Formulation design for optimal high-shear wet granulation using on-line torque measurements

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ABSTRACT

An alternative procedure for achieving formulation design in a high-shear wet granulation process has been developed. Particularly, a new formulation map has been proposed which describes the onset of a significant granule growth as a function of the formulation variables (diluent, dry and liquid binder). Granule growth has been monitored using on-line impeller torque and evaluated as changes in granule particle size distribution with respect to the dry formulation. It is shown how the onset of granule growth is denoted by an abrupt increase in the torque value requires the amount of binder liquid added to be greater than a certain threshold that is identified here as 'minimum liquid volume'. This minimum liquid volume is determined as a function of dry binder type, amount, hygroscopicity and particle size distribution of diluent. It is also demonstrated how this formulation map can be constructed from independent measurements of binder glass transition temperatures using a static humidity conditioning system.

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1. Introduction

Pharmaceutical high-shear wet granulation consists in agglomeration of different particles through liquid addition and vigorous mixing. The typical formulation consists of an active ingredient (API), one or more diluents (which are also called fillers) in powder form and a polymeric binder, added as dry powder in the initial mix or dissolved in the granulating liquid (Ennis, 2006; Holm, 1997). Granulation is used to mask unfavourable properties of a drug; primarily to prevent segregation of the constituents of the powder mix, to improve the flow properties and compaction characteristics of the mix (Litster and Ennis, 1999; Ennis, 2006). It is usually performed in three phases (Gokhale et al., 2006): (1) homogenization of dry powders; (2) liquid addition; (3) wet massing with liquid feeding system switched off. Granulation can be affected by a number of variables, including process parameters as well as material properties.

Currently it is not completely clear how to correlate process and formulation parameters with granule properties evolution. Furthermore, initial granule formation phase and subsequent growth/breakage mechanisms are not completely understood. This situation has made the prediction of granule properties and thus of the process end-point difficult, as pointed out e.g. by Faure et al. (2001) and Mort (2005). As such, there is a need to gain a better understanding of the granulation process in order to produce a consistent product from batch to batch.

A variety of process monitoring methods has been explored for this purpose. Acoustic emission for example has shown possibilities for granulation end-point detection (Briens et al., 2007; Daniher et al., 2008). However, at present, power consumption or impeller torque value is the most widespread methods to monitor the agglomeration process from the initial granule formation phase (Landin et al., 1995, 1996; Betz et al., 2004). Granulation process evolution described in terms of power consumption and impeller torque profiles has been traditionally subdivided in different phases (Leuenberger et al., 2009). A first slight increase in power consumption or torque value is usually related to nuclei formation and moisture sorption without the formation of liquid bridges. This stage precedes a rapid increase in the profile slope, due to the attainment of the pendular state (formation of liquid bridges). A subsequent plateau phase in the profile 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 (Leuenberger, 1982).

Some recent research trends focused on each single agglomeration phase, such as nucleation (Wildeboer et al., 2005) and growth (Tardos et al., 1997, 2004; Tardos, 2005).

Nevertheless the attention has been primarily devoted to end-point determination whereas less effort has been put on the

Table 1
Formulation composition for granulation trials with different binder type and amount.

Experiment	Diluent type and amount (% w/w)	Microcrystalline cellulose (MCC) amount (% w/w)	Binder type and amount (% w/w)	Croscarmellose sodium amount (% w/w)
1	Lactose monohydrate 150 M, 76.0%	20%	HPMC, 2.5%	1.5%
2	Lactose monohydrate 150 M, 73.5%	20%	HPMC, 5.0%	1.5%
3	Lactose monohydrate 150 M, 71.0%	20%	HPMC, 7.5%	1.5%
4	Lactose monohydrate 150 M, 68.5%	20%	HPMC, 10.0%	1.5%
5	Lactose monohydrate 150 M, 76.0%	20%	PVP, 2.5%	1.5%
6	Lactose monohydrate 150 M, 73.5%	20%	PVP, 5.0%	1.5%
7	Lactose monohydrate 150 M, 71.0%	20%	PVP, 7.5%	1.5%
8	Lactose monohydrate 150 M, 76.0%	20%	PVP, 10%	1.5%

understating of the granulation on-set. In addition, particles have been often considered inert materials, i.e. interactions between solid particles and liquid have been rarely contemplated. As an attempt to correlate physical and chemical interactions between liquid and solid with the mechanical behaviour of the wet constituents, Palzer (2005) used the concept of glass transition to describe desired and undesired agglomeration in amorphous powders.

In this paper the glass transition concept coupled with on-line impeller torque measurements has been used to give a description of the early stage of the agglomeration process in high-shear wet granulation process, and particularly the onset of significant granule growth, here identified as granulation onset. It has been demonstrated that the granulation onset can be identified as abrupt increase in torque when the amount of binder liquid added exceeds a certain threshold indicated here as minimum liquid volume (MLV).

In particular, a new formulation map has been developed which combines the key elements of the formulation, namely diluent, dry binder and liquid binder (note that water which can be viewed also as granulation process parameter is regarded here only in light of its properties as binder). From this map the minimum liquid volume necessary for appreciable granule growth is a function of formulation composition. It is also shown how this formulation map can be constructed from independent measurements of dry binder glass transition temperatures using a static humidity conditioning system.

2. Materials and methods

Variations of a common active-free pharmaceutical formulation were chosen as materials for the study due to their standard and well-known characteristics.

Lactose monohydrate 60 mesh (Capsulac® 60, Molkerei Meggle Wasserburg GmbH & Co. KG, Wasserburg, Germany), lactose monohydrate 150 mesh (Lactochem® Regular Powder 150 M, Friesland Foods, Zwolte, The Netherlands), lactose monohydrate 200 mesh (Pharmatose® 200 M, DMV-Fonterra Excipients, Nörten-Hardenberg, Germany), lactose monohydrate 400 mesh (Sorbolac® 400, Molkerei Meggle Wasserburg GmbH & Co. KG, Wasserburg, Germany), and microcrystalline cellulose (MCC) (Pharmacel® 101, DMV International, Veghel, The Netherlands) were used as diluents. Croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer, Philadelphia, USA) was used as disintegrants while

the solid binders were hydroxypropylmethylcellulose (HPMC) (Pharmacoat® 603/Methocel® E5, Shin-Etsu Chemicals, Niigata, Japan) and 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 vessel volume, 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. Formulation was composed of two diluents (lactose and cellulose), a solid binder and a disintegrant. The fill level of the vessel was about 40% and the total mass of powder was 400 g for each experiment. All the experiments have been stopped immediately after liquid addition so that the massing phase was not performed. Granulating liquid was added through a tube with a 1 mm diameter by a computer-controlled dosimeter.

Two sets of experiments have been conducted. First, three granulation experiments have been carried out to determine the influence of the impeller speed on the shape of the torque profiles and the particle size distribution of the final granules at constant formulation. The formulation (on a weight basis) consisted of approximately: lactose monohydrate 150 M (73.5%), microcrystalline cellulose (20%), HPMC (5%) and croscarmellose sodium (1.5%). The process parameter values were set as follows: the impeller speed at 500, 850 or 1200 rpm, whereas the total amount of liquid and liquid addition flow rate have always been fixed at 100 ml and 10 ml/min respectively.

A second set of granulation experiments has been 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), in order to determine the influence of formulation variables on impeller torque profiles and particle size distribution of granules after liquid addition, for a total of 11 runs.

Changes in formulation composition involved binder type (HPMC or PVP) and amount (in the range of 2.5–10.0%, w/w) as detailed in Table 1 and main diluent (i.e. lactose monohydrate) PSD as indicated in Table 2.

Granule samples were taken immediately after the end of the wetting time and dried. Drying was performed in two ventilated phases: a first gentle drying in oven for 10 h with ambient temperature and pressure (20 °C and 1 bar), and a second drying in oven for 1 h with a temperature of 50 °C and a pressure of 5 mbar. This procedure was followed for minimizing incidental alteration in par-

Table 2
Formulation composition for granulation trials with lactose monohydrate having different particle size distribution.

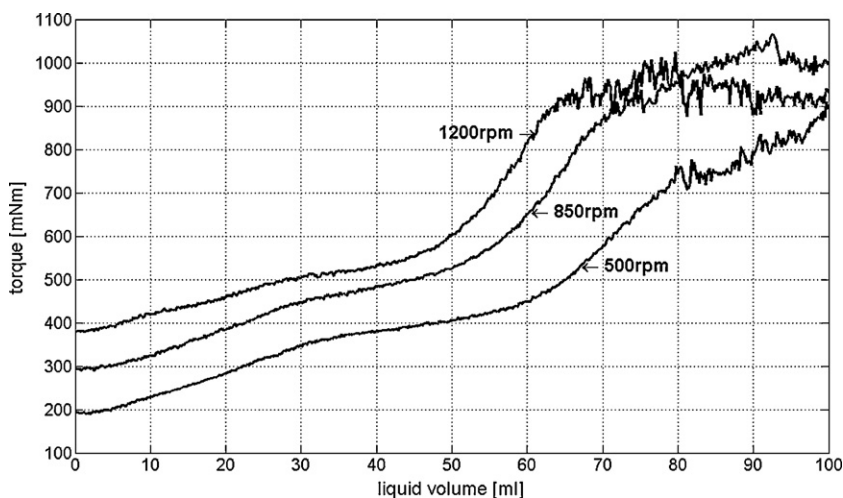| Experiment	Diluent type and amount (% w/w)	Microcrystalline cellulose amount (% w/w)	Binder type and amount (% w/w)	Croscarmellose sodium amount (% w/w)
9	Lactose monohydrate 60 M, 73.5%	20%	HPMC, 5.0%	1.5%
10	Lactose monohydrate 200 M, 73.5%	20%	HPMC, 5.0%	1.5%
11	Lactose monohydrate 400 M, 73.5%	20%	HPMC, 5.0%	1.5%

Fig. 1. Effect of impeller speed on impeller torque profiles. Torque data obtained during the first set of granulation experiments (see Table 1) plotted versus the amount of liquid added. The formulation is same for all the runs (i.e. 73.5% (w/w) lactose monohydrate 150 M, 20% (w/w) microcrystalline cellulose, 5% (w/w) HPMC and 1.5% (w/w) croscarmellose sodium).

ticle size distribution due to drying method (e.g. attrition in fluid bed dryer, caking in oven at high temperature).

Granules particle size distribution was characterized by sieve 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.

Water sorption isotherms at 25 °C for HPMC and PVP were determined using a gravimetric analysis system (IGAsorp, Hiden Isochema, Warrington, UK). 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 of 12 h.

Curves representing influence of water content on binder glass transition temperature were determined as follows: HPMC and PVP duplicate samples were kept in a series of 4 hermetic vessels arranged with saturated salt solutions covering a wide range of relative humidity (11–95% RH): about 500 mg samples were weighted and spread through a thin layer (about 0.5 mm). Glass transition

temperature for each sample was measured by temperature modulated differential scanning calorimetry (TMDSC) (TA Instruments Q2000, with T_0 technology). TMDSC experimental procedure was as follows: after a first equilibration stage at 80 °C and then at −50 °C for 5 min (heating rate respectively 10 °C/min and −10 °C/min). Samples were taken to a maximum heating temperature of 120 °C with a 5 °C/min heating rate, 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. Water content in binder samples was measured using the Karl–Fisher method.

3. Results and discussion

Impeller torque profiles obtained from the first set of experiments (i.e. at constant formulation) are shown in Fig. 1 as a function of the added liquid, for three different impeller speeds (500, 850 and 1200 rpm). As can be noticed, plotting torque values versus liquid volume instead of time as typically performed, the shape of the profiles obtained with different impeller speed is very similar. It is also
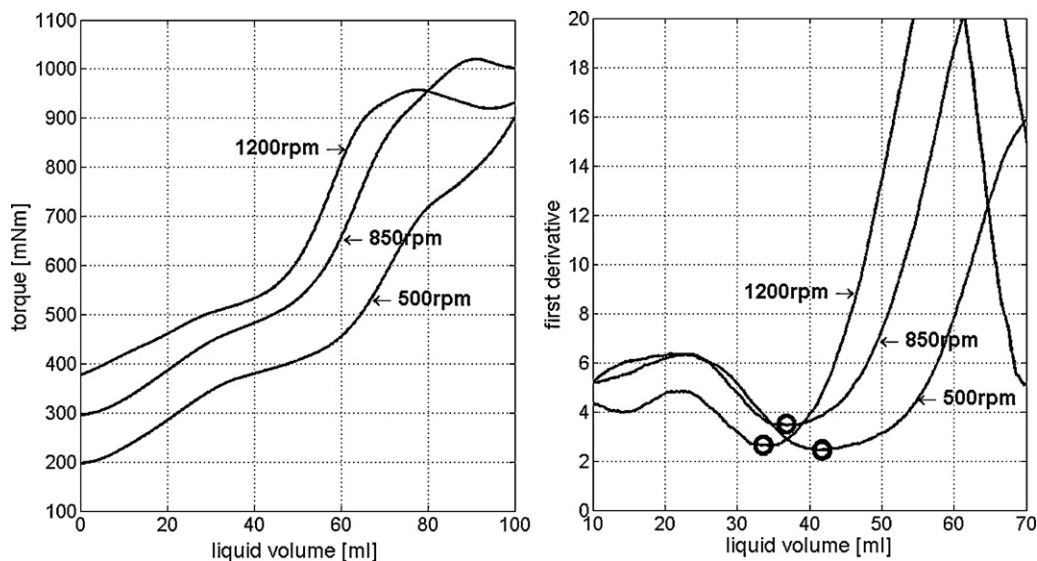

Fig. 2. (a) Effect of impeller speed on the impeller torque profiles of Fig. 1 after numerical filtering and corresponding (b) first derivatives with minimum value determination (circles).
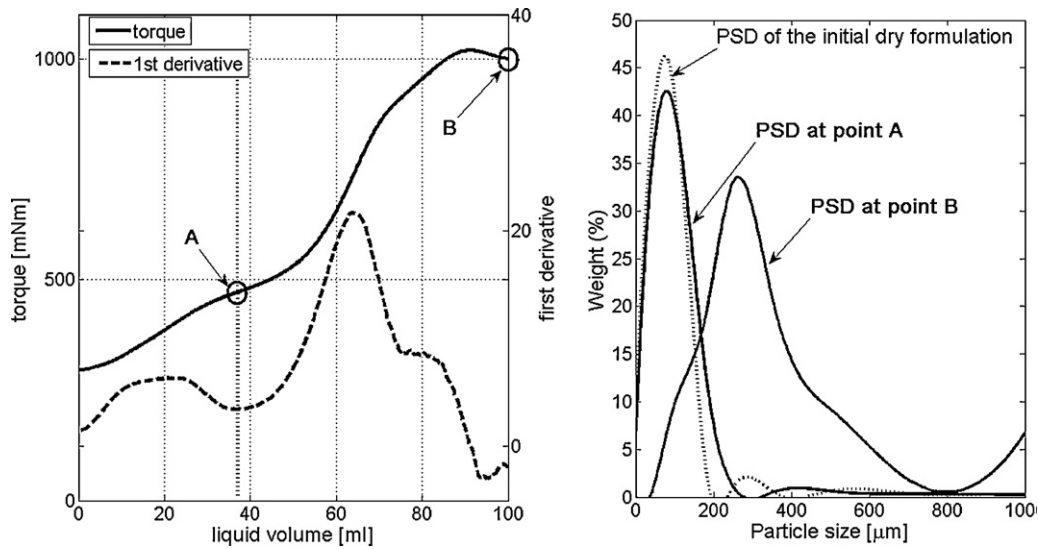
Fig. 3. Correlation between torque and granule particle size distribution: (a) impeller torque profile and corresponding first derivative (dashed line) obtained adding 40 ml of water (up to point A) and 100 ml of water (up to point B) and (b) granule PSD obtained at point A and at point B of (a) and comparison with PSD of dry formulation (dashed line).

evident that torque increases almost proportionally with increasing the stirring speed. This may suggest identifying a scaling factor for the impeller speed which, for a given formulation, allows all the profiles to collapse on a single master curve, greatly reducing the number of experiments to be run as it has been performed for the dry phase by Knight et al. (2001).

Focusing on the shape of the profiles in Fig. 1, it can be seen that initially the torque value increases slightly and linearly with the amount of liquid, indicating a progressive densification of the mixture. A decrease of the slope is then observed, in all cases, which is interpreted as lubrication of the mass, which reduces the strength of the bulk and consequently the stress on the impeller. When the volume of the added water is larger than a certain value, an abrupt increase in torque occurs.

As can be seen in Fig. 1, the torque profiles can be rather noisy. In order to obtain a precise determination of the torque value corresponding to the steep increase in the profile, the torque curves have been numerically filtered. The resulting profiles are shown in Fig. 2a. The first derivative was then calculated and also plotted as a function of the added liquid in Fig. 2b. A minimum in the curves

can be visibly located just before the steep torque increase (marked by the circles in Fig. 2b). The corresponding liquid volume has been identified as the minimum liquid volume (MLV) required to yield substantial agglomeration of the mass for a given operating condition. MLV will be used in the following as a distinctive, clearly identifiable and reproducible feature of the granulation process.

In the second set of experiments the impeller velocity of 850 rpm (middle curve in Fig. 2a) has been chosen as reference. To monitor the evolution of the PSD during the granulation process, this experiment has been run in duplicate; once stopped after the addition of 40 ml of liquid only (point A in Fig. 3a) and the other after the addition of the entire amount of water of 100 ml (point B in Fig. 3a).

The granules obtained from both trials have been sampled for PSD determination. The PSD of these two trials have then been compared with the PSD of the initial dry formulation in Fig. 3b.

As can be seen in Fig. 3b, the PSD of the granule obtained with 40 ml of liquid (curve A) is almost superimposable to the PSD of the initial dry formulation (dashed curve in Fig. 3b). On the contrary, a significant deviation from the dry formulation is observed with the PSD obtained with 100 ml of added liquid (curve B). This observa-
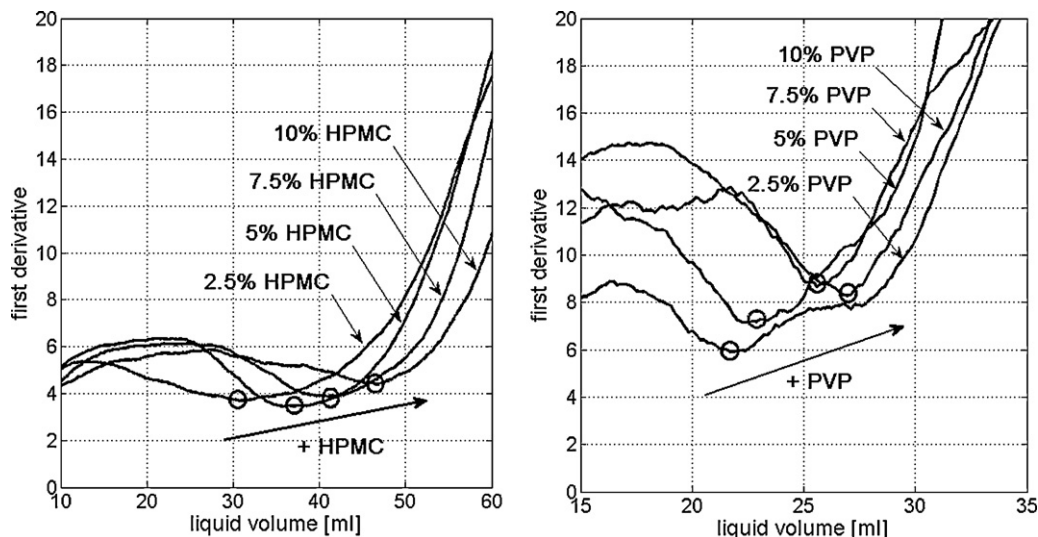

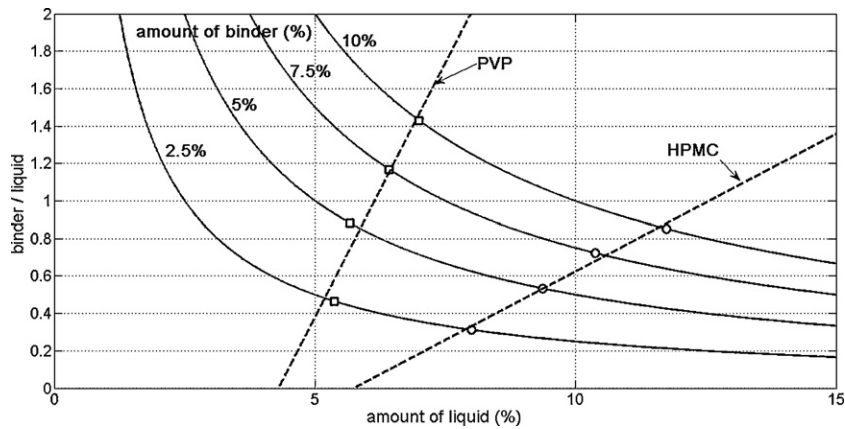**Fig. 4.** Effect of different concentration of HPMC (a) and PVP (b) on MLV determination.

Fig. 5. Determination of on-set conditions for granule growth according to the type (HPMC or PVP) and amount of binder and liquid added. The ratio between the amount of binder and liquid is plotted against the amount of liquid for different binder concentrations. The MLV determined experimentally for PVP and HPMC is also displayed (squares and circles respectively).

tion indicates that most of the agglomeration process occurs after 40 ml of liquid are added to the system. Remarkably, 40 ml corresponds to the liquid volume required to increase significantly the torque value (Fig. 2b) and consequently can be considered as the minimum liquid volume (MLV) required to start most granulation process. Similar conclusions could be deduced from the experimental data presented for example by Ritala et al. (1988): dicalcium phosphate was granulated with different binder solutions observing an abrupt increase in mean granule diameter when the liquid saturation exceeds certain specific values.

Having identified the MLV as marker of the granulation onset, a dedicated experimentation has been designed (as detailed in Tables 1 and 2) to understand the impact of the formulation components on the MLV.

Two common binders (i.e. HPMC and PVP), added as dry powder in the initial powder mix, in the usual range for pharmaceutical wet granulation (i.e. from 2.5 to 10%, w/w), have been tested.

Fig. 4 summarizes the results obtained with the two binders at the various concentrations on the MLV determination. As can be appreciated, the onset of granulation, measured as MLV, is delayed (that is a higher amount of liquid is required) with increasing the binder amount, with both HPMC and PVP. MLV increase resulted to be greater for HPMC than PVP. In addition, the rate of torque increase with PVP is higher than that with HPMC (Fig. 4a and b). It is suggested that this fact is due to a more relevant hygroscopicity of the PVP powder as compared with HPMC, which determines a faster formation of a viscous solution.

Plotting the ratio between the amount of binder and liquid versus the amount of liquid, hyperbolas parametric in the binder amount are obtained (Fig. 5). Each of these curves describes the evolution of the granulation process in terms of added liquid for different amount of binder present in the formulation. The minimum liquid volume determined experimentally for both HPMC and PVP is also indicated on each curve. As noted above (refer Fig. 4) the MLV increases with the binder amount for both HPMC and PVP. Interestingly, as the MLV increases with increasing the binder concentration, the ratio binder/liquid does not remain constant, as it would have been expected the MLV being a simple function of the solubility of the binder. Since changes in the amount of binder in the formulation are reflected into the amount of diluent (as per Table 1), from the results outlined above it can be concluded that diluent hygroscopicity also plays a role in MLV determination.

To separate and quantify the effect of diluent and binder on the onset of granulation, a simplified representation of the relationship among formulation components in the granulation process is pro-

posed (Fig. 6a). The key players of the process that is liquid binder, dry binder and diluents (lactose monohydrate and microcrystalline cellulose) represent the vertex of a ternary diagram.

The dry formulation mix is represented by a point on binder–diluent axis. With the addition of water, the point in the diagram representing the actual granulation mix moves from binder–diluent axis towards the 100% liquid vertex. This ternary
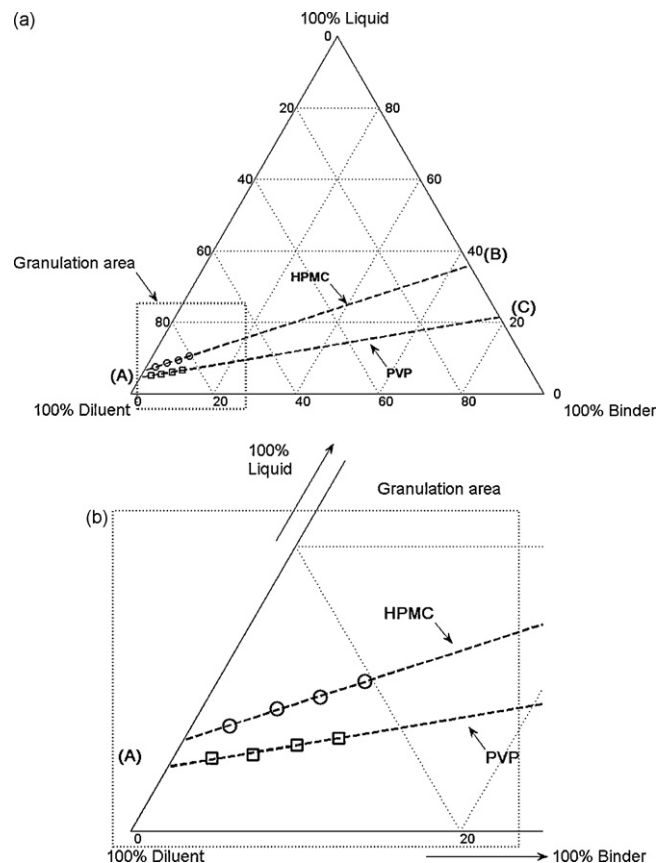

Fig. 6. Formulation map: (a) ternary diagram where each vertex represents the weight composition of the key components of the granulation mix, namely main diluent (lactose monohydrate and microcrystalline cellulose), dry binder (HPMC or PVP) and liquid (water); (b) inset focusing on the most common granulation area. Circles and squares label MLV experimentally determined for HPMC and PVP respectively; the points on the diagram for concentrations of binder other than those tested are interpolated.
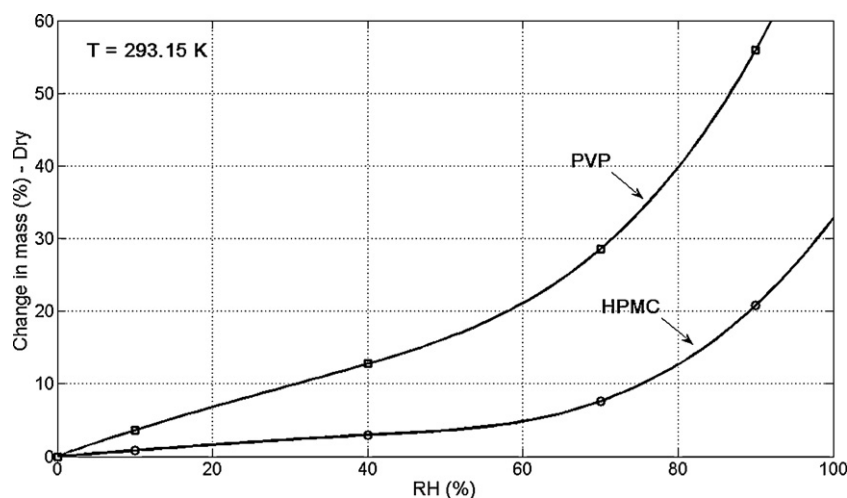
Fig. 7. Moisture sorption isotherms for HPMC (circles) and PVP (squares) at 25 °C.

diagram can be viewed as a granulation map on which the granulation process can be followed (as weight fractions or percentage of the ternary mixture) given the initial formulation composition. In practice granulation area is typically limited to high diluent concentration values as pointed out in Fig. 6b which enlarges the bottom-left corner of the diagram.

The MLV measured from Table 1 experiments are projected in the map (symbols in Fig. 6). As can be observed in Fig. 6b the MLV for HPMC and PVP lie on two straight, non-parallel lines, confirming the non-obvious influence of the liquid amount on the binder action already observed from Fig. 5.

Interestingly, the curves constructed by interpolating the MLV values experimentally obtained for HPMC and PVP intersect the diluent–liquid axis (corresponding to 0% binder) very closely to each other (point (A) of Fig. 6). This value represents the water absorbed by the diluent powders and therefore not accessible for the binder. On the contrary, the water absorbed by the binder is indicated by the intersection on binder–liquid axis (i.e. 0% diluent). In this case, the intersection obtained by interpolating the experimental MLV values is clearly different for the two binders, as marked by the points (B) and (C) in Fig. 6, reflecting their different interaction with the granulating liquid (water).

From this representation, it can be easily concluded that the onset of granulation for a given formulation is identified by a single, binder-specific curve. This curve, as shown in the following, can be constructed from independent measurements on the diluents (initial moisture) and the binder–liquid mixture.

A physical interpretation for conditions (A), (B) and (C) in Fig. 6, is also proposed as per the following mechanism:

(1) water drops on the powder bed and penetrates into the diluent and binder particles;
(2) part of the water is absorbed by the hygroscopic diluents;
(3) the remaining water is absorbed by the binder and acts as plasticizer, decreasing its glass transition temperature, T_g;
(4) when the T_g of the binder–water mixture equals the local temperature, the binder becomes sticky, as indicated by the abrupt sudden increase in the measured torque, and granule growth accelerates.

As experimentally verified, the maximum water amounts absorbed from diluent and binder (steps 3 and 4) in granulation 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 hygroscopicity and on the mixing energy and efficiency.

In order to determine hygroscopicity of HPMC and PVP, moisture sorption isotherms (25 °C) have been measured by hygrometry. Results are shown in Fig. 7, where the weight gain of the binder is reported as a function of the ambient percentage relative humidity (RH%). As can be noticed, water absorption is extremely non-linear, dramatically increasing at elevated RH%, especially for PVP which thus exhibits a much larger hygroscopicity than HPMC.

Glass transition temperature of the moisturized binders, has also been determined. For this purpose, samples of HPMC and PVP have been prepared with a certain degree of absorbed water by placing them in a closed vessel, at different RH%, for 2 weeks, assuming equilibrium is finally attained after such a long time.

Glass transition temperature of wet binder samples was estimated using Gordon–Taylor (1952) equation:

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

which is a weighted average of the single component's T_g's, corrected by an empirical factor (k) to take into account the water contribution. T_{g1} is the glass transition temperature of the dry binder and T_{g2} that of water (equal to -138 °C), while w_1 and w_2 are the weight fractions. k values for different water–binder systems have been calculated e.g. by Hancock and Zografi (1994).

Eq. (1) is used to derive mathematically the amount of water, w_2^*, that results in $T_g = T_a$, where T_a is the operating temperature (e.g. ambient):

$$w_2^* = \frac{T_{g1} - T_a}{k(T_a - T_{g2}) + (T_{g1} - T_a)} \tag{2}$$

This water amount is the quantity needed for the binder glass transition and the formation of a highly viscous mixture. To further improve the accuracy of the fitting of our experimental data, a more recent equation to determine T_g (Hancock and Zografi, 1994) has also been utilized. This equation introduces an additional quadratic function of composition to the Gordon–Taylor equation, Eq. (1). The resulting T_g is:

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} + q w_1 w_2 \tag{3}$$

where q is an empirical constant reflecting binder–water interaction. Through Eq. (3) it has been calculated the theoretical water amounts which satisfy the $T_g = T_a$ condition.
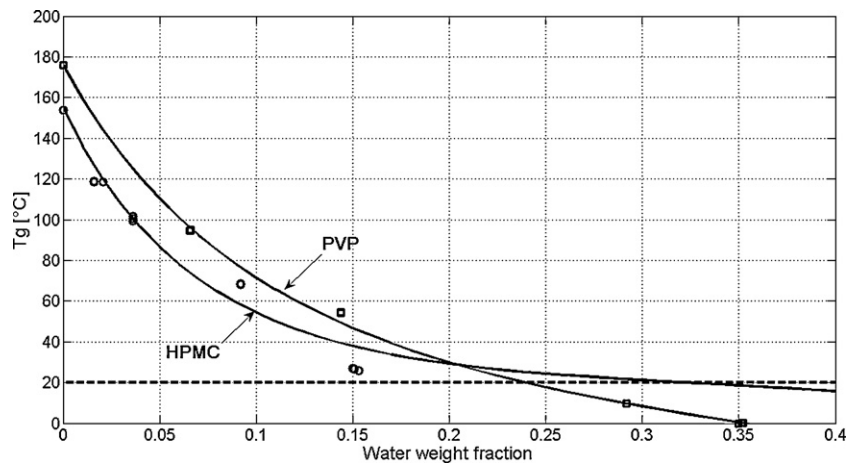
Fig. 8. Glass transition temperature as a function of the equilibrium water content in samples of HPMC (circles) and PVP (squares); continuous lines are obtained by fitting experimental data to modified Gordon–Taylor equation, Eq. (3); the dashed line shows ambient temperature as reference.

The curves obtained by fitting the glass transition temperatures experimentally determined for the different wet samples using Eq. (3) are illustrated in Fig. 8. The condition $T_g = T_a$ corresponds to the intersection between the data fitted curves and the ambient temperature (see Fig. 8).

Note that Eq. (3) fits experimental T_g's for the system PVP/water better than for the HPMC/water one. This is due to the fact that the data fitting for HPMC was performed on a lower number of experimental points at high water weight fraction values. Since HPMC is less hygroscopic than PVP (see Fig. 7) it was not possible to moisturize HPMC samples under static condition with a water weight fraction higher than 20% at RH% lower than 90%.

The water weight fractions at which the glass transition temperature is equal to that of the ambient (i.e. 0.24 and 0.32 for PVP and HPMC respectively) are in agreement with water amounts determined from Fig. 6, that is point (B) and (C) (i.e. 0.21 and 0.36 for PVP and HPMC respectively).

To sum up, it is remarkable that the onset of the granulation for a given formulation can be determined from a triangular plot, like the one presented in Fig. 6, that is constructed from independent measurements of moisture content of diluents (point A in Fig. 6) and binder–water ratio (points B and C in Fig. 6) yielding $T_g = T_a$.

Noteworthy, points B and C in Fig. 6 are derived from measurements of equilibrium data as illustrated in Fig. 8. Discrepancies between actual and equilibrium data might arise in case the water absorption kinetics within the granulator bowl is not fast enough to approach the equilibrium. This could depend on binder hygroscopicity, on its competition with diluents in moisture absorption and on the mixing energy,

The above-mentioned competition for water among diluents and binder has been investigated further by varying the particle size distribution (PSD) of the main diluent (i.e. lactose monohydrate) while keeping the relative proportion of the formulation components constant. Lactose monohydrate 60, 150, 200 or 400 mesh has been tested as indicated in Table 2. Resulting torque profiles (after filtering) and first derivative are shown in Fig. 9. As can be appreciated MLV identification is straightforward with coarse lactose monohydrate (i.e. 60 M and 150 M). On the contrary, it is hard to identify MLV for the finer lactose monohydrate (200 and 400 mesh).

First derivative for granulation trials performed with lactose monohydrate 400 mesh is significantly more irregular than that with coarser lactose, as it can be deduced in Fig. 9b. It is hypothesized that this difference in behaviour is due to sticking of the wet
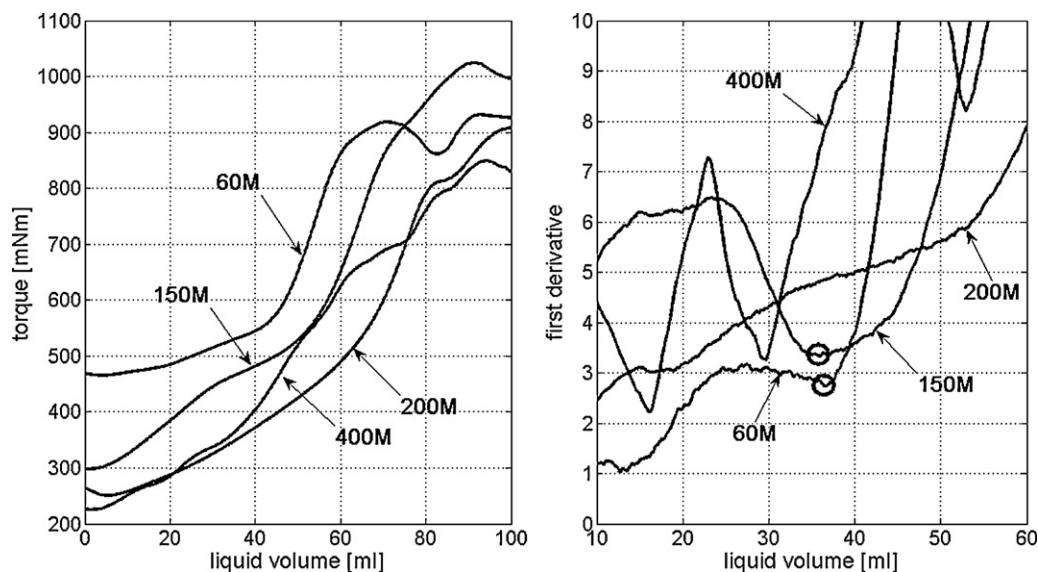

Fig. 9. Effect of particle size distribution of the main diluent lactose monohydrate on torque profiles: (a) filtered profiles and (b) first derivatives with minimum value determination (circles).

powder mix on the granulator wall. The sticking was observed by the visual inspection of the wet powder through a spy-hole during the granulation. First derivative for the mixture with lactose monohydrate 200 mesh shows a more regular torque increase but does not show a minimum, as a consequence the MLV could not be determined. The proposed interpretation is that a different growth mechanism occurs (e.g. layering growth mechanism). We can conclude from this set of experiments that at least for the cases in which the minimum on the torque first derivative can be identified there is not much difference between the minimum water amount required varying the lactose mesh (i.e. 60 and 150 mesh in Fig. 9b). This may suggest that the MLV is independent of the particle dimension of the diluent and therefore is a function only of its chemical nature and hygroscopicity.

4. Conclusions

This work was aimed at developing more systematic and quantitative criteria for high-shear wet granulation design on the basis of the single components physical properties. A novel formulation map has been proposed which describes the onset of granulation as a function of the formulation variables (diluent, dry and liquid binder).

The granulation progress is characterized through impeller torque measurements and time measurements of granule particle size distribution. When plotting the torque profiles as a function of the amount of liquid added an abrupt increase in torque is observed that is associated to the actual onset of granulation interpreted as beginning of a significant granule growth (on the basis of the granule PSD). This abrupt change in torque is quantitatively determined as minimum in the first derivative of the torque profile with respect to the added liquid. The amount of liquid at which the torque derivative is at its minimum is designated here as minimum liquid volume (MLV).

MLV is greatly dependent on the formulation. It is shown how to determine MLV as a function of the formulation constituents. A triangular 'formulation map' in which the vertex represent the diluent, dry and liquid binder is constructed. It is demonstrated how the points on the edges of the triangle can be determined by independent measurement of the diluents hygroscopic capacity and the glass transition of the binder–water system. The granulation onset values for the different formulations can be then extrapolated from this diagram. Note that the actual kinetics of the physical processes within the granulator may lead to slight departures from the predictions based on equilibrium data. Notwithstanding these discrepancies, we believe that the method outlined in this paper has a huge potential to increase the predictability of different formulations on the basis of the physical properties of the single component.

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