Abstract

High-shear wet granulation is commonly used in many industries such as in the pharmaceutical industry to convert fine cohesive powders into dense and round granules. The purpose of this work was to determine the effects of some important powder properties (crystalline or amorphous nature, hygroscopicty, solubility and particle size) and process variables (liquid addition rate, impeller speed) on the early stages of the granulation process and on drug distribution in granules obtained by high-shear wet granulation. The glass transition concept coupled with on-line impeller torque monitoring and measurements of the time evolution of the particle size distribution were used to study mixtures of pharmaceutical excipients and some common active ingredients. In particular a formulation map for estimating the minimum amount of liquid binder required to induce appreciable granule growth is presented, thus outlining a new method to considerably increase the predictability of the behaviour of different formulations on the basis of the physical properties of each single component. The description of the effects of the wetting condition on drug uniformity content in some formulations with hydrophobic active ingredients is given as well.

Keywords: wet granulation, high shear mixer, glass transition, hydrophobic active ingredient

Introduction

High-shear wet granulation (HSWG) is often performed in many industries such as the pharmaceutical industry to convert fine cohesive powders into dense and round granules. Granules are produced by mixing and wetting a powdered mixture composed typically of a drug, some excipients and a solid binder. The overall purpose of HSWG is to obtain a final product with improved characteristics such as better flowability, compressibility and reduced segregation potential of the components and in particular of the drug. It is a batch operation carried out in a stainless steel bowl equipped with an impeller and a chopper. It is usually performed in three phases: homogenization of dry powders, liquid binder addition and wet massing without further liquid addition. The correlation between process/formulation variables and granule property evolution is not fully understood, and deeper insight of the granule growth process is required to obtain a consistent product from batch to batch.

Motor power consumption and impeller torque have been used to study the granule growth process since they depend on the cohesive force of the wet mass or the tensile strength of the agglomerates, which in turn are supposed to depend on the saturation degree of the powder mixture. In particular they increase suddenly when the pendular state is reached, and become relatively constant by adding further liquid as soon as an equilibrium between granule growth and breakage is attained.

Although attention has often been devoted to the end-point determination, much less effort has been put on the understanding of the onset of granulation. Accordingly, the initial granule formation phase and subsequent growth/breakage mechanisms are not completely clear, so that prediction of granule properties remains difficult. In addition, granule growth behaviour in HSWG has often been described considering primary particles as inert materials held...
strong effects on the granule nucleation and subsequent growth behaviour within the initial mixture, for example, can have both amorphous and crystalline pharmaceutical powders, and were granulated using deionized water at 20 °C.

Two experimental sets without pharmaceutical active ingredients and one set with active ingredients are presented here. Firstly, granulation experiments were carried out to determine the influence of the impeller speed on impeller torque profiles and on the particle size distribution of the final granules. At this stage, the powder mixture composition was held constant and was (on a weight basis): lactose monohydrate 150M (73.5%), microcrystalline cellulose (20%), HPMC (5%) and croscarmellose sodium (1.5%). Variables were: the impeller speed 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.

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

This experimentation was designed to determine the role of two different dry amorphous binders in 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).

The third set of granulation experiments was carried out comparing the effect of three different crystalline active ingredients. The active ingredient was either acetylsalicylic acid, paracetamol or caffeine. The formulation was composed of: active ingredient (50%), lactose monohydrate 150M (23.5%), microcrystalline cellulose (20%), PVP (5%) and croscarmellose sodium (1.5%). Impeller speed during wetting was set at 500 or 1200 rpm, liquid flow rate at 8 or 12 ml/min according to the experiment. In order to emphasize the critical role of water addition (amount and distribution) in the early phases of the process and its implication on drug uniformity content, the three drugs all presented low hygroscopicity and solubility, but different average particle sizes (62, 113, 328 μm for paracetamol, caffeine and acetylsalicylic acid, respectively).

In order to investigate only the initial phases of granule formation and growth, all three sets of experiments were stopped at the end of the liquid addition phase, so wet massing was not performed. The volumetric fill level of the vessel was 40% for a weight of powder of about 400 g.

2. Materials and methods

All the 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. The granulator was able to measure and record impeller torque during granulation. Formulations were mixtures of both amorphous and crystalline pharmaceutical powders, and the wetting phase. However, powders used in industry may interact differently with the wetting agent, modifying their properties. An amorphous powder within the initial mixture, for example, can have strong effects on the granule nucleation and subsequent growth behaviour. Moreover, despite the essential importance of some specific powders in the formulation such as the active substance in pharmaceutical HSWG, relatively few works have presented a detailed analysis of the role of drug characteristics (such as drug type, particle size and shape, hygroscopicity) in granule nucleation and growth kinetics. Differences in physical properties between drug and excipients or non-optimal process conditions may lead to selective agglomeration of certain components, causing content uniformity problems.

The role of various components differing in their amorphous or crystalline nature (specifically solid amorphous binders and crystalline drugs) are investigated here during the initial phase of the granulation process, i.e. during wetting. The glass transition concept for amorphous powders, coupled with online impeller torque measurements, has been used to identify the onset of granulation intended as the onset of significant granule growth. The onset of granulation has been identified as an abrupt increase in torque when the amount of added liquid binder exceeds a critical threshold. In particular, a formulation map has been developed which groups the elements of the formulation in three classes, namely diluent, dry binder and liquid binder. The critical amount of liquid can be correctly predicted by this map as a function of the formulation composition under some limitations. The effects of the active crystalline ingredients on the granulation process are also analysed by torque measurements. Particularly, the influence of some important particle characteristics such as size and hygroscopicity on the granule growth behaviour has been analysed. The effects of changes in process variables such as impeller speed or liquid flow rate have been considered as well.
3. Results and discussion

3.1 On the onset of granule growth

Typical impeller torque profiles obtained from experiments are shown in the inset of Fig. 1 as a function of the added liquid at three different impeller speeds (500, 850 and 1200 rpm). It can be observed that torque increases almost proportionally with increasing the stirring speed and that the profiles show a similar shape. Initially, torque values increase slightly with the amount of liquid, indicating a progressive densification of the mixture due to the action of capillary forces. The subsequent decrease of the slope is interpreted as lubrication of the mass, which reduces the stress on the impeller. When the added volume of water is larger than a certain value, an abrupt increase in torque is observed. The changes of slope can be studied by the first derivative of the torque profiles after numerical filtering in order to eliminate noise. A minimum in the curves can be visibly located just before the steep torque increase (marked by the circles in Fig. 1.)

To monitor the PSD evolution during agglomeration, digital images of the powders were taken to obtain a more accurate description of the nucleation phase. The operative conditions of the 850 rpm experiments were chosen as a reference and samples were progressively collected during granulation at different moisture contents (20, 40, 60, 80% of water addition). Some binary images of the samples are compared in Fig. 2 with torque and torque first derivative profiles. Visual inspection of the images shows that a substantial increase in the size of the granules occurs after the addition of 40% out of 100ml of water (or 10% on batch weight), which corresponds roughly to the minimum in the derivative profile.

The corresponding liquid volume has therefore been identified as the critical liquid amount (or minimum liquid volume) required to yield substantial agglomeration of the mass for a given operating condition. This critical value will be used in the subsequent analyses as a distinctive, clearly identifiable and reproducible feature of the granulation process.

3.2 On the role of amorphous components

Having identified a critical amount of liquid as the marker of the onset of granulation, an explanation of what happens at the inflection point of the torque profile (or the minimum in the derivative profile) is required. Such an explanation can be found when considering the granulation process in the light of the glass transition theory.

When water is added to the dry powder mixture, the nuclei formation phase can start as described by the nucleation regime map proposed by Litster et al.\textsuperscript{15}. Absorbed water is then split up among the formulation components on the basis of their hygroscopicity, and in particular the water absorbed by the dry amorphous binder acts as a strong plasticizer decreasing the amorphous binder glass transition temperature $T_g$. Decreasing the binder $T_g$ down to the powder temperature (equal to ambient temperature) increases the molecular mobility of the binder and leads to migration of the amorphous material into the

![Fig. 1](image-url) Effect of impeller speed on impeller torque profiles (inset) and torque derivative profiles as a function of added liquid binder (water). The minimum on the derivative profile is marked with circles.
water on the particle surface. This creates a highly viscous layer on the binder particle surface, causing a significant increase in stickiness and promoting the agglomeration process\(^{16,17}\). As a consequence, the impeller torque value rapidly increases at the inflection point and the granule growth accelerates as qualitatively shown in Fig. 2. A formulation map is furthermore proposed in order to isolate the contribution of the amorphous binder to the water uptake. Each of the vertexes in the ternary diagram represents a main component (diluents, dry binder or liquid binder), whereas each edge represents a binary component combination.

The measured critical water amounts are represented in the ternary diagram by several markers where the dry binder (HPMC = circles; PVP = squares) ranges from 1 to 10%. As can be observed in Fig. 3, the markers are arranged in two straight lines which represent a specific diluent-dry binder-liquid system and which intersect the diluent-liquid and the binder-liquid axes. HPMC and PVP lines intersect the diluent-liquid axis very close to each other, outlining point (1). This point represents the water amount absorbed by the diluents and that is 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.

A dry formulation composition (0% liquid) can be identified as a point on the binder-diluent axis. With the addition of water, the point representing the actual composition of the granulating mixture moves from the binder-diluent axis along the dashed lines towards the 100% liquid vertex. Once the HPMC or PVP lines and the dashed line (corresponding to a given dry formulation composition) are defined, it is possible to use the diagram in a predictive way by determining the critical amount of liquid from their intersection.

In order to define the HPMC or the PVP lines, however, points (1), (2) and (3) are required. Points (2) and (3) can be estimated by a glass transition temperature measurement using the Gordon-Taylor equation\(^{18}\). The curves representing the glass transition temperature as a function of the equilibrium water content for HPMC and PVP are shown in Fig. 4.

The glass transition temperature of a wet binder sample has been estimated using the modified Gordon-Taylor equation in order to best fit the experimental data:
where \( k \) is an empirical constant, \( T_{g_1} \) is the dry binder glass transition temperature, \( T_{g_2} \) is the water glass transition temperature (-138°C), \( w_1 \) and \( w_2 \) are the binder and water weight fractions (with \( w_1 = 1-w_2 \)), respectively, and \( q \) is an empirical constant reflecting the specific binder-water interaction.

Assuming the reference condition:

\[ T_g = T_a \approx T_{powder}, \]  

where \( T_i \) is the ambient temperature expected to be equal to the powder temperature \( T_{powder} \), the corresponding water content \( w_2^* \) can be expressed as fol-

Fig. 3 Representation of the effect of the main formulation components on the critical water amount through a ternary diagram. Vertexes represent the key component: diluent (lactose monohydrate and microcrystalline cellulose), dry binder (HPMC or PVP) and liquid (water). The shaded zone corresponds to the granulation area which is of practical interest.

Fig. 4 Glass transition temperature as a function of water content in samples of (a) PVP and (b) HPMC: comparison between the experimental data, literature\(^\text{39}\) and the dotted line representing experimental data and literature fitted to the modified Gordon-Taylor model\(^\text{29}\).
\[ w_2^* = w_2(T_g \approx T_{\text{powder}}). \]  

(3)

The experimental and literature data\(^{(19)}\) in Fig. 4 were fitted to the Equation (1). The intersection between the glass transition curves and the ambient temperature gives the water amount required to obtain the dry binder glass transition and the formation of a highly viscous mixture.

It can be noted in Fig. 4 that the literature and the experimental data for PVP are in close agreement and are accurately fitted by the modified Gordon-Taylor model. The estimated moisture content required for the glass transition is 0.24. Agreement between experimental and literature data for HPMC is less satisfactory. Moreover, the maximum attainable moisture content for an HPMC sample in static conditions at 90% is about 0.20. As a consequence, not only the fitting of data is less accurate but also an extrapolation is required to estimate the moisture content for the HPMC glass transition. The value derived from extrapolation is 0.33 and should be treated with great caution. Nonetheless, the estimated values of moisture content for glass transition (0.24 and 0.33) and points (2) and (3) in Fig. 3 (0.21 and 0.36 for PVP and HPMC, respectively) are in satisfactory agreement, suggesting that points (2) and (3) can be determined by static \(T_g\) measurements.

The water amount absorbed by the hygroscopic diluent components in point (1) can be roughly estimated by the water sorption isotherms in Fig. 5. The RH% at which the PVP glass transition occurs (corresponding to the water content \(w_2^*\)) can be considered as a reference condition for identification of the contribution of each hygroscopic diluent. Note that the dry binder (amorphous and water-soluble) has a higher hygroscopicity when compared to the diluents. For this reason, HPMC or PVP can be considered as the most important binding agent, while the other fillers (MCC and lactose, both crystalline) can be considered as sole diluents, which absorb water but have a weak binding strength.

The presence of a further component in the mixture, such as an active ingredient, can be taken into account by the map whenever its behaviour with respect to the liquid binder is known. This simply means to classify the drug as a diluent or as a binder according to its nature (amorphous or crystalline) and its hygroscopicity.

3.3 On the role of crystalline components

The water amount in crystalline powders generally increases slightly with the relative humidity and their mechanical properties do not change (below the solubilisation conditions). Moreover, the dissolution process of crystalline structures is much slower than that of amorphous ones due to the lower permeability of the crystalline matrix and the endothermic dissolution process\(^{(12)}\). These considerations further justify the choice of considering crystalline MCC and lactose as sole diluents in the previous analysis. Let’s now consider in more detail the interaction of different crystalline powders with the liquid binder, in particular when they are the active ingredient.

![Fig. 5](image-url)  

**Fig. 5**  
Sorption isotherms (25°C) of the formulation components: PVP (squares), HPMC (circles), MCC (diamonds) and lactose monohydrate (circles).
is of major interest since liquid-active interaction can influence the final drug content uniformity.

Following again the approach based on the use of torque curves and their derivatives, we found that the powder mixture with the three different drugs considered for this study presented different liquid requirements in order to yield the sudden increase in torque profiles. Liquid amounts (%w/w on the initial batch size) corresponding to the inflection point in torque profiles (i.e. minimum in first derivative profiles) can be compared in Fig. 6 at different operating conditions. As can be seen, the critical liquid amount clearly discriminates between the three different active ingredients. In particular it is possible to find a correlation with the drug particle size. In particular, the larger the particle size, the lower is the liquid amount corresponding to the inflection point in torque profiles and required to start most of the granule growth. For example, inflection points for paracetamol occurred on average after 10% water was added, whereas for acetylsalicylic acid about 5% water was required. Also, process conditions made a difference on the critical liquid amounts required to achieve torque profile inflection.

The finer the drug particle size, the larger the differences between the critical liquid amounts at low and high rotational speed (LS and HS, respectively, in Fig. 6). Especially for paracetamol, it can be noted that higher liquid amounts are necessary when the impeller speed is lower. Moreover, the highest liquid flow rate (HF) gives higher liquid amount percentages.

Summarizing, a finer particle size, lower impeller speed and higher liquid flow rate seem to cause a higher demand of liquid for the torque inflection point. According to the theory proposed by Leuenberger and co-workers, a higher liquid amount required for the torque inflection point also means that a higher liquid content is required to reach the pendular state and start the liquid bridge formation. So if the torque inflection point can be associated to the bridge formation, and a higher water amount is required for torque inflection when operating in poor wetting conditions (low impeller speed and high liquid flow rate), it can be argued that it is not the volume of the bridges but their number that is important. Poor wetting tends to give few large bridges (in contrast to optimal wetting which gives several small and homogeneously distributed bridges), and in order to increase their number, a higher liquid amount is required. This speculation is not in conflict with the glass transition theory since in the presence of amorphous particles, a larger concentrated volume of liquid would probably give a lower viscosity increase than small distributed bridges, since the resulting solution would be more diluted.

Wetting conditions are also of major importance for obtaining an optimal drug distribution, especially when the drug has a poor affinity with water. To investigate this problem, size fractions corresponding

![Graph](image1)

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

for paracetamol and caffeine might be due to unsat-
to the presence of lumps and less wet areas, thus
suggested that a poorer liquid distribution might lead
occurred when the impeller speed is higher.

bution and poor wetting (see
explained by considering breakage phenomena that
ganule growth of hydrophilic materials tends to take
place selectively, as described by Belohlav et al. 10.
As a matter of fact, each active ingredient used in the
present research showed poor hygroscopicity and
poor solubility compared to the two main excipients.
These differences can therefore be considered as a
potential cause of selective agglomeration. It can be
noted in Fig. 7 that most of content uniformity prob-
lems occurred with paracetamol, especially at lower
impeller speed. Paracetamol-based granules obtained
using the lowest impeller speed and highest liquid
flow rate showed the highest discrepancies: a higher
drug content in the larger granules and a very low
drug content in the x<sub>50</sub> size fraction. Caffeine-based
granules obtained with the lowest impeller speed also
showed content uniformity problems and a lower
drug concentration in the x<sub>50</sub> size fraction. On the
other hand, granules with acetylsalicylic acid showed
the highest gap at high impeller speed and liquid flow
rate. In this case, the drug content was the highest in
the fines and non-granulated product. The approach
developed by Litster, Hapgood and co-workers 5,20
can be considered in order to explain the discrepan-
cies between actual and ideal drug content. Accord-
ing to this approach, a finer particle size determines
a higher liquid penetration time, thus worsening the
liquid distribution within the wet mass.

Moreover, a lower impeller speed and higher liq-
uid flow rate determine a higher dimensionless spray
flux number and consequently a worse liquid distribu-
tion and poor wetting (see Fig. 8). It is therefore
suggested that a poorer liquid distribution might lead
to the presence of lumps and less wet areas, thus
worsening drug distribution as well.

Whereas the cause of content uniformity issues
for paracetamol and caffeine might be due to unsat-
satisfactory liquid distribution conditions, the high
concentration of acetylsalicylic acid in the fines can be
explained by considering breakage phenomena that
occur when the impeller speed is higher.

These phenomena might be the cause of the layer-
ning mechanism detected with SEM image analysis
(Fig. 9). The use of a higher liquid flow rate probably
led to less homogeneous wetting conditions, thus
promoting the formation of less lubricated areas and
more intensive breakage phenomena.

Conclusions

This work was aimed at developing more sys-
tematic and quantitative criteria for high-shear wet
granulation design on the basis of the physical prop-
erties of the individual components. A formulation
map has been presented which describes the onset
of granulation as a function of three formulation
variables: diluent, dry and liquid binder. Component
classification in these three groups was performed
according to their nature (amorphous or crystalline)
and hygroscopicity. Results show that it is possible
to carry out an early assessment of the critical liquid
volume required to start most of the granule growth
through an application of a Gordon-Taylor model and
by performing some independent measurements of
the initial formulation properties. The critical liquid
amount was also unambiguously determined by on-
line torque measurements in order to verify map
predictions. Torque measurements were also used to
study the effect of crystalline components in the for-
mulation. In particular three hydrophobic drugs were
considered since their uniform distribution into gran-
ulated products is of major interest. Results show the
critical role of the wetting conditions. It was observed
that the critical liquid amount increases with decreas-
ing drug particle size. Different growth mechanisms
were proposed in order to explain content uniformity
discrepancies. For smaller particle sizes (paracetamol
and caffeine), a selective agglomeration of the hydro-
phobic drug was observed because of poor wetting
(high liquid flow rate and low mixing speed), while
for larger particles (acetylsalicylic acid), problems of
content uniformity were observed with ideally good
wetting conditions (high mixing rate and low liquid
flow rate) - probably because of the poor lubrication
of the powder and the consequent particle breakage
in the presence of intensive mixing.

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Fig. 7  Content uniformity analysis results: distribution of paracetamol, caffeine and acetylsalicylic acid in $x_{10}$ (a), $x_{50}$ (b) and $x_{90}$ (c) size fraction. Process conditions: LS – lower impeller speed (500 rpm), HS – higher impeller speed (1200 rpm), LF – lower liquid flow rate (8 ml/min) and HF – higher liquid flow rate (12 ml/min).

Fig. 8  Critical liquid amount and content uniformity problems as a function of penetration time and dimensionless spray flux number$^{15,20}$. 

Fig. 9  SEM images of granules with different drugs. The layering mechanism is particular evident for acetylsalicylic acid-based granules, where large crystals are covered by fragments.
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