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High shear mixer granulation using food grade binders with different thickening power

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Abstract
Mixer agglomeration and in particular high shear wet granulation is a unit operation typically used in the pharmaceutical industry to improve the flowability, the compressibility, the dosing accuracy during tableting or the content uniformity of a blend. Thanks to its advantages (production of spherical and dense granules, reduction of production time), this technique can be potentially successful also in the food industry as for example in the production of dietary supplements. In this work four thickening agents (povidone, maltodextrin, k-carrageenan and xanthan gum) have been tested to study their effects on the granule growth behavior and on some technologically relevant granule properties (size, shape, strength and flowability). Experiments highlighted the full feasibility of the process and the possibility of using these agents to get products with satisfactory technological properties. The dependence of product properties on the formulation variables (water and binder amount) has been analyzed according to a multivariate approach and a robust predictive tool for the granule size has been developed. Furthermore it was observed that a reduced amount of binding liquid (water) can be used in presence of strongly thickening binders with a reduction up to 25%. This would decrease drying time and energy requirement and be beneficial especially in the food and food supply industry where products have generally lower added value than in the pharmaceutical one and reducing production costs is critical.

Keywords: high-shear granulation, thickening agent, povidone, maltodextrin, k-carrgeenan, xanthan gum

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1. Introduction

In various industries, fine powders are produced in agglomerated form by dosing a liquid binder onto a mechanically agitated blend of powders. This process is called mixer agglomeration (or wet granulation in pharmaceutics) in order to differentiate it from other wet agglomeration processes such as fluid bed or spray-drying agglomeration (Forny et al., 2009). Wet granulation can be achieved in mechanically agitated mixers and can be classified into two main types according to the intensity of mixing: low shear or high shear processes (Knight et al. 2001; Cavinato et al., 2013; Paul, Atiemo-Obeng & Kresta, 2003). Among these techniques, high shear wet granulation has the advantage that mixing, wetting and massing can be performed simultaneously, in a few minutes, using the same equipment. Moreover the comparable higher shear-stress generates denser and relatively more spherical granules. The intensity of the mixing process, however, can lead rapidly to overgranulation with adverse effects on granule properties (Leuenberger et al. 2009). In general, any process and formulation factor able to modify the basic mechanisms of agglomeration produces granules with different final properties. Therefore, being able to control each stage of this process is critical (Leuenberger et al. 2009; Cavinato et al., 2010a).

In this context, process and formulation variables related to the binder are considered to be of major importance (Tardos et al., 1997; Simons et al., 2004, Cavinato et al., 2010b).

Mixer agglomeration, and in particular high shear wet granulation, is a unit operation typical of the pharmaceutical with the aim of improving flowability, compressibility, and dosage accuracy during tableting, or the content uniformity of a blend (Litster & Ennis, 2004). As well as the active ingredient, these formulations can contain one or more diluents for improving bulk handling, and a binder to facilitate granule growth. Additional wetting and stabilizing agents, colorants, disintegrants and lubricants can be present if required.

Mixer agglomeration is also applied with success to some food powders such as protein powders, culinary powders, powder blends for the preparation of desserts, starch, bakery mixes and flavor powders. Water, water-based binder solutions or dispersions containing carbohydrates or hydrocolloids, lecithin, molasses or melted fat can be used as binders. The viscosity of these is comparatively higher than those used in pharmaceutics and food supplements. In this case, the aim of the operation is to improve flowability, avoid lumping during rehydration, encapsulate sensitive components, or simply to improve the visual appearance of the product (Forny et al. 2009).

Binder materials added to water are usually natural or synthetic water soluble polymers that may be used as solutions, but they may also be added to the dry powder mix. The nature of the binder, and the method of adding it, affect the granule growth kinetics and properties of the final product (Litster & Ennis, 2004; Palzer, 2009; Palzer, 2005). In particular, the use of alternative binders and binding techniques is challenging for the food and food supply industries which need to expand the range of binders with respect to those normally used in pharmaceutical granulation processes (Boerefijn et al., 2009, Cavinato et al., 2010b).

The aim of the present research was therefore to evaluate the effect of four ingredients generally used in the food and food supply industry as thickening agents, on the granule growth behavior of granules produced by wet granulation in a high shear mixer (which is a typical pharmaceutical process). The binders selected for the experiments were povidone, maltodextrin, k-carrageenan and xanthan gum, four polymers with different thickening powers. When placed in water, the four selected binders form viscous colloidal dispersions and therefore have the potential for use as

binders in the agglomeration process. With the exception of povidone, which is commonly used in the pharmaceutical industry for this reason, the others are not used as binders in granulation processes and therefore need to be tested. These binders were mixed with cellulose microcrystalline and the mixture was granulated in a laboratory scale high shear mixer using water as granulating liquid. Due to the different thickening powers of the solid binders, the dispersions resulting from wetting the mixtures of cellulose microcrystalline and solid binders presented clearly different viscosities and thus different behaviours during the granulation process. As a consequence, a major aim of this study was to verify the feasibility of the process with such binders and to evaluate their effect on several technological properties of the microcrystalline cellulose (MCC) granules produced. Granule size and shape, flowability, and strength have been be evaluated. An additional aim was to collect some evidence of the possibility of reducing the amount of water required for granulation by using binders with different thickening powers. Less water would indeed reduce drying time and energy costs and would be beneficial especially in the food and food supply industries where products have generally lower added value than in the pharmaceutical industry, and cost optimization is critical.

2. Materials and methods

2.1. Materials

The formulations were kept as simple as possible and the powder blends were constituted by Microcrystalline cellulose T1 (MCC) and polymeric solid binders chosen from Povidone K30 (Ph. Eur.), Maltodextrin (USP-NF 23), Xanthan gum (Ph. Eur. USP.) and K-carrageenan (Gelcarine GP 911, KC). A brief description of the binder characteristics follows:

- Polyvinylpyrrolidone (PVP), also commonly known as povidone, is a water-soluble polymer made from the monomer N-vinylpyrrolidone. It is used as a binder in pharmaceutical wet granulation and tabletting (for example with effervescent tablets), as a filmogen agent in coating and as a disintegrant agent (Hamed, Moe, Khankari & Hontz, 2005). As a food additive, it is a stabilizer (E1201) and a fining agent (for example in winemaking).
- Maltodextrin (MD), is a moderately or non-sweet mixture of polymers. It is produced by partial hydrolysis of starch and used as a stabilizer and thickening agent (for example in the production of soft drinks and candies) in the food industry (E1400) or as a coating material (Smith, 2011).
- K-carrageenan (KC) are linear sulfated polysaccharides that are extracted from red algae (*Kappaphycus spp., Eucheuma spp., Chondrus spp. and Gigartina spp.*). They are widely used in the food industry (E407), for their gelling, thickening and stabilizing properties (for example in dairy and meat products) or as coating materials in encapsulation processes (Smith, 2011).
- Xanthan gum (XG) is a polysaccharide produced by aerobic fermentation of glucose, sucrose or lactose by the bacterium *Xanthomonas campestris*. It is used as a stabilizer and thickening agent in food preparation (E415) (Barbosa-Cànovas et al. Hong, 2005) and as a pharmaceutical thickening agent.

MCC, PVP, MD and XG were purchased from Acef (Fiorenziuola D'Arda, Italy); KC instead was obtained from FMC BioPolymer (Pennsylvania, USA). Distillate water at 20°C was used as liquid binder.

2.2. Viscometric characterization of water binder dispersions

The thickening potential of the polymers was tested by dispersing different amounts of solid binder into water at 20°C under intense stirring for 60 minutes until complete dispersion was obtained. Water dispersions with increasing concentrations of the binders were then characterized by viscometric measurements (Rotovisco RV20, Haake, Germany, coupled to the rheocontroller RC 20 with a M5 sensor system). Measurements were taken at shear rates from 0 to 700 s^{-1} at 20°C using NV equipment. On the basis of these measurements, the binders were divided in two groups: binders with low thickening power (MD, PVP) and binders with high thickening power (KC, XG) as will be clear from results in section 3.

2.3. Granulation procedure

Granulation experiments were carried out using a lab-scale high shear mixer (Rotolab®, Zanchetta SpA, Italy) as described in previous work by Franceschinis et al. (2011). Briefly, the main part of the apparatus is a 2-liter thermostated bowl equipped with an impeller (minimum 120 rpm, maximum 1200 rpm speed) and a chopper with a working speed of 3000 rpm.
The granulation procedure was standardized on the basis of preliminary trials. In particular, 200 g batches, composed of cellulose microcrystalline (MCC) and different amounts of solid binders were dry-mixed using an impeller speed of 120 rpm for 10 min. After the pre-mixing stage, water was added by dripping from a feeding point onto the dry blend of powders at a constant feed rate of 10 ml/min. At the end of the wetting phase, a massing phase was performed with the liquid feeding system switched off and the impeller speed increased to 800 rpm for 2.5 min. At the end of the granulation procedure, granules were dried at 40°C until constant weight was achieved. Dry granules were sieved to remove lumps larger than 3 mm and stored in well-closed bags before characterization. Additional granulation experiments were performed using 100% (w/w) of MCC (i.e. no solid binder in the formulation) and different amounts of water as granulating liquid (260, 270 and 280 ml respectively).

2.4 Experimental plan

Some preliminary granulation experiments permitted to select the composition ranges for the amount of binder and water, and also the choice of experimental plan. Ranges for the experimental variables are resumed in Table 1.
It can be seen that in the case of binders with low thickening power (MD, PVP), it was possible to fix a lower and an upper limit for both water and binder amount. However, in the case of binders with high thickening power (KC, XG), it was possible to vary only the binder amount, while the amount of water had to be fixed.

In order to identify a mathematical model able to describe and predict the effects of the selected formulation variables on the final granule properties (i.e. the experimental responses), an experimental design technique was used (Eriksson, Johansson, Kettaneh-Wold, Wikstrom & Wold, 2008). It was assumed that the final technological properties of the granules were related to the

formulation variables studied by a first order polynomial model with the general form reported in Eq. (1).

$$Y_j = b_{i,j} + b_{i+1,j} X_{i+1} + \varepsilon_j \quad (1)$$

Where Y_j are the experimental responses which correspond to the measured *j-th* properties of the granules, $b_{i,j}$ (with $i = 0, 1, \ldots, n$) are the coefficients of the linear model to be estimated, X_{i+1} are the codified formulation variables studied and ε_j is the error estimate.

2.4.1 Experimental plan for binders with low thickening power (MD, PVP)

For the binder with low thickening power (MD, PVP) it was possible to evaluate simultaneously the effect of the two formulation variables X_1 (amount of binder) and X_2 (amount of water), and eq. 1 takes the form:

$$Y_j = b_{0,j} + b_{1,j} X_1 + b_{2,j} X_2 + \varepsilon_j \quad (2)$$

The experiments required to estimate the coefficients of this model were planned using a Doehlert design (Mathieu et al., 1999). This design involves seven experiments where X_1 was studied at five levels and X_2 at three levels as reported in codified terms in Table 2. The center-point of the experimental domain (experiment 7) was replicated in order to evaluate the experimental variance. The experimental runs were carried out in an entirely random sequence.

2.4.2 Experimental plan for binders with high thickening power (KC, XG)

For the binders with high thickening power (KC and XG), since the granulation process was much more sensitive to formulation variations (in particular amount of water), only the concentration of the binder could be changed while the amount of water had to be fixed (see Table 3). In order to have a term of comparison, an additional series of granulation experiments without solid binder, i.e. having 100% (w/w) of MCC with three different amounts of water (260, 270, 280 ml) were also performed.

2.5. Granules characterization

2.5.1. Granule size distribution

The analysis of the particle size distribution, PSD, was performed on 100 g of granulated product with the following set of sieves: 2000, 1000, 800, 600, 500, 400, 300 and 63 μm. A vibrating apparatus (AS 200 control, Retsch, Germany) was used at medium vibration level for 10 min. The fractions were collected and then weighed. The d_{50} was calculated from the results of the PSD analysis (Litster & Ennis, 2004).

2.5.2. Shape analysis

Fifty granules, randomly selected in the 1000-2000 μm size range from each batch, were used for shape analysis. Digital pictures of the granules were taken (digital camera: DBK-61BUC02, 1/2" CMOS, 2048x1536, The Imaging Source, Bremen, Germany) mounted on an inverted microscope (Olympus IX51, Hamburg, Germany). Granules were analyzed under

magnification of 40X. Pictures were acquired with commercial software (IC Capture v1.3) and analyzed with the free software Image Tool PC (ImageTool©, Copyright 2008, Evans Technology, Inc.).
The shape of the granules was expressed in terms of roundness. Roundness can be computed as:

$$\Phi_R = \frac{4\pi A}{P^2} \quad (3)$$

where A is the granule projected area and P is the granule outline length (projected perimeter). Resulting roundness values are found between 0 and 1. The greater the value, the rounder the object. The mean and standard deviations over the fifty granules were then calculated.

2.5.3. Flowability of granules

Measurements of bulk densities were performed to evaluate product flowability. The Hausner Ratio, HR, which is the ratio between tap and poured density, was evaluated (Santomaso et al., 2003). Granules in the 1000-2000 μm size range for each batch were collected in a 25 cm^3 cup and the tap density was measured after 800 taps. HR has a theoretical minimum value equal to 1 which correspond to the maximum flowability; as the ratio increases the flowability decreases.

2.5.4. Crushing strength of single granules

The crushing strength of fifty granules, randomly selected in the 1000-2000 μm size range for each batch, was evaluated under uniaxial compression using a texture analyzer (Stable Micro System mod. TA-HDi Texture Analyser) operating with a 250 kg load cell. The granule was placed in the lower flat plate, centered under the 6 mm diameter upper punch, which then moved downwards at a constant rate of 0.1 mm/s until 80% of the strain was reached. Force-time plots were recorded using the texture analyzer pc software (Texture Expert Exceed, Stable Micro System, Surrey, UK). The mean and standard deviations were then calculated.

3. Results and Discussion

The four binders selected for this study (PVP, MD, KC and XG) were preliminarily characterized by viscometric measurements. Water dispersions of the binders with increasing concentrations were analyzed and the data obtained are presented in Fig. 1. It can be observed that PVP and MD dispersions at equilibrium (i.e after complete dispersion in water) yield much less viscous dispersions than XG and KC, with a difference of two orders of magnitude, for the same concentration of polymer.
During the granulation process, however, the water is progressively poured onto the powder mixture containing the solid binder. Consequently, the viscosity of the binding liquid resulting from the progressive hydration of the polymer within the wet bulk is unknown, but certainly increases with time as soon as the binder starts to disperse into the water. In order to verify that the trends of viscosity observed at equilibrium (Fig. 1) are also respected during the wetting and dispersion stages, a kinetic study was performed on the four selected binders. Fig. 2 shows the increase of

viscosity of the dispersion with time. This dynamic picture is expected to be more closely related to the real conditions inside the granulator than equilibrium data, at least during the first stages of the process. However, it can be observed that after a few minutes, the viscosity values for all the binders follow the same ranking observed for the equilibrium data in Fig. 1. Since the wetting time for the granulation processes was always longer than 20 minutes, the dispersion kinetics should not impact significantly on the overall agglomeration process. However, it is interesting to note that the kinetics of hydration is not necessarily related to the thickening power of the polymers at equilibrium. PVP and MD present slightly higher kinetics of hydration than XG and KC since they reach the plateau within 5 min, while XG and KC require longer (≥10 min). Therefore, the thickening power is different from the thickening tendency of the polymers.

On the basis of viscosity measurements, the four solid binders were divided in two groups: binders with low thickening power (MD, PVP) and with high thickening power (KC, XG) for which granulation experiments were planned differently.

3.1. Binders with low thickening power

In the case of binders with low thickening power, a Doehlert experimental design - as previously reported - was used to investigate the effects of water and binder amount on final granule properties. The products of the granulation were characterized from a technological point of view by sieve analysis, image analysis (for shape), flowability and mechanical properties measurements (granule strength). Except for the PSD, the other measurements (shape, flowability and granule strength) were carried out on granules of the 1000-2000 μm size fraction.

The experimental responses (i.e. final granule properties) obtained from the planned granulation experiment are shown in Table 4 for MD and PVP binders respectively.

The experimental responses considered are: Y_1 which represents the median diameter (d_{50}) extracted from the cumulative PSD; Y_2 which is the roundness (Φ_R) of the particles; Y_3 which quantify flowability using the Hausner Ratio (HR) and Y_4 which is the strength of the granules (Σ_B).

In order to verify the dependence of these responses on formulation variables (binder and water amount), an analysis of variance was performed. Results show that for the low viscosity binders only the median diameter was significantly influenced by the selected formulation variables. On the other hand, no significant differences were observed in shape, flowability and strength between the granules produced with different amounts of the same binder.

A multilinear regression analysis was then performed on the median diameter, d_{50}, with the software for statistical analysis NemrodW (Mathieu et al., 1999) in order to obtain the values of the mathematical coefficient of the linear model. Table 5 gives the estimated coefficients for each binder. The validity of the multilinear regression was further confirmed by the values of R^2.

For the low viscosity binders the values of the coefficients estimated in Table 5 can be used to predict the amount of water or binder needed to obtain a granulate with the desired median diameter. In particular for systems containing binders with low thickening power the value of both the independent variables can be extrapolated from the isoresponse surfaces shown in the two dimensional representation in Fig. 3.

In the isoresponse surfaces graph, each line represents *the locus* of the points in the experimental domain which have a constant median diameter or, in other words, all the combinations of binder and water amounts which give granules with a defined and constant d_{50}.

To be able to use the model as a predictive tool, however, it must be preliminarily validated with some independent experiments which are different from the initial experimental plan. For this reason, a point in the experimental domain with coordinates X_1=-0.5 and X_2= -0.5 was selected. It corresponds to the red star in Fig. 3a with 3% (w/w) of MD and 238 ml of water. The predicted value for the median diameter according to the model was Y_1 = 527.14 + 73.5 (−0.5) + 70.67 (−0.5) = 454 μm. The corresponding experiments were repeated twice and gave a median diameter of 463±35 μm, which is very close to that predicted.
The effect of the formulation variables on d_{50} can also be analyzed separately. Fig. 4 shows the dependence of the median diameter on the water and binder amounts respectively. In both cases it increases with the increase in binder and amounts of water (experimental variables). In general, MD based granules show a slightly higher sensitivity to the experimental variables with respect to PVP.

3.2. Binders with high thickening power

In the case of the experiments using binders with high viscogenic powers, it was only possible to vary the amount of binder, while the amount of water remained fixed. This was due to the very high sensitivity of the powder mixture to the water content, which rapidly led to overgranulation.
Therefore, all experiments with these binders were carried out with a fixed amount of water. The experimental responses obtained from the granulation experiments are summarized in Table 6 for KC and XG binders. From the analysis of variance it was observed that not only the mean diameter, d_{50}, but also the strength of the granules, $\sum_B$, for these binders were significantly dependent on the binder amount. Fig. 5 shows that d_{50} and $\sum_B$ both increase with binder amount and that the d_{50} in particular shows a linear trend with respect to the binder content. The linear regression equation for d_{50} has parameters as reported in Table 7. The formulations containing XG gave experimental responses more sensitive to formulation changes than those containing KC as can be appreciated from the higher slopes of the trends.

3.3. Reduction of water amount

Reducing the amount of water needed to yield a granule with satisfying technological properties (for example a d_{50}~500 μm as median diameter) can be beneficial in terms of time, energy consumption and costs during the subsequent step of drying. In order to explore the effects of binder viscosity on the amount of liquid required to granulate, three additional granulation tests have been performed using only water as the granulating binder (260, 270, 280 ml). This meant that the solid was 100% MCC without any binder. All the three experiments gave acceptable granulated products characterized by increasingly higher median diameters (531, 570, 620 μm respectively). With the aim of minimizing the water to be used in the process, the formulation with the lowest amount of water i.e. 260 ml (therefore yielding d_{50} = 531 μm granules) was selected as reference. The amount of water required to obtain the same median diameter with the four selected solid binders in the powder mixture was then calculated by extrapolation using the linear model of eq. 2 with the parameters taken from Table 5 for PVP and MD from Table 7 for KC and XG. All these values can be compared as summarized in Table 8. It can be noted that the amount of water required to attain granules of a constant size (d_{50} = 531 μm in this case) decreases with the thickening power of the binder. With XG, the amount of water was reduced to 210 ml corresponding to a reduction of 25% with respect to the case without solid binder.

3.4. Difference between binders

The data analysis carried out so far has shown that some experimental responses (or granule properties) such as granule shape and flowability did not change significantly by varying the binder content. However, some differences can be observed if granules obtained with different binders are compared. Fig. 6 shows that granules obtained with high thickening power binders presented a more regular shape than those obtained with low viscosity binders and, in particular, those containing KC were the most round. On the other hand, if the data from the additional trials are also included in the analysis, it can be observed that the granules without any binder (100% MCC) were the more irregular. The slight increase in roundness with viscosity is probably related to the higher shear resistance of the wet granules to the application of mechanical stress by the impeller. This increased shear resistance corresponds to a reduction in the deformation Stokes number, St_{def}, in which the externally applied kinetic energy on the granules is compared with the energy required for the deformation of the granule (Tardos, 1997; Litster & Ennis, 2004). The ratio is the St_{def}:

$$St_{def} = \frac{\rho v_c^2}{2\sigma_y} \tag{4}$$

in which v_c is the representative collision velocity of the granules within the mixer (proportional to the impeller tip speed) and σ_y the dynamic granule strength (proportional to the viscosity of the binder (van den Dries & Vromans, 2002). Keeping the operating condition (impeller speed) constant, and increasing the binder viscosity, decreases the St_{def} and moves the system (with a reduced amount of water) from the crumb to the steady growth regime (Litster & Ennis, 2004). In this way, breakage of the granules is prevented and for longer granulation time, in our experiments, the granules become increasingly rounder under the rolling action of the moving bulk. As a consequence of this enhanced roundness, KC granules were also the most free-flowing ones as shown in Fig. 7. As a final remark, it should be noted that, in general, there is a correlation between shape and flowability. However, in one case for XG, a higher flowability was expected based on the shape data. It is probable that shape alone cannot entirely explain the flowability of the granules, since other variables not analyzed here - such as surface roughness or stickiness generated by ambient humidity - may affect the result.

4. Conclusions

Four different solid binders were granulated with different amounts of microcrystalline cellulose and the results compared. The experimental campaign has confirmed the possibility of using these alternative binders and has shown the feasibility of the process which has demonstrated to be robust and predictable. Results show that final median diameter can be controlled by the formulation variables considered. It has also been verified that the amounts of water and solid binder required to yield a product with satisfactory technological properties decrease with increased solid binder in water viscosity, and with XG the amount of water was reduced by up to 25%. It is important to point out that the morphological properties of the resulting granules were also dependent on the

viscosity of the solid binder. In particular, binders with greater thickening power (KC and XG binder) produced more spherical granules.

References

Barbosa-Cánovas, G.V., Ortega-Rivas, E., Juliano, P., & Hong, Y. (2005). *Food Powder: physical properties, processing, and functionality.* Kluwer Academic/Plenum Publishers , New York.

Boerefijn, R., Juvin, P.-Y., & Garzon, P. (2009). A narrow size distribution on a high shear mixer by applying a flux number approach. *Powder Technology*, *189*, 172-176.

Cavinato, M., Bresciani, M., Machin, M., Bellazzi, G., Canu, P., & Santomaso, A.C. (2010a). Formulation design for optimal high-shear wet granulation using on-line torque measurements. *International Journal of Pharmaceutics, 387,* 48-55.

Cavinato, M., Franceschinis, E., Cavallari, S., Realdon, R., & Santomaso, A.C. (2010b). Relationship between particle shape and some process variables in high shear wet granulation using binders of different viscosity. *Chemical Engineering Journal*, *164,* 292-298.

Cavinato, M., Artoni, R., Bresciani, M., Canu, P., & Santomaso, A.C. (2013). Scale-up effects on flow patterns in high shear mixing of cohesive powders. *Chemical Engineering Science, , 102*, 1-9.

Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikstrom, C., & Wold, S. (2008). *Design of experiments: Principle and Applications*, Umetrics Academy, Umea Sweden.

Ferreira, S.L.C., dos Santos, W.N.L, Quintella, C.M., Neto, B.B., & Bosque-Sendra, J.M. (2004). Doehlert matrix: a chemometric tool for analytical chemistry-review. *Talanta, 63,* 1061-1067.

Forny, L., Marabi, A., & Palzer, S. (2009). Wetting, disintegration and dissolution of agglomerated water soluble powders. *9th International Symposium on Agglomeration*, *Sheffield, UK*

Franceschinis, E., Bortoletto, C., Perissutti, B., Dal Zotto, M., Voinovich, D., & Realdon, N. (2011). Self-emulsifying pellets in a lab-scale high shear mixer: Formulation and production design. *Powder Technology*, *207,* 113-118.

Hamed, E., Moe, D., Khankari, R., & Hontz, J. (2005). Binders and Solvents, *Handbook of Pharmaceutical Granulation Technology* ,second edition, ed. Parikh D.M. (Taylor & Francis Group, Boca Raton), 112.

Knight, P.C., Seville, J.P.K., Wellm, A.B., & Instone, T. (2001). Prediction of impeller torque in high shear powder mixers. *Chemical Engineering Science, 56,* 4457-4471.

Leuenberger, H., Puchkov, M., Krausbauer, E., & Betz, G. (2009). Manufacturing pharmaceutical granules: Is the granulation end-point a myth? *Powder Technology, 189,* 141-148.

Litster, J.D., & Ennis, B. (2004). *The science and engineering of granulation processes*. Kluwer.

Mathieu, D., Nony, J., & Phan-Tan-Luu, R. (1999). NEMRODW (New Efficient Technology for Research using Optimal Design) software, LPRAI, Marseille.

Palzer, S. (2005). The effect of glass transition on the desired and undesired agglomeration of amorphous food powders. *Chemical Engineering Science, 60,* 3959-3968.

Palzer S. (2009). Influence of material properties on the agglomeration of water-soluble amorphous particles. *Powder Technology, 189,* 318-326.

Paul, E.L., Atiemo-Obeng, V.A., & Kresta, S.M. (Eds.) (2003). *Handbook of Industrial Mixing: Science and Practice*. Wiley-Interscience, John Wiley & Sons, Inc., Hoboken, New Jersey.

Santomaso, A.C., Lazzaro, P., & Canu, P. (2003). Powder flowability and density ratios: the impact of granules packing. *Chemical Engineering Science*, *58,* 2857-2874.

Simons, S.J.R., Rossetti, D., Pagliai, P., Ward, R., & Fitzpatrick, S. (2004). Predicting the performance of granulation binders through micro-mechanistic observations. *Powder Technology*, 140, 280-289.

Smith, P.G. (2011). *Introduction to Food Process Engineering*, 2nd ed., Springer, New York.

Tardos, G.I., Kahn, M., & Mort, P. (1997). Critical parameters and limiting conditions in binder granulation of fine powders. *Powder Technology, 94,* 245-258.

van den Dries, K., & Vromans, H. (2002). Relationship between inhomogeneity phenomena and granule growth mechanisms in a high-shear mixer. *International Journal of Pharmaceutics, 247,* 167-177.

TABLES

Table 1. Ranges of the formulation variables (amount of binder and water) studied for binders with low and high thickening power.

	Binder		Water	
Binders with high viscogenic power	**Lower limit [%]**	**Upper limit [%]**	**Lower limit [ml]**	**Upper limit [ml]**
MD	2	6	232	258
PVP	2	6	232	258
Binders with low viscogenic power	**Lower limit [%]**	**Upper limit [%]**	**Fixed limit [ml]**	
KC	0.5	1.25	220	
XG	0.25	0.75	210	

Table 2. Doehlert design used to study the effect of the codified variables X_1 (binder amount) and X_2 (water amount) studied at 5 and 3 levels respectively in the case of binder with low thickening power.

Experiment	X_1	X_2	Binder (%)	Water (ml)
1	0	0	6	245
2	1	0	2	245
3	0.5	0.866	5	258
4	-1	0	3	232
5	-0.5	-0.866	5	232
6	0.5	-0.866	3	258
7	-0.5	0.866	4	245

Franceschinis, E., Santomaso, A.C., Trotter, A., Realdon, N. High shear mixer granulation using food grade binders with different thickening power (2014) *Food Research International, 64, 711-717.*
DOI: 10.1016/j.foodres.2014.08.005

Table 3. Experimental plan for binders with high thickening power. Water amount was fixed for each polymer.

Binder	Experiment	Binder (%)	Water (ml)
KC	1	0.50	220
	2	0.75	220
	3	1.0	220
	4	1.25	220
XG	1	0.25	210
	2	0.50	210
	3	0.75	210

Table 4. Technological properties of the granules containing MD or PVP.

Binder	Exp.	Y_1 d_{50} (µm)	Y_2 Φ_R (-)	Y_3 HR (-)	Y_4 Σ_B (kN)
MD	1	625	0.68±0.05	1.07±0.02	22.4±8.7
	2	493	0.71±0.05	1.07±0.02	15.3±6.1
	3	600	0.70±0.05	1.08±0.00	23.1±7.3
	4	389	0.70±0.04	1.07±0.01	13.0±5.2
	5	500	0.73±0.05	1.09±0.01	18.3±7.6
	6	534	0.68±0.05	1.07±0.01	22.1±7.2
	7[a]	549±20	0.70±0.05	1.08±0.01	19.5±7.4
PVP	1	581	0.69±0.05	1.10±0.01	19.8±5.3
	2	493	0.71±0.06	1.09±0.01	10.9±4.5
	3	581	0.70±0.04	1.10±0.01	23.3±7.3
	4	472	0.70±0.01	1.10±0.01	13.0±5.2
	5	507	0.69±0.06	1.10±0.01	18.3±7.6
	6	550	0.68±0.05	1.10±0.01	22.1±7.2
	7[a]	540±32	0.68±0.06	1.11±0.01	19.5±7.4

[a]Experiments repeated 3 times

Franceschinis, E., Santomaso, A.C., Trotter, A., Realdon, N. High shear mixer granulation using food grade binders with different thickening power (2014) *Food Research International, 64, 711-717.*
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Table 5. Coefficient values obtained from the multivariate linear regression analysis of the size (median diameter) of the granules based on MD and PVP.

MD		**PVP**	
Coefficients	**Value**	**Coefficients**	**Value**
b_0	527.14	b_0	532.00
b_1	73.50	b_1	40.33
b_2	70.67	b_2	43.88
Coefficient of regression	**Value**	**Coefficient of regression**	**Value**
R^2	0.858	R^2	0.974

Table 6. Technological properties of the granules containing KC or XG.

Binder	**Exp.**	Y_1 d_{50} (µm)	Y_2 Φ_R (-)	Y_3 HR (-)	Y_4 Σ_B (kN)
KC	1	574	0.72±0.07	1.09±0.01	9.7±3.5
	2	700	0.79±0.04	1.06±0.01	17.7±4.4
	3	811	0.74±0.04	1.07±0.02	20.6±3.6
	4[a]	900±71[a]	0.76±0.05	1.07±0.00	23.1±5.2
XG	1	550	0.72±0.06	1.09±0.02	13.2±5.3
	2	615	0.72±0.06	1.09±0.01	14.0±3.2
	3[a]	865±56[a]	0.71±0.06	1.09±0.01	29.2±5.9

[a]Experiments repeated 3 times

Table 7. Coefficients of the linear model $y = b_0 + b_1x$ obtained by least squares regression analysis of the d_{50} obtained with KC and XG binders.

KC		**XG**	
Coefficients	**Value**	**Coefficients**	**Value**
b_0	365.10	b_0	371.67
b_1	435.60	b_1	610.00
Coefficient of regression	**Value**	**Coefficient of regression**	**Value**
R^2	0.994	R^2	0.921

Franceschinis, E., Santomaso, A.C., Trotter, A., Realdon, N. High shear mixer granulation using food grade binders with different thickening power (2014) *Food Research International, 64, 711-717.*
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Table 8. Comparison between binders with different thickening power and amounts of water required to yield granules with d_{50} = 531 µm.

Powder	Binder	Amount of binder (%)	Amount of water (ml)	Water/MCC (%)
MCC	-	0	260	130
MCC	MD	5.0	230	115
MCC	PVP	4.5	230	115
MCC	KC	0.40	220	110
MCC	XG	0.25	210	105

FIGURES

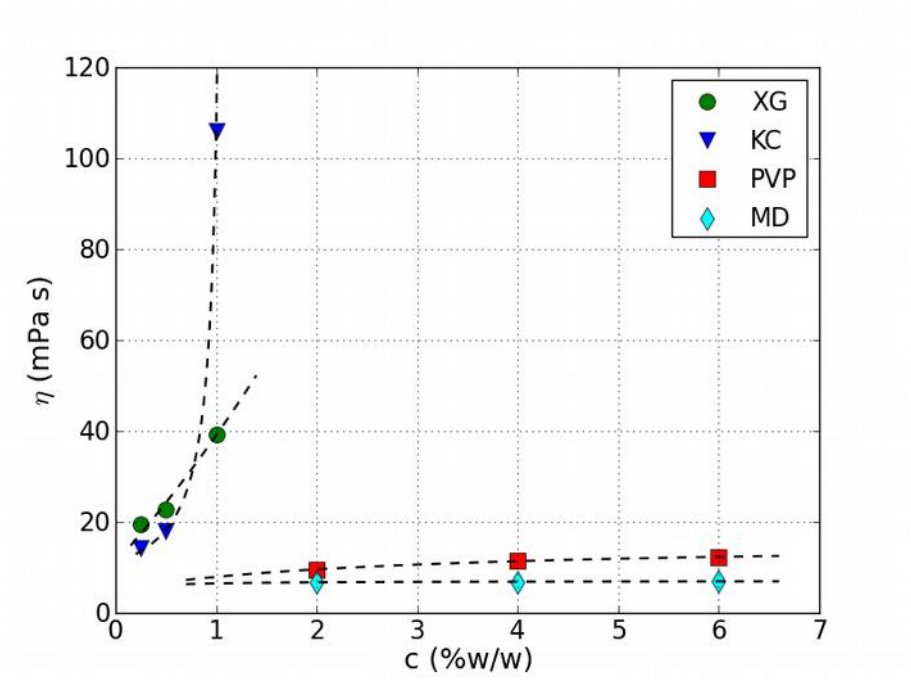

Fig. 1. Dispersion viscosity for the selected binders as a function of the concentration in water.

Franceschinis, E., Santomaso, A.C., Trotter, A., Realdon, N. High shear mixer granulation using food grade binders with different thickening power (2014) *Food Research International, 64, 711-717.*
DOI: 10.1016/j.foodres.2014.08.005

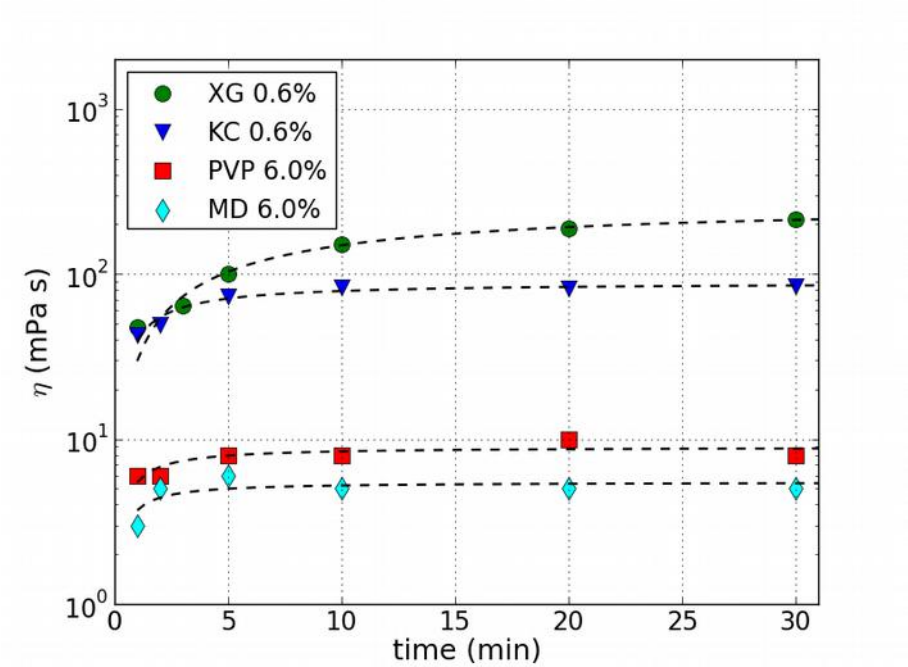

Fig. 2. The thickening tendency of the selected polymers is the result of a combination of different rate processes with different kinetics (dispersion, hydration, gelification). In general, polymers giving lower viscosity dispersions (PVP, MD) hydrate faster than those yielding greater viscosity (KC, XG).

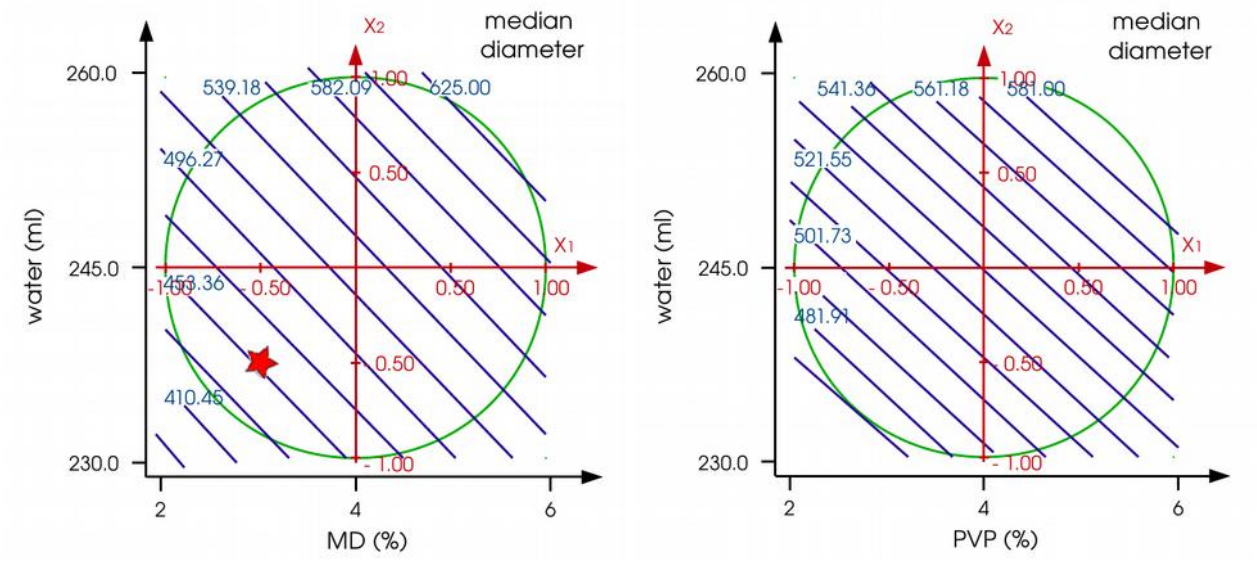

Fig. 3. Two dimensional representation of the isoresponse planes obtained from the multivariate regression analysis for the selected variable d_{50}: a) MD based granules. The star represents the additional granulation performed to validate the model; b) PVP based granules.

Franceschinis, E., Santomaso, A.C., Trotter, A., Realdon, N. High shear mixer granulation using food grade binders with different thickening power (2014) *Food Research International, 64, 711-717.*
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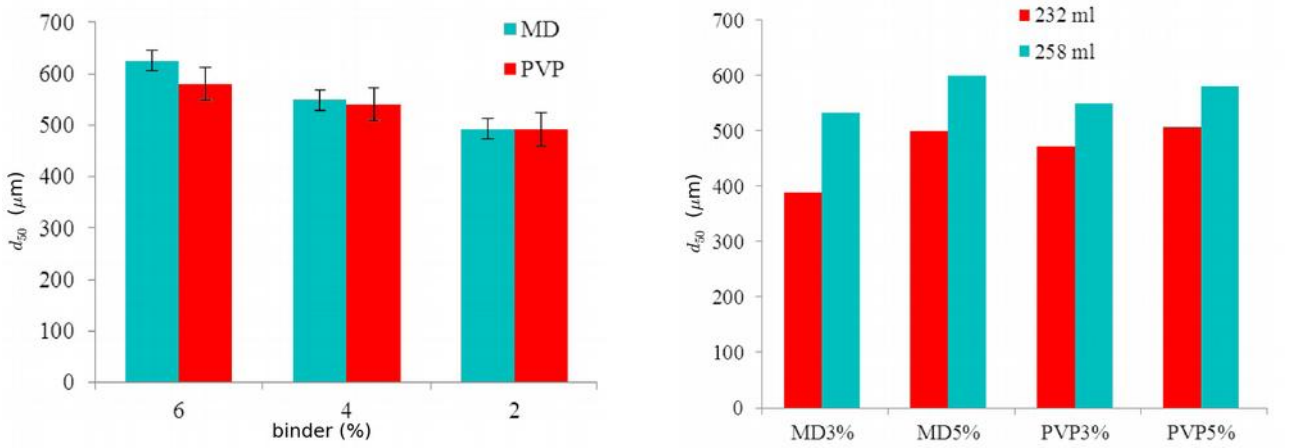

Fig. 4. Effect of the experimental variable analyzed singularly on the d_{50}: a) effect of solid binder amount on granules produced with 245 ml of water; b) effect of amount of water.

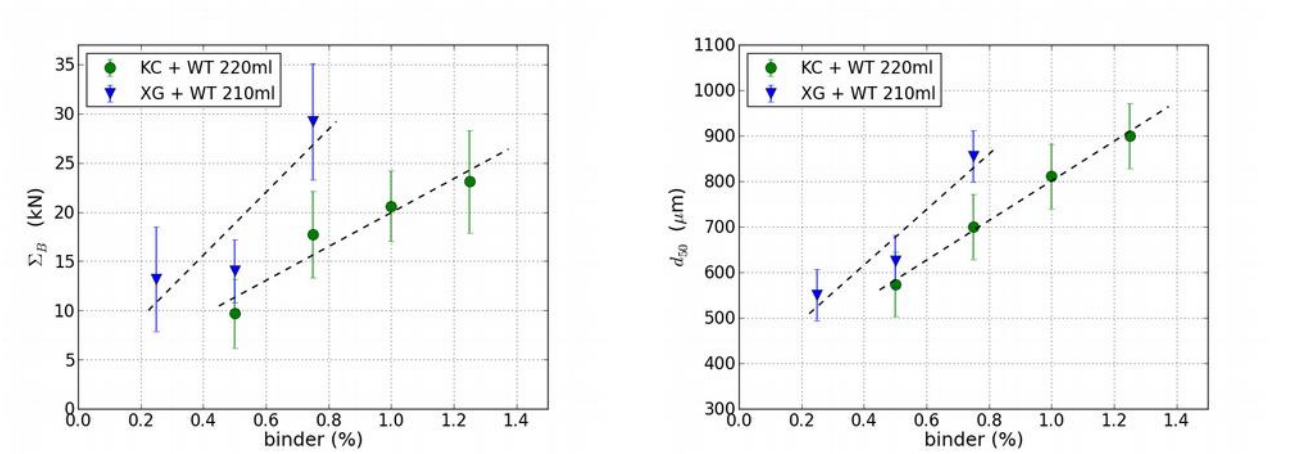

Fig. 5. Dependence of a) median diameter d_{50} and b) granule strength $\sum_B$ on binder amount for KC and XG binder based granules.

Franceschinis, E., Santomaso, A.C., Trotter, A., Realdon, N. High shear mixer granulation using food grade binders with different thickening power (2014) *Food Research International, 64, 711-717.*
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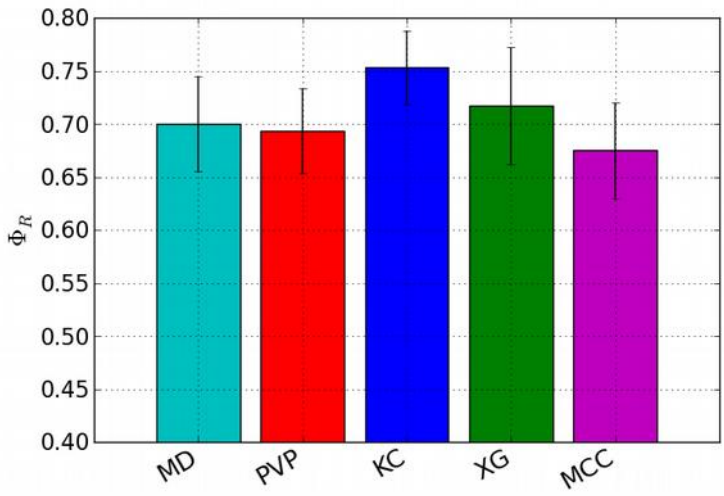

Fig. 6. Granule roundness with different binders. Even though the same operating conditions have been used for granulating, the granules based on the two binders with higher thickening power are more regular.

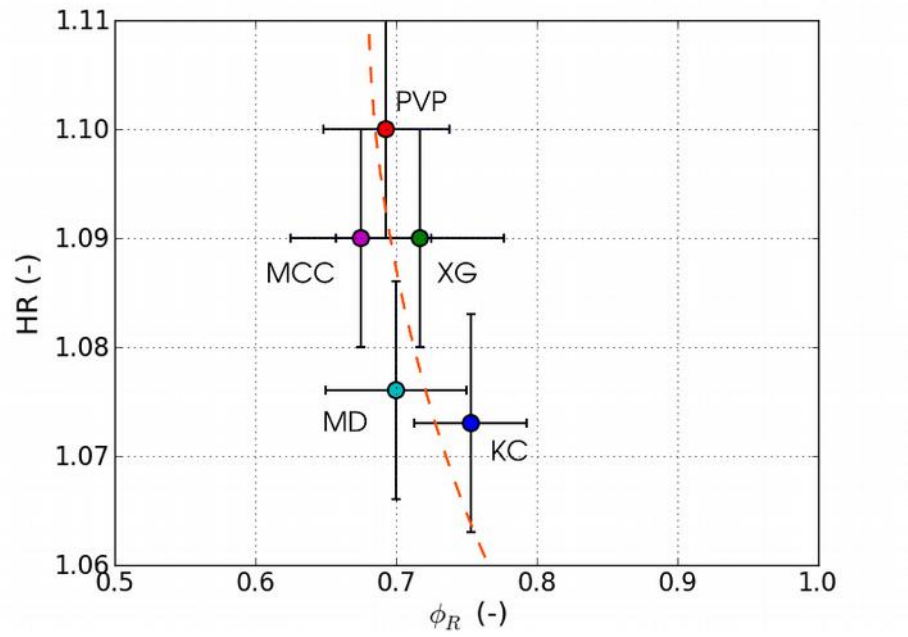

Fig. 7. Comparison between shape (roundness) and flowability (HR). Rounder granules show a slightly greater flow propensity.