

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

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Abstract

In this paper the glass transition concept coupled with on-line impeller torque measurements and measurements of the particle size distribution time evolution has been used to give a description of the early stage of the agglomeration process in high-shear wet granulation.

A new formulation map is presented which describes the onset of significant granule growth as a function of the key formulation variables (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 function of type, quantity, hygroscopicity and particle size distribution of diluent and solid binder. This map can be constructed from a priori glass transition measurements using static humidity conditioning system and by fitting the experimentally obtained data using a modified Gordon-Taylor equation

Keywords: wet granulation; high-shear mixer; glass transition; water uptake

1. Introduction

Pharmaceutical industry frequently applies high shear wet granulation to powder mixture in order to improve the particle characteristics, the homogeneity and the flowability properties (Litster and Ennis, 1999; Ennis, 2006). High shear wet granulation is therefore an example of particle design, since an initial powder mixture composed by a drug and some excipient can be transformed in design structured agglomerates through liquid addition and vigorous mixing (Knight, 2001).

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 granule properties. Many efforts have been made with a view to engineering the process, splitting up the agglomeration process in different stages, such as the initial granule formation phase or nucleation (Wildeboer et al., 2005), the granule growth and breakage (Iveson and Litster, 1998). However, wet granulation has practically remained more an art than a science, as pointed out by Iveson et al. (2001).

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

Several and varied methods have been explored for this purpose. Briens et al. (2007) and Daniher et al. (2008) 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 (Landin et al., 2005; Landin et al., 1996; Betz et al., 2004). The power consumption or impeller torque profiles have been traditionally subdivided in different phases, as described by Leuenberger et al. (2009): (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), (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 (Leuenberger, 1982).

Modern and scientific approaches to granulation understanding aim at splitting and analyzing every single agglomeration phase. In this work we focus on the early stage of the growth phase and the potential of on-line impeller torque measurements to monitor the granule growth. While most research has been primarily devoted to end-point determination, less effort has been dedicated to the understanding of the granulation on-set.

In addition, particles have been often considered inert materials, i.e. interactions between solid particles and liquid have been seldom considered. Notable exceptions are those of few authors which explained the agglomeration of different powder mixtures as a consequence of an increased powder stickiness (Fitzpatrick, 2007) or a change in the deformability and viscosity of the wet mass (Palzer, 2005) when the powder temperature is below the material glass transition temperature.

In this paper 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 torque when the amount of binder liquid added exceeds a critical threshold indicated here as minimum liquid volume (MLV).

The experimental results have been therefore 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 dry binder glass transition temperature.

2. Materials and methods

Variations of a common, active-free pharmaceutical formulation have been considered.

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 about 40%. Granulating liquid was added through a tube with a 1 mm diameter by a computer controlled dosimeter.

Two experimental sets have been performed. In the first set three granulation experiments have been 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 (kept) constant and was (on weight basis): lactose monohydrate 150M (73.5%), microcrystalline cellulose (20%), HPMC (5%) and croscarmellose sodium (1.5%). All the experiments have been 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 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).

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.

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%	

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. We carried out a first gentle drying at constant temperature and pressure (20°C and 1 bar), and a second drying in a 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 particle size distribution (PSD) due to 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 inch CCD (Jai, CV-300) and interfaced with a Image Tool PC program (ImageTool©, Copyright 2008, Evans Technology, Inc.).

Curves representing influence of water content on binder glass transition temperature were determined by DSC. HPMC and PVP duplicate samples (about 500mg) were preconditioned in a atmosphere at given RH%. Samples were weighted and spread as a thin layer (about 0.5mm) in a series of 4 hermetic vessels, where the humidity was maintained by saturated salt solutions covering a wide range of relative humidity (11–95% 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°C/min and -10°C/min); then heating up to a maximum temperature of 120°C (5°C/min), using a modulation amplitude of $\pm 1^\circ\text{C}$ 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 has been performed to analyze the effect of impeller speed on the shape of torque profiles, at constant formulation.

Figure 1(a) shows the numerically filtered torque profiles obtained from the first granulation experiments as a function of the added liquid.

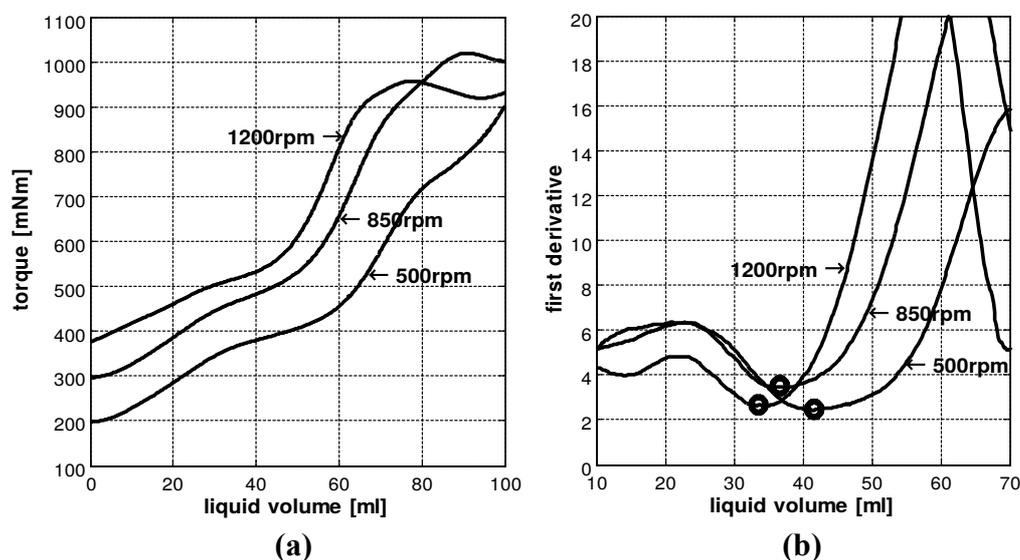


Figure 1 Results of the first experimental set: (a) impeller torque as a function of the liquid addition at different impeller speed and constant formulation and (b) determination of the points corresponding to the first derivative minimum value (circles)

As can be seen, the shape of the profiles obtained using different impeller speed is very similar. In accordance with the explanation proposed by Leuenberger et al. (2009), torque profiles can be divided in different phases, characterizing different stages during the agglomeration process. At first, 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 as an increased lubrication of the mass which causes a decrease of the stresses on the impeller. A sudden increase in the slope can be noticed 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 better identify the liquid volume required to obtain the pendular state, the first derivative has been calculated and plotted as a function of added liquid in Figure 1(b). As can be noticed in Figure 1(b), the minimum value in the first derivative profile does not strongly depend on the impeller speed, suggesting it may depend mainly on formulation properties.

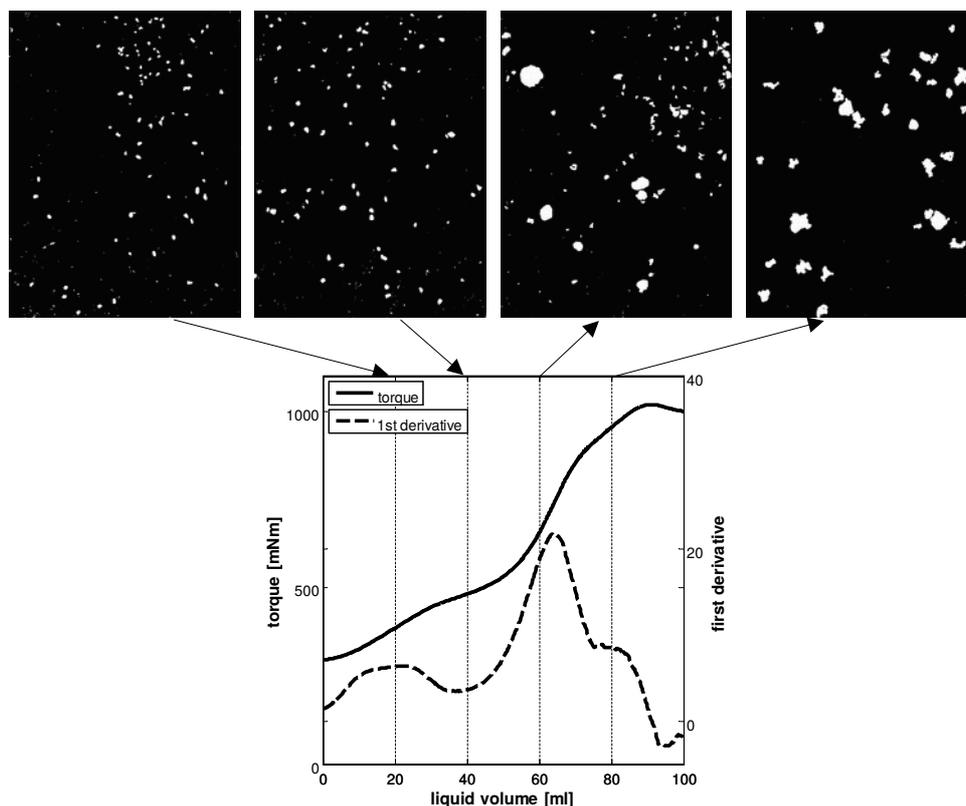


Figure 2 Effect of the moisture content on the granule size evolution during the granulation process: pictures of the granules show a negligible growth until the point A (Figure 2), whereas larger agglomerates can be counted after this point

In order to monitor the PSD evolution during the agglomeration image analysis has been used to obtain a more accurate description of the agglomeration phase. The operative conditions of the middle curve in Figure 1(a) (that at 850 rpm) have been chosen as 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 Figure 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% of the 100ml 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 has been repeated and stopped after two different quantities of liquid have been added (40 and 100ml respectively). Sieve analysis has been carried out in order to compare the PSDs. In Figure 3a point A was obtained interrupting the experiment at the condition of minimum value in the derivative profile while point B represents the condition immediately after all the liquid has been added. Figure 3b instead shows the corresponding PSDs. The PSD of the dry formulation has been added also. Figure shows 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 beginning from the point A.

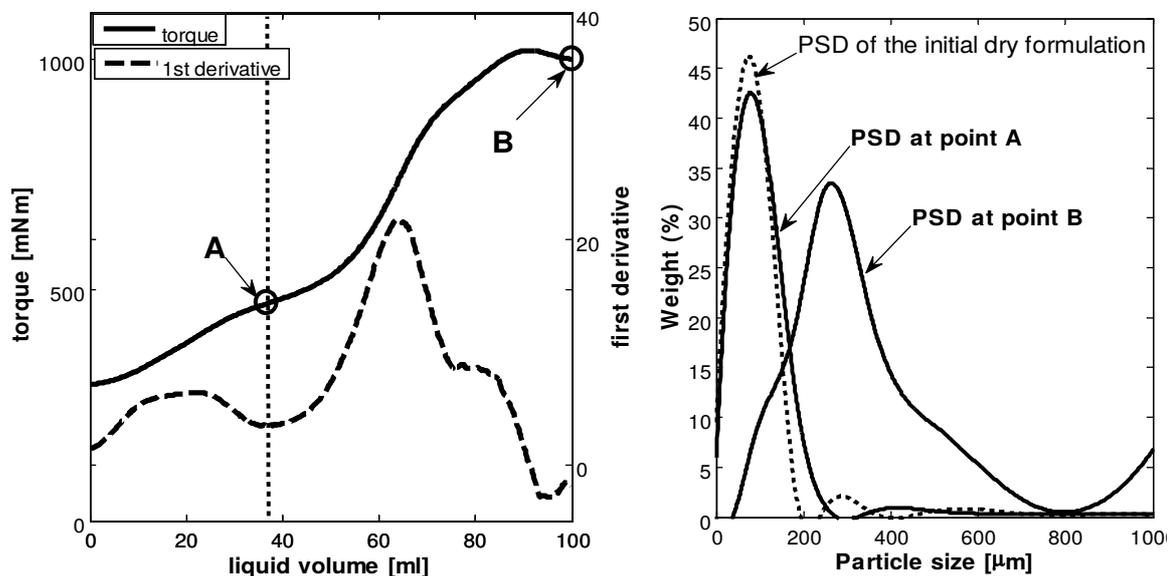


Figure 3 Results of the sieve analysis carried out in order to compare the PSD at point A (before the sudden increase in the slope) with the PSD at the end of the experiment

As can be inferred from Figure 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. (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.

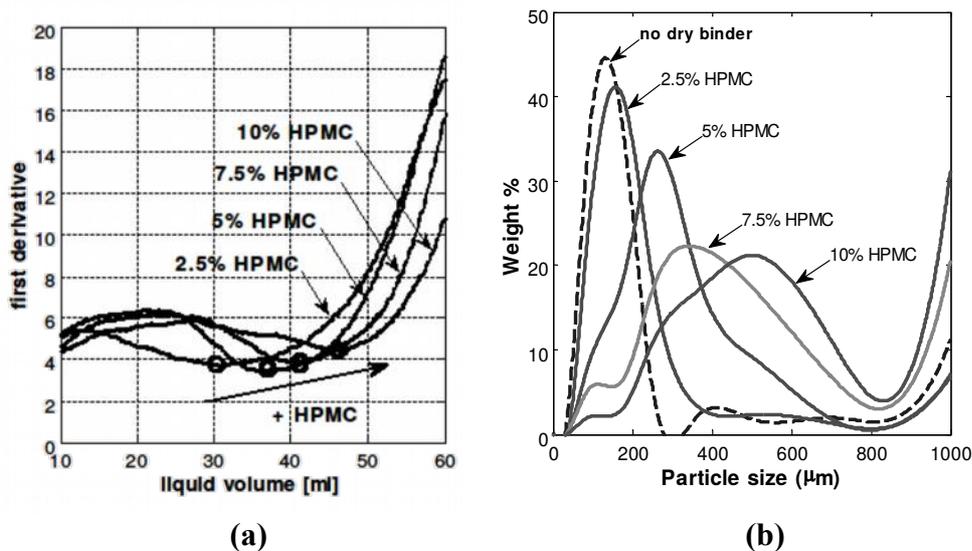


Figure 4 Effect of different concentration of (a) HPMC on MLV determination and (b) PSD at the end of the granulation experiments

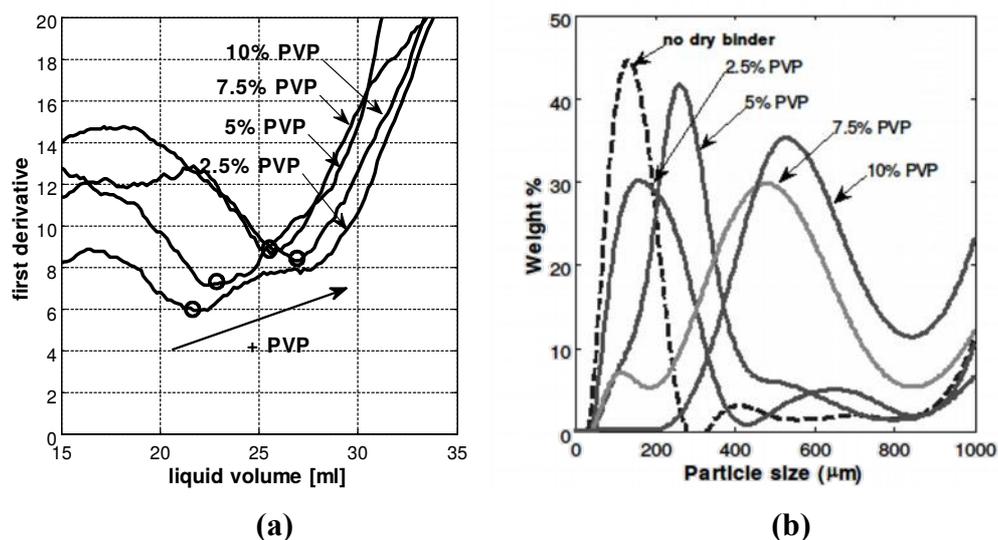


Figure 5 Effect of different concentration of (a) PVP on MLV determination and (b) PSD at the end of the granulation experiments

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

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

Figures 4 and 5 summarize the results obtained in terms of first derivative of the torque profiles, with the two binders at the various concentrations. MLV's have been determined as local minimum of the first derivative. The same Figures also report the PSD measured (sieve analysis) at the end of the granulation experiments. The relatively large weight fraction on the 1000 μm sieve is partially due to caking in the oven at high temperature.

As can be appreciated, the onset of granulation is delayed (that means a higher amount of liquid is required) with increasing the binder amount, 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 (Figures 4a vs 5a). 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.

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. 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 (compare PSDs in Figures 4a and 5a with 3b) thus indicating an unimportant agglomeration process.

In order to explain the dissimilar growth behaviour due to a different dry binder concentration, the diagram in Figure 6 has been considered. It represents the static yield strength of the wet granules as a function of the pore saturation (Ennis, 2006; Rumpf, 1962).

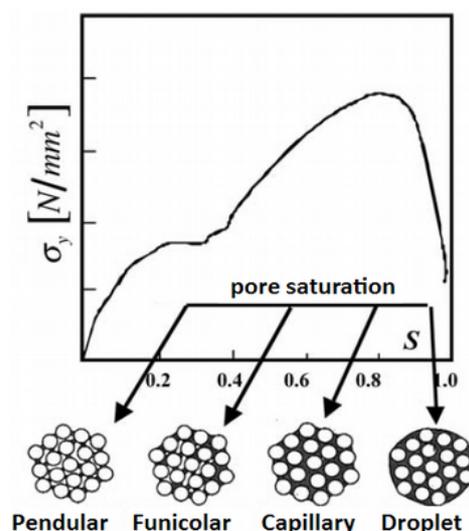


Figure 6 Static yield strength of the wet granule as a function of the pore saturation (Ennis, 2006; Rumpf, 1962)

As pointed out by Leuenberger et al. (2009), the point A 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 and they often contain 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 allows the agglomeration process (Fitzpatrick, 2007; Palzer, 2005).

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 Figure 3).

Palzer (2008) described the strength of the adhesion forces as a sum of two contributors: the hygro-capacity 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 sign of the increase in the viscosity due to the absorbed water.

The formulation processed in this work presents two main fillers (lactose monohydrate and MCC) and a dry binder (HPMC or PVP). The dry binder presents a higher hygro-capacity and a much higher hygro-sensitivity in comparison to the fillers. For this reason dry binder (HPMC or PVP) can be considered as the main binding agent and the two fillers can be considered as a sole diluent, which absorbs water but has a weakly binding strength.

In order to separate and quantify the effect of the key formulation components on the MLV, a triangular formulation map has been proposed (Figure 7).

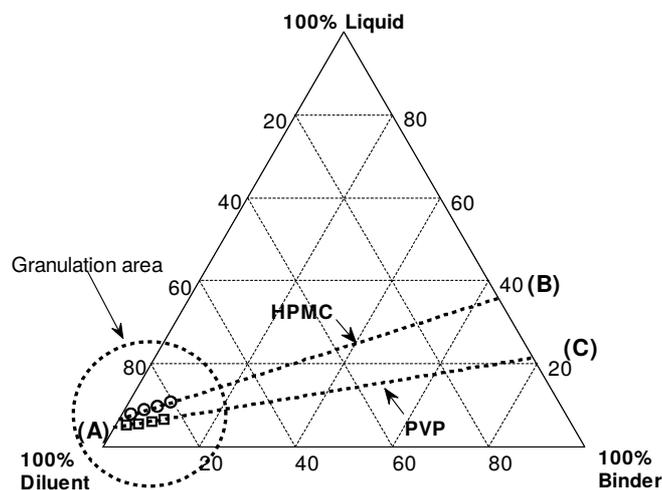


Figure 7 Formulation map: representation of the effect of the main formulation components on MLV through a ternary diagram. Each vertex represents a key component, that is the main diluent (lactose monohydrate and microcrystalline cellulose), dry binder (HPMC or PVP) and liquid (water). MLV experimentally determined in presence of HPMC or PVP are respectively marked with circles and squares

The combinations of the main formulation components (diluent, dry binder and liquid binder) can be well represent in a ternary diagram, figure 7, 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 (Figures 4 and 5) are represented in the ternary diagram by markers (HPMC = circles; PVP = squares).

As can be observed in Figure 7, 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 Figure 7. 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 a common pharmaceutical formulation 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. (2001);
- 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. (2001), 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 and on 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 Figure 8.

Glass transition temperature of wet binder sample can be roughly estimated using Gordon-Taylor equation (Gordon and Taylor, 1952):

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \quad \text{Eq (1)}$$

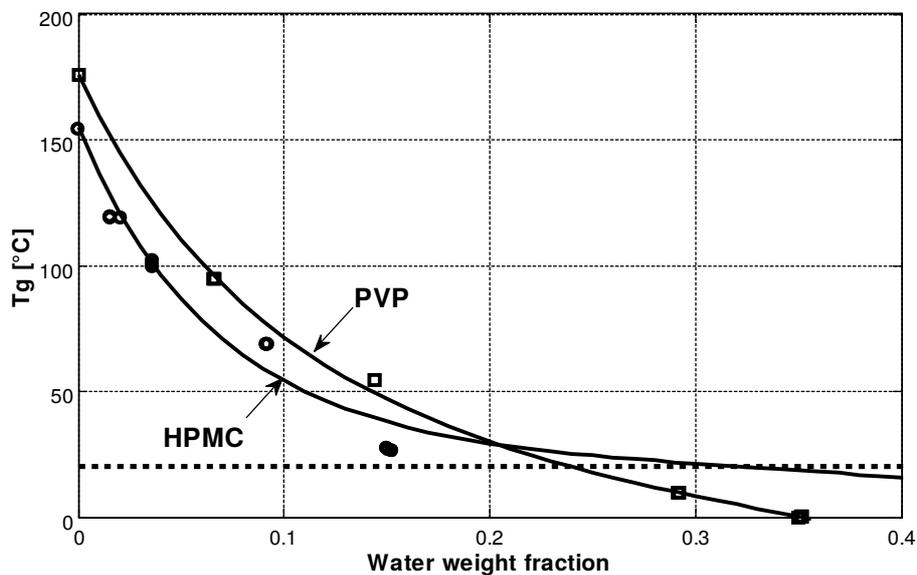


Figure 8 Glass transition temperature as a function of water content in samples of HPMC (○) and PVP (□), continuous lines represent data fitting by modified Gordon-Taylor model (Hancock and Zografí, 1994); the dashed line represents nominal ambient temperature.

where k is an empirical constant, T_{g1} is the dry binder glass transition temperature, T_{g2} is the water glass transition temperature (-138°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 Zografí (1994).

Assuming the reference condition:

$$T_g = T_a \approx T_p \tag{Eq (2)}$$

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

$$w_2^* = w_2(T_g \approx T_p) \tag{Eq (3)}$$

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

Experimental data in Figure 8 have been fitted to a modified Gordon-Taylor-type model (Hancock and Zografí, 1994). As can be seen in Figure 8, the intersection between the glass transition curves and the ambient temperature gives the water amount required to obtain the dry binder glass transition.

Table 2 shows an appreciable agreement between the water weight fractions at which the glass transition temperature is equal to that of the powder (or ambient temperature) (i.e. Figure 8) and the water amounts determined from the formulation map (point (B) and (C) in Figure 7).

Table 2

Binder type	Water weight fraction from formulation map (Figure 7)	Water weight fraction from Tg curves (Figure 8)
HPMC	0.36	0.32
PVP	0.21	0.24

In conclusion, it has been demonstrated that it is possible to construct the ternary diagram in Figure 7 from independent glass transition temperature measurements (Figure 8): Table 2 shows a good agreement between the point (B) and (C) in Figure 7 and the independent measurement results. A small difference between the values can be evaluated in Table 2 for each binder type. This difference could 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.

4. Conclusions

The role of formulation variables, such as binder type and amount have been analyzed monitoring impeller torque and PSD evolution during high-shear granulation experiments. The analysis of torque profiles as a function of added liquid binder (water) has identified the existence of a minimum liquid amount required to strongly increase torque value and to start most granule growth. The initial powder mixture has been ideally split in two main components (diluent and binder) according to their expected behaviour with respect to the liquid binder - hygro-capacity and hygro-sensitivity in accordance with Palzer (2005) original ideas - and minimum liquid amount data points obtained for different formulation compositions have been marked on a triangular diagram. The diagram, through a graphical construction, highlights the interactions between binder-water and diluent-water pairs.

Interactions between different binders (HPMC and PVP) and water have been analyzed considering plasticizing effect of water on the polymeric binder: different binder samples with different water content have been analyzed and experimental data have been fitted on a Gordon-Taylor based model.

Equilibrium water amount which assures the decrease of binder glass transition temperature down to operating temperature (ambient temperature) has been correlated to water volume resulting from triangular diagram construction and some considerations on water absorption kinetics have been made.

Results show that it is possible to carry out an early assessment of the minimum liquid volume required to start most granule growth through an application of a Gordon-Taylor model or performing some independent measurements of the initial formulation properties. These operations

can be supported by the use of a triangular diagram in order to perform a first formulation design or prevent alteration due to changes in formulation composition.

6. References

- Betz, G., P. J. Bürgin and H. Leuenberger (2004). Power consumption measurement and temperature recording during granulation. *Int. Jou. Pharm.*, 272, 137-149.
- Briens, L., D. Daniher, and A. Tallevi (2007). Monitoring high-shear granulation using sound and vibration measurements. *International Journal Pharmaceutics*, 331, 54-60.
- Daniher, D., L. Briens, A. Tallevi (2008). End-point detection in high-shear granulation using sound and vibration signal analysis. *Powder Technology*, 181, 130-136.
- Ennis, B. J. (2006). *Theory of Granulation: an Engineering Perspective*, in: D.M. Parikh (2nd Ed.), *Handbook of Pharmaceutical Granulation Technology*. Taylor and Francis Group, New York (U.S.A.).
- Fitzpatrick, J.J. (2007); Particle properties and the design of solid food particle processing operations. *Food and Bioproducts Processing*, 85, 4, 308-314.
- Gordon M. and J.S. Taylor (1952). Ideal co-polymers and the second order transitions of synthetic rubbers. 1. Non-crystalline co-polymers. *J. Appl. Chem.*, 2:493-500.
- Hancock, B. C. and G. Zografı (1994). The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharm. Res.*, 11(4).
- Iveson S.M., Litster J.D. (1998), Growth regime map for liquid-bound granules, *AIChE Journal* 44, 1510–1518.
- Iveson S.M., Litster J.D., Hapgood K. and Ennis B.J. (2001). Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review, *Powder Technology* 117 (1–2), 3–39.
- Knight P.C. (2001). Structuring agglomerated products for improved performance, *Powder Technology* 119 (1), 14–25.
- Landin, M., R. C. Rowe and P. York (1995). Characterization of wet powder masses with a mixer torque rheometer. 3. Nonlinear effects of shaft speed and sample weight. *Jou. Pharm. Sci.*, 84/5, 557-560.
- Landin, M., P. York, M. J. Cliff, R. C. Rowe and A. J. Wigmore (1996). The effect of batch size on scale-up of pharmaceutical granulation in a fixed bowl mixer-granulator. *Int. Jou. Pharm.*, 134, 243-246.
- Leuenberger, H. (1982). Granulation, new techniques, *Pharm. Acta Helvetica* 57 (3) 72–82.
- Leuenberger, H., M. Puchkov, E. Krausbauer and G. Betz (2009). Manufacturing pharmaceutical granules: Is the granulation end-point a myth?, *Powder Technology*, 189, 141-148.
- Litster, J.D. and B. J. Ennis (1999). Size reduction and size enlargement, in: Perry, R. H. and D. W. Green (1999). *Perry's Chemical Engineers' Handbook*. McGraw-Hill Companies, New York (U.S.A.).
- Litster J.D., Hapgood K.P., Michaels J.N., Sims A., Roberts M., Kameneni S.K., Hsu T. (2001), Liquid distribution in wet granulation: dimensionless spray flux, *Powder Technology* 114, 29–32.
- Palzer S. (2005), The effect of glass transition on the desired and undesired agglomeration of amorphous food powders, *Chemical Engineering Science* 60, 3959-3968.

M. Cavinato, M. Bresciani, M. Machin, G. Bellazzi, P. Canu, A. Santomaso The development of a novel formulation map for the optimization of high shear wet granulation (2010) Chemical Engineering Journal 164, 350–358.
DOI: [10.1016/j.cej.2010.05.006](https://doi.org/10.1016/j.cej.2010.05.006)

Ritala, M., Holm, P., Schaefer, T., Kristensen, H. G. (1988). Influence of Liquid Bonding Strength on Power Consumption During Granulation in a High Shear Mixer. *Drug Development and Industrial Pharmacy*, 14:8, 1041 – 1060.

Rumpf H , (1962). The strength of granules and agglomerates. In: Knepper WA, ed. *Agglomeration*.

New York: Interscience, 379–414.

Wildeboer, W.J., Litster, J.D., Cameron, I.T.(2005). Modelling nucleation in wet granulation. *Chem. Eng. Sci.*, 60, 3751 – 3761.