description of the agglomeration phase. The operative conditions of the middle curve in Fig. 1(a) (that at 850 rpm) have been chosen as a reference and several samples have been collected during the granulation at different moisture contents (20, 40, 60, 80% of water addition). Since the dimension of collected samples were too small (1–2 g) to perform a sieve analysis, images of the samples were taken with a digital camcorder interfaced to an image analysis program. The binary images of the samples can be observed in Fig. 2 and compared with torque and torque first derivative profiles. The simple visual inspection of the images shows that a substantial increase of the size of the granules occurs after the addition of 40% out of 100 ml of water which correspond to the minimum in the derivative profile.

In order to confirm this behaviour and to consider the particle size distribution of the whole batch (not just of a small sample), the experiment was repeated and stopped after the addition of two different quantities of liquid (40 and 100 ml, respectively). Sieve analysis was carried out in order to compare the PSDs. Point A in Fig. 3(a) was obtained interrupting the experiment at the condition of minimum value in the derivative profile. Whereas point B represents the condition immediately after all the liquid was added. Fig. 3(b) shows the corresponding PSDs (the PSD of the dry formulation has been also added). As can be noted in Fig. 3(b), there is a negligible difference between the PSD of the dry formulation and the PSD obtained at point A. A substantial difference between the point A and the point B can be instead appreciated, thus indicating that most of the granulation process occurs after the point A.

As can be inferred from Figs. 2 and 3, the point A corresponds to the liquid volume required to increase significantly torque value (i.e. minimum in the first derivative profile) and in this sense can be considered as the minimum liquid volume (MLV) required to start most granulation process.

Similar results were presented by some authors, for example by Ritala et al. [16]: dicalcium phosphate was granulated with different binder solutions observing an abrupt increase in mean granule diameter when the liquid saturation exceeded certain specific values.

It is also interesting to note the role of the dry binder on the torque profile shape and on the PSD obtained at the end of the experiment. As shown in Fig. 4(a), the impeller torque profile obtained without the dry binder does not show the sudden increase in the slope of the torque profile after about 40 ml. As a matter of fact, the PSD of the product without the dry binder is very similar to the PSD of the initial dry formulation thus indicating an unimportant and slower agglomeration process (compare PSDs in Fig. 4(b)).

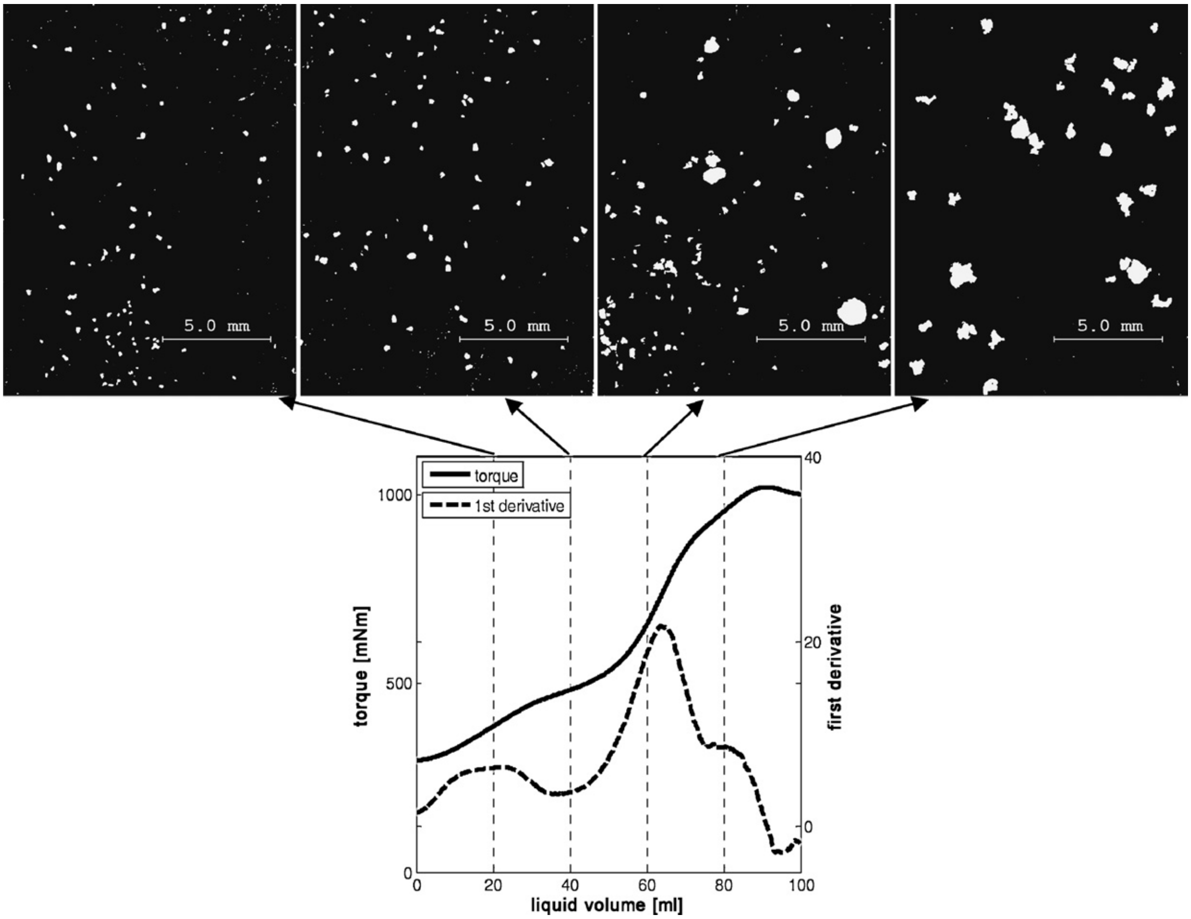

Fig. 2. Effect of the moisture content on the granule size evolution during the granulation process: pictures of the granules show a negligible growth until the about 40 ml, whereas larger agglomerates can be counted after this point.

Having identified the MLV as a marker of the granulation onset, the second part of the experimentation has been designed to understand the impact of the formulation components on the MLV (as detailed in Table 1).

Particularly, two dry binder types (HPMC and PVP) at different amounts (i.e. from 2.5 to 10%, w/w) were tested within the formulation of the first experimental set.

Figs. 5 and 6 summarize the results obtained in terms of first derivative of the torque profiles, with the two binders at various concentrations. MLVs were determined as local minimum of the first derivative. Figs. 5 and 6 also report the PSD measured (sieve analysis) at the end of the granulation experiments. The relatively large weight fraction on the 1000 μm sieve was partially due to caking in the oven at high temperature.

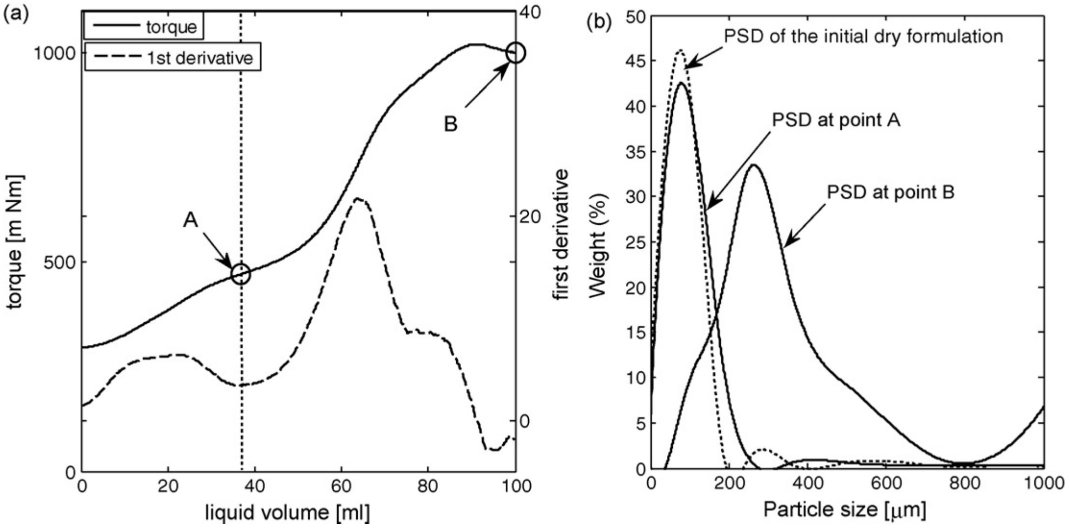

Fig. 3. Results of the sieve analysis carried out in order to compare the PSD at point A (before the sudden increase in the slope) with the PSD at the end of the experiment.

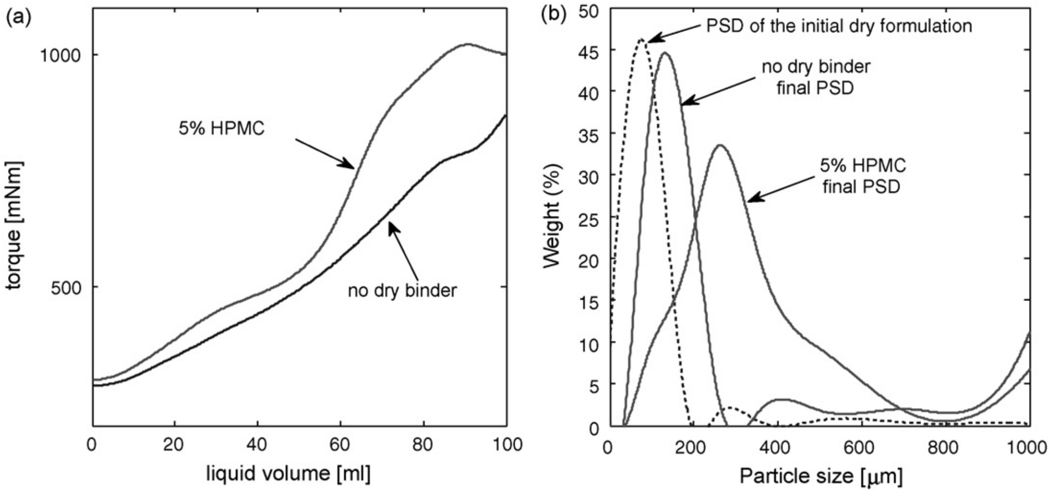

Fig. 4. Comparison between the granulation experiments carried out with or without the dry binder: (a) comparison between the torque profiles and (b) the PSDs at the end of the granulation process.

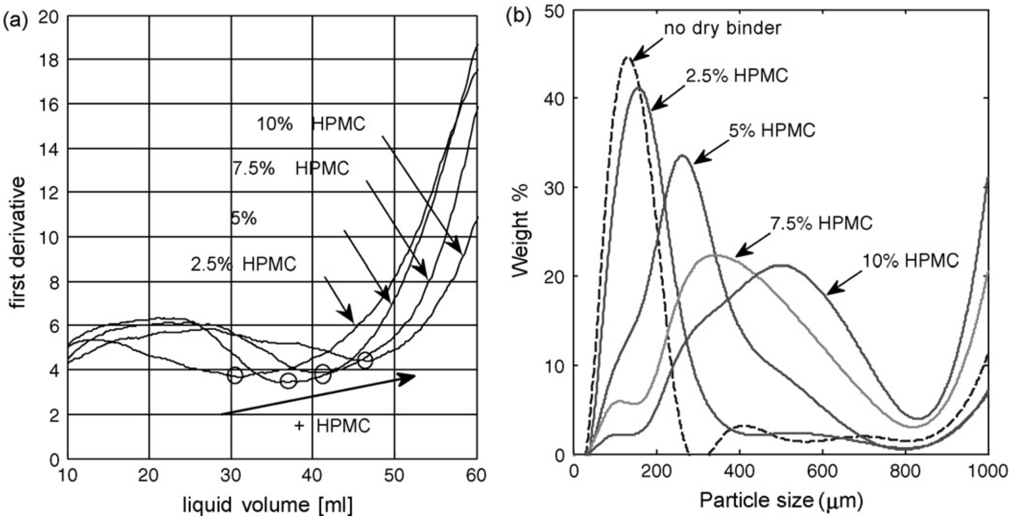

Fig. 5. Effect of different concentration of (a) HPMC on MLV determination and (b) PSD at the end of the granulation experiments.

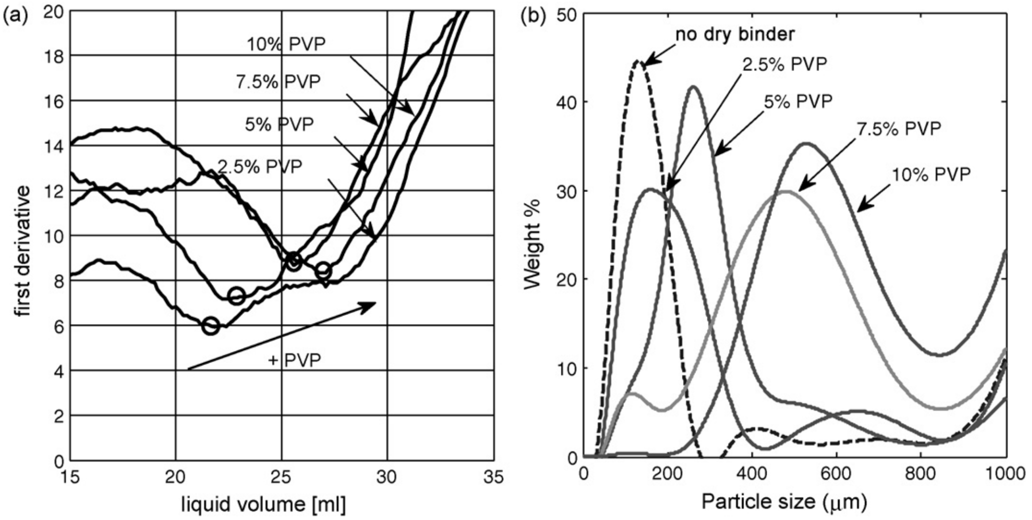

Fig. 6. Effect of different concentration of (a) PVP on MLV determination and (b) PSD at the end of the granulation experiments.

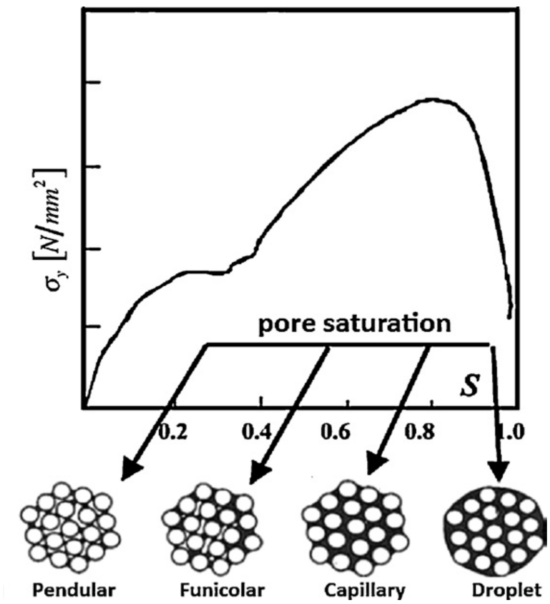

Fig. 7. Static yield strength of the wet granule as a function of the pore saturation [2,17].

As can be appreciated, the onset of granulation is delayed with increasing the binder amount (that means a higher amount of liquid is required), with both HPMC and PVP. MLV increase is larger for HPMC than PVP.

In addition, the rate of torque increase with PVP is higher than that with HPMC (Figs. 5(a) and 6(a)). It is suggested that this fact is due to a more relevant hygroscopicity of the PVP powder as compared with HPMC. The higher hygroscopicity determines a faster formation of a viscous solution.

The comparison between the PSDs of the final granules obtained using various dry binder concentrations highlights the essential role of the dry binder in the agglomeration process.

In order to explain the dissimilar growth behaviour due to a different dry binder concentration, the scheme in Fig. 7 can be considered. It represents the static yield strength of the wet granules as a function of the pore saturation [2,17].

As pointed out by Leuenberger et al. [12], the point A (see Fig. 3) indicates the achievement of the pendular state. This state of pore filling causes the formation of the first liquid bridges and the beginning of the granule growth.

However powder particles can be composed by crystalline or amorphous material or both. Adding water means decreasing the glass transition temperature of the amorphous material since water is a strong plasticizer. When the powder temperature is close to the glass transition temperature, the molecular mobility increases and leads to the migration of the amorphous material into the water on the particle surface. The increase in viscosity of the material on the particle surface causes a significant increase in stickiness which promotes the agglomeration process [14,15].

The penetration of the water into the capillaries leads to the achievement of the pendular state and, in presence of an amorphous material, the starting of stickiness (point A in Fig. 3).

Palzer [18] described the strength of the adhesion forces as a sum of two contributes: the hygro-capacity (or hygroscopicity) and the hygro-sensitivity of the powder. The hygro-capacity is the ability to bind water by absorption in the molecular matrix or on the surface area, whereas the hygro-sensitivity is a marker of the increase in the viscosity due to the absorbed water.

Accordingly, amorphous water-soluble particles absorb important amounts of water (high hygro-capacity) and the variation of their visco-elastic properties is usually considerable (high hygro-sensitivity). On the other hand, the water amount in crystalline powders generally increases slightly with the relative humidity and their mechanical properties do not change (below the solubilization conditions). Moreover, the dissolution process of crystalline structures is much slower due to the lower permeability of the crystalline matrix and the endothermic dissolution process [19].

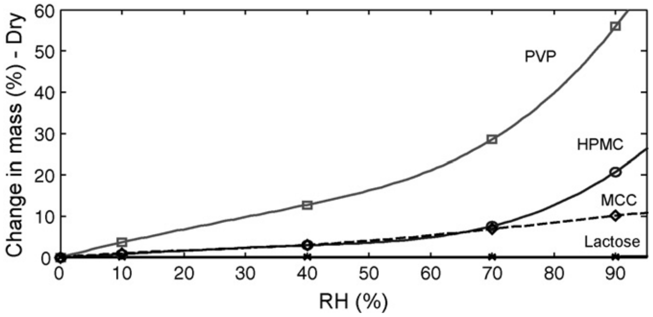

Fig. 8. Sorption isotherms (25 °C) of the formulation components: PVP (squares), HPMC (circles), MCC (diamonds) and lactose monohydrate (crosses).

The processed formulation presented:

- Two main fillers: lactose monohydrate (mainly crystalline, water-soluble) and MCC (mainly crystalline, water-insoluble).
- Dry binder: HPMC or PVP (both amorphous, water-soluble).

The hygro-capacity of the formulation components can be described by the water sorption isotherms in Fig. 8.

The dry binder, amorphous and water-soluble in nature, presents a higher hygro-capacity and a much higher hygro-sensitivity in comparison to the fillers. For this reason the dry binder (HPMC or PVP) can be considered as the most important binding agent and the two fillers can be considered as a sole diluent, which absorbs water but has a weakly binding strength. As can be noticed in Fig. 8, PVP presents a higher hygro-capacity (or hygroscopicity) than HPMC. It is suggested that this fact leads to an advance formation of the viscous bridges (Figs. 5(a) and 6(a)).

In order to separate and quantify the effect of the key formulation components on the MLV, a triangular formulation map has been proposed (Fig. 9): the combinations of the main formulation

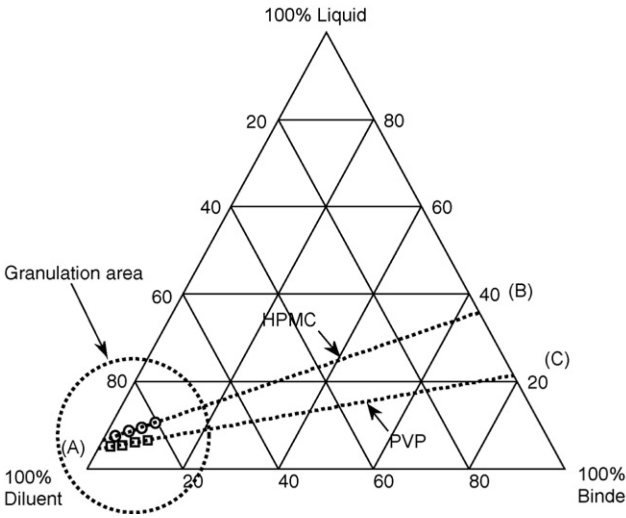

Fig. 9. Formulation map: representation of the effect of the main formulation components on MLV through a ternary diagram. Each vertex represents a key component: the main diluent (lactose monohydrate and microcrystalline cellulose), dry binder (HPMC or PVP) and liquid (water). The MLV are experimentally determined in presence of HPMC or PVP and are marked with circles and squares, respectively.

components (diluent, dry binder and liquid binder) can be effectively represented in the ternary diagram where each component is pure in a vertex.

Dry formulation composition can be identified as a point on binder–diluent axis. With the addition of water, the point representing the actual composition of the granulation system moves from the binder–diluent axis towards the liquid vertex.

MLV experimentally measured from Table 1 experiments (Figs. 5 and 6) are represented in the ternary diagram by some markers (HPMC = circles; PVP = squares).

As can be observed in Fig. 9, the markers arrange in two straight lines. Each line represents a specific diluent–dry binder–liquid system and intersects the diluent–liquid and the binder–liquid axes.

Interestingly, the HPMC line and PVP line intersect the diluent–liquid axis very close to each other, outlining point A in Fig. 9. This point represents the water amount absorbed by the fillers and therefore not available for the dry binder. On the other hand, the intersection between the straight line and the binder–liquid axis appears to be strongly binder-specific. This difference clearly denotes a different dry binder–water interaction.

According to the previous explanation in the light of the glass transition concept, the agglomeration process of the powder mixture can be described as follows:

(1) Absorption of the granulating liquid and nucleation: the nuclei formation phase can be described by the nucleation regime map proposed by Litster et al. [20].
(2) Water is split up among the formulation components on the basis of the hygro-capacity of each component.
(3) Water absorbed by the dry binder works as plasticizer and decrease the dry binder glass transition temperature T_g.
(4) When the water addition decreases binder T_g to equal the powder temperature (i.e. ambient temperature), the binder becomes sticky, the impeller torque value rapidly increases and the growth accelerates. The bridges between the particles are mainly due to the stickiness, which causes stronger attractive interactions between the surfaces.

As pointed out by Iveson et al. [6], the liquid may not have enough time to reach the equilibrium state therefore the maximum water amounts absorbed from diluent and binder (steps 2 and 3) are not equilibrium values: it is hypothesized that agreement between the theoretical equilibrium value and the actual absorbed water amount mainly depends on the different component hygro-capacity (Fig. 8) and on the water sorption kinetics, which is also affected by the mixing energy and efficiency.

In order to determine the effect of water content on HPMC and PVP glass transition temperatures, dry binder samples have been maintained in closed vessel at different relative humidity, as explained above. The curves representing glass transition temperature as a function of the equilibrium water content for HPMC and PVP are shown in Fig. 10.

Glass transition temperature of wet binder sample can be roughly estimated using Gordon–Taylor equation [21]:

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \tag{1}$$

where k is an empirical constant, T_{g1} is the dry binder glass transition temperature, T_{g2} is the water glass transition temperature ($-138\,^\circ$C), w_1 and w_2 are, respectively the binder and water weight fractions (with $w_1 = 1 - w_2$).

k values for different binder types have been calculated for example by Hancock and Zografi [22]. In the same work, Hancock and Zografi [22] proposed a modified Gordon–Taylor equation in order to best fit the experimental data: this equation introduces an additional quadratic parameter in Eq. (1). The resulting T_g is:

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} + q w_1 w_2 \tag{2}$$

where q is an empirical constant reflecting the specific binder–water interaction.

Assuming the reference condition:

$$T_g = T_a \approx T_{\text{powder}}, \tag{3}$$

where T_a is the ambient temperature expected to be equal to the powder temperature T_{powder}, the corresponding water content w_2^* can be expressed as follows:

$$w_2^* = w_2(T_g \approx T_{\text{powder}}), \tag{4}$$

This water amount is the quantity needed for the dry binder glass transition and the formation of a highly viscous mixture.

Experimental and literature data [22] in Fig. 10 were fitted to Eq. (2). As can be seen in Fig. 10, the intersection between the glass tran-

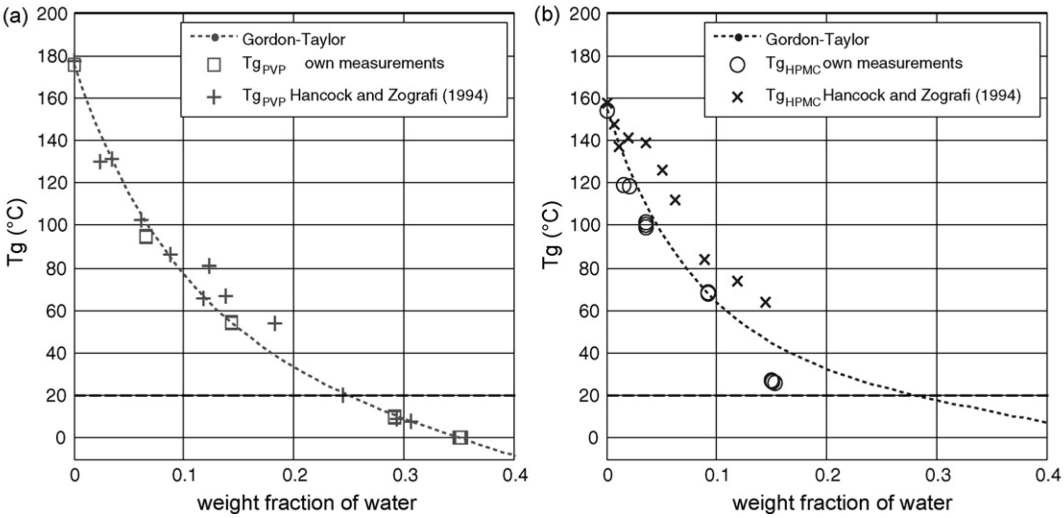

Fig. 10. Glass transition temperature as a function of water content in samples of (a) PVP and (b) HPMC: comparison between the experimental data, literature [22] and the dotted line representing experimental data and literature fitted to modified Gordon–Taylor model [22].

sition curves and the ambient temperature gives the water amount required to obtain the dry binder glass transition.

It can be noted in Fig. 10 that the literature and the experimental data for the PVP are in agreement, thoroughly fitted to the modified Gordon–Taylor model. The moisture content required for the glass transition is furthermore in agreement with the water amount identified by point (C) in Fig. 9 (respectively 0.24 in Fig. 10 and 0.22 in Fig. 9). The point (C) can thus be easily determined using static T_g measurements. As a first estimation, the water amount absorbed by the hygroscopic diluent components in point (A) can be measured from Fig. 8: the RH% at which the PVP glass transition occurs (corresponding to the water content w_2^*) can be considered as a reference condition for the identification of the contribution of each hygroscopic component.

Regarding the HPMC glass transition temperatures, the agreement between experimental and literature data is fairly satisfactory except for the last experimental measurement (water weight fraction of about 0.15). Moreover, the maximum attainable moisture content for a HPMC sample in static conditions at 90% is about 0.20. This fact leads to a lower number of experimental points at high moisture contents compared to the PVP–water system. For this reason the data fitting for HPMC is not as suitable as for PVP. This fact could explain the discrepancy between the moisture content required for the glass transition and the point (B) (respectively about 0.29 in Fig. 10 and 0.36 in Fig. 9). The delay in the actual moisture content – point (B) – compared to the equilibrium value obtained with static measurements could also be explained by considering the non-ideal water sorption kinetics in the granulator, which depends on many variables, e.g. the mixing energy, the nucleation conditions, the competition between the diluent and the binder in the water sorption mechanism and in the binding process. Since the mixing energy can be optimized in order to get a good liquid distribution [20], the competition between the diluent and the dry binder in the water sorption kinetics plays an important role. It follows that the competition is less critical when the dry binder is much more hygroscopic and hygro-sensitive than the diluent (e.g. PVP as dry binder). Whereas the diluent hygroscopicity is comparable to the dry binder hygroscopicity, the water sorption competition is more complex and needs further investigation to elucidate its role on the MLV determination.

4. Conclusions

The present research analyzes the role of some important formulation properties (e.g. glass transition temperature, hygroscopicity) on the early stage of the granule growth during a high shear wet granulation process. A pharmaceutical powder mixture containing amorphous and crystalline particles was processed. The agglomeration process was monitored using on-line impeller torque measurements and systematic PSD analysis (sieve and image analysis).

The analysis of the torque profiles plotted as a function of the added water revealed the presence of a minimum liquid volume (MLV) required to strongly increase the torque value (i.e. the resistance of the wet mass to mixing) and to start most of the granule growth. The MLV was then chosen as a reference point and then a detailed study of the role of the powder properties in the granulation mechanism was carried out. As a result of this research, the initial powder mixture was ideally split into two main components (diluents and dry binder) according to their expected hygro-capacity and hygro-sensitivity [15].

A new formulation map was therefore proposed in order to simplify the granulation system: a ternary diagram, through a graphical construction, identifies the moisture content required to make the dry binder sticky (i.e. required to yield the binder glass transition) and the water amount absorbed by the diluent. The initial dry formulation is represented by a point on the diluent–dry binder axis.

The interactions between the dry binders (HPMC and PVP) and water were analyzed performing independent measurements of the glass transition temperature at different moisture content and fitting the experimental data with a Gordon–Taylor based equation. The water sorption isotherm for each formulation component was measured as well. A method for obtaining the most important points on the edges of the formulation map using these independent measurements has therefore been proposed.

Results show that it is possible to carry out an early assessment of the minimum liquid volume required to start most of the granule growth through an application of a Gordon–Taylor model and performing some independent measurements of the initial formulation properties. It has been demonstrated that the procedure can easily be applied when the dry binder is clearly more hygroscopic and hygro-sensitive than the diluent. On the other hand, the competition dry binder/diluent in the water sorption might promote discrepancies between the actual and the predicted-equilibrium based values. In spite of these last considerations, the method proposed in this work can be considered a helpful tool for the formulation design and has a considerable potential to increase the predictability of the granule growth behaviour as a function of the formulation composition.

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