UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Head Office:
Università degli Studi di Padova

Department:
Department of Pharmaceutical and Pharmacological Sciences

Ph.D. COURSE IN: Molecular Sciences
CURRICULUM: Pharmaceutical Sciences
SERIES: XXXI

RHEOLOGICAL CHARACTERIZATION AS A TOOL FOR HIGH-SHEAR WET GRANULATION PROCESS DEVELOPMENT

Coordinator: Prof. Leonard Prins
Supervisor: Dott.ssa Erica Franceschinis
Co-Supervisor: Dott. Ing. Andrea Claudio Santomaso
Ch.mo Prof. Nicola Realdon

Ph.D. student : Roberto Baggio

Abstract

Granulation is one of the most crucial processes for the pharmaceutical industry. It allows to improve the tabletability and the flowing properties of the powdered formulations. Moreover granules production reduces the dust presence in the working environment improving the operator safety. Several granulation techniques exist and are divided in two main groups: dry and wet granulation processes. Among these, high-shear mixer is one of the most employed wet granulation techniques in the pharmaceutical industries. Despite its wide application, the complete control of the process is far to be achieved. This is mainly due to the several variables which affect the resulting product; in fact high-shear wet granulation (HSWG) presents several process parameters which need to be controlled and most of them are formulation dependent. For this reason the process development is particularly difficult with this technique, with the risk for high-shear mixers to become the last choice when a new formulation needs to be granulated. However, the characteristics of granules produced in a high-shear mixer are strongly affected by the rheology of the wet mass which is processed; thus, it could be a useful tool to obtain preliminary indications about the evolution of the high-shear wet granulation process. Several works in literature studied the application of the on-line and off-line wet mass rheology for process control, end-point determination and scale-up. Despite those studies, it is still not possible to employ wet mass rheology unambiguously to predict the granulation process. The possibility to predict several aspects of the granulation process, such as: the amount of liquid binder which need to be employed, the granules growth regimes and the parameters which have a important impact on the granules characteristics, would be of dramatic importance for process development and in particular from a Quality-by-Design (QbD) perspective. The aim of the present work is to investigate the possibility of employing a mixer torque rheometer to predict: the amount of liquid for the process, the granules growth mechanisms and the critical process parameters using different formulations. Results obtained in the first phase of the project have shown that an easy and fast prediction of the optimal liquid amount, required to produce granules with acceptable technological properties, could be carried out by a rheological characterization using a mixer torque rheometer. Moreover the application of the second derivative to the torque profile have permitted to develop a reliable method to identify the optimal value of L/S, following confirmed by granulation experiments.

In the second phase, evaluation of the wet granules strength (expressed as consistency) has permitted to highlight a relationship between wet granule cohesion and the granules growth regimes. In particular, the value of wet mass consistency showed to be indicative of the growth mechanism followed by the granules during the process. In order to predict, and not only to describe, the granule growth mechanism, the torque evolution of wet masses was registered along time and it was used to evaluate the maximum value of the wet mass cohesion, corresponding to the Torque peak. Torque peak showed to be directly related to the final consistency of the granules produced with the same formulation and thus it could be used for the granules growth regimes prediction.

Finally in the last phase of the project was also investigated the possibility to predict the critical process parameters of the HSWG process through rheological measurements. Results highlighted that Torque peak could represent a potential tool for critical process parameters assessments.

Moreover it seems able to give important indications about the granule growth kinetic for those formulations which presented a steady growth regime. In particular, torque peak seemed to be a feasible tool for the prediction of the parameters which had the most significant impact on the mean diameter of the granules. In fact, the data acquired with the mixer torque rheometer in terms of Torque peak showed good accordance with the results obtained from granulation experiments. In conclusion, the results achieved with this study demonstrated the possibility of employing the wet mass rheology to predict several aspects of the high-shear wet granulation process and gain the necessary knowledge to improve the process development phase.

Contents

Chapter 1

General Introduction

Chapter 2

Liquid amount prediction for high-shear granulation

Chapter 3

Rheology of wet masses as a useful tool to predict the evolution of the granulation process

Chapter 4

Rheological characterization of powders: a useful tool to predict the influence of different process parameters on granules growth

Chapter 1

General Introduction

1.1 The granulation process

Granules are agglomerates of fine particles produced through different type of equipments. Granulation process is performed to improve the characteristics of starting materials such as flowing properties, tabletability and bulk density. Moreover it ensures the uniformity of particulate formulations preventing the segregation of active principal ingredients (API) and dust formation, thus improving the operator safety [1]. Granules produced are then used as a pharmaceutical dosage form themselves but more often are an intermediate for tablet production. Several granulation processes exist and they can be roughly divided in two main types: dry granulation and wet granulation processes. Among dry granulation processes, roll compaction is a continuous process widely employed in the pharmaceutical, chemical and food industry for the manufacturing of agglomerates. This technique has been in use for many years, but recently it gained a new scientific attention [1]. Roller compaction process consists on the formation of a compacted ribbon compressing the starting powders through two counter-rotating rolls. The produced ribbon is following milled and screened to produce the final granules of the desired size. The advantages compared with wet granulation, is the possibility to avoid the use of liquid binders making this technique feasible for moisture-sensitive materials and no drying steps are necessary [1]. Moreover the roller compactor works in continuous; this application is of emerging importance in the pharmaceutical industry environment. The drawbacks of this technique are: the densification of the material which can lead to loss on tabletability [2] and the amount of fines which are still present at the end of the process, which can be reduced using a dry binder [3].

Wet granulation is performed adding a granulation liquid to a moving powder bed. The powder mixture is mechanically mixed during the process. Generally in this technologies a binder is employed, which can be in a liquid or solid form. The solid binder can be solubilized in the granulation liquid which is following added to the formulation; otherwise it can be blended with the powder mixture and subsequently activated by the granulating liquid. The excipient acting as a binder can be a polymeric molecule which has the specific role of connecting the initial particle together. However the role of binder is often played by other excipients of the formulation, such as diluents, which can partially solubilize and form liquid bridges between the particles which will become solid after re-crystallization. Moreover the binder can be a low melting polymer which can be added after melting or as powder in the formulation mixture and following activated through heating the powder mass. Finally granules are dried or cooled to strengthen the binder bridges which form the agglomerates. Several equipments are employed for wet granulation: low shear and high-shear granulators, fluidized bed granulators and twin-screws granulators are the most common in the pharmaceutical industry. Low-shear mixers, such as planetary mixers and rotating drums are simple technologies for granules production. The agglomerates produced with such equipments are characterized by a low density due to the limited energy exerted to the wet mass [4]. On the other hand, high-shear mixers are characterized by the high energy applied to the granules. They present a main blade which fluidizes the starting materials while the granulating liquid is added to the moving powders through a nozzle. The produced granules are characterized by a spheroid shape and a high level of density. The high-shear mixer will be further discussed more in detail in the following section as it is the technique employed in this thesis. The main advantages of high-shear mixers are the short granulation time, the lower amount of liquid employed compared with other systems which is associated with a reduction of the drying time, and the possibility of having a one-pot process. The main disadvantage is the densification of the granules which can lead to a loss in tabletability [5–7]. Fluidized bed equipments are characterized by the presence of an ascending air stream deputed to the fluidization of the starting materials. The liquid binder is sprayed through a nozzle on the moving powders; the position of the nozzle can be different depending on the equipment or the manufacturer. The granules produced using this technique are generally characterized by a high porosity. The main advantages of this process are the narrow size distribution and flowing properties of resulting granules, the reduced overall process time due to the fact that all the steps (wetting, granulation and drying) are performed in the same equipment [8]. These characteristics make the granules produced using the fluidized bed, particularly feasible for tablet production [9]. The drawbacks of this technique are the fact it is not suitable to process moisture-sensitive materials and moreover it presents scale-up issues, as all the other batch-wise wet granulation techniques. Finally, an emerging technique is the twin-screw granulation process. This process works kneading a powder mixture using two co-rotating screws with a modular configuration, which allows the efficient mixing of the starting materials, the homogeneous distribution of the liquid binder within the powders and the densification of the formed granules. The main advantages of this process are typical of the continuous processes as: the improved efficiency, less product development time and an easier scale-up; moreover the screw configuration can be changed leading to a high design flexibility [10]. The downsides of this process are time consuming cleaning procedures and the difficulty to define the batch [11].

1.2 High-shear mixer (HSM)

High-shear wet granulation is a batch-wise process. Nowadays, it is one of the most employed technique in the pharmaceutical and detergent industries for size enlargement of powders in order to improve flow characteristics of poor flowing materials [12]. The main advantages of high-shear wet granulation are the following [6,7]:

- Efficient blending of the powder mixture, thus avoiding the need of an additional mixing step before the granulation;
- Short processing time;
- Lower amount of liquid required for granulation, thus reducing the drying phase and the energy required for solvent evaporation;
- The possibility to efficiently spread viscous binders among the granulating powders.

However this technique presents some drawbacks which can limit its application [7]:

- Production of dense granules which can lead to a loss of tabletability;
- The use of liquid binder limits its application to moisture and heat sensitive ingredients;
- The numerous parameters which need to be controlled during the process make difficult the development and the scale-up of a formulation.

High-shear mixers are characterized by a vigorous agitation of the wet masses which confers to the resulting granules a typical higher density compared with agglomerates produced using other granulation techniques [12]. High-shear mixers can be divided in vertical axis and horizontal axis equipments; vertical axis HSM are the most employed in the pharmaceutical industries.

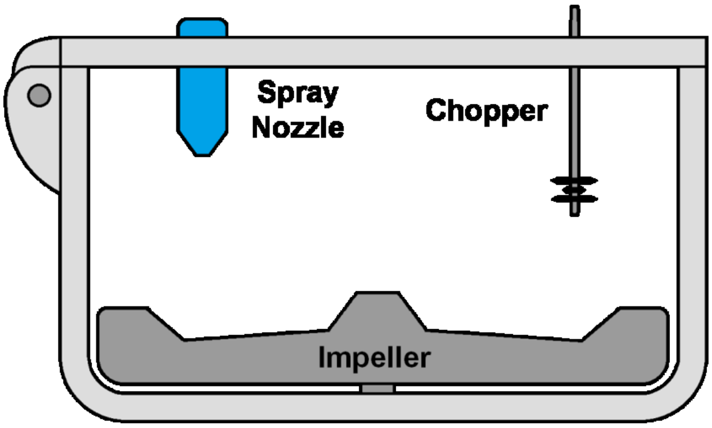


Figure 1.1: Typical layout of a vertical bottom driven high-shear mixer. In the picture are indicated the main components: the impeller, the chopper and the spray nozzle.

The typical layout of a vertical axis high-shear mixer is shown in Figure 1.1. This equipment is composed of a mixing bowl in which are present two mixing tool: a main blade called impeller and a secondary blade called chopper. The impeller is generally a three shaft blade deputed to the mass flow into the granulator and can be top driven or bottom driven (referring to the position of the engine deputed to the impeller motion). Several different designs of the impeller exist on the market and have a strong influence on the characteristics of the final granules [13]. The impeller fluidizes the powders allowing an efficient mixing of the formulation ingredients, a homogeneous distribution of the granulating liquid on the powder bed and the vigorous agitation of the wet mass during the granulation phase. The secondary blade called chopper is characterized by a small size and a high rotational speed. Its role is to break lumps which might form during the granulation process [12]. Powder and granules motion into the HSM is of paramount importance for the final characteristics of the product as it drives the consolidation of the granules. Two flux regimes are presented in literature during high-shear wet granulation: the bumping regime and the roping regime[12]. A graphical representation of the two regimes is shown in the Figure 1.2.

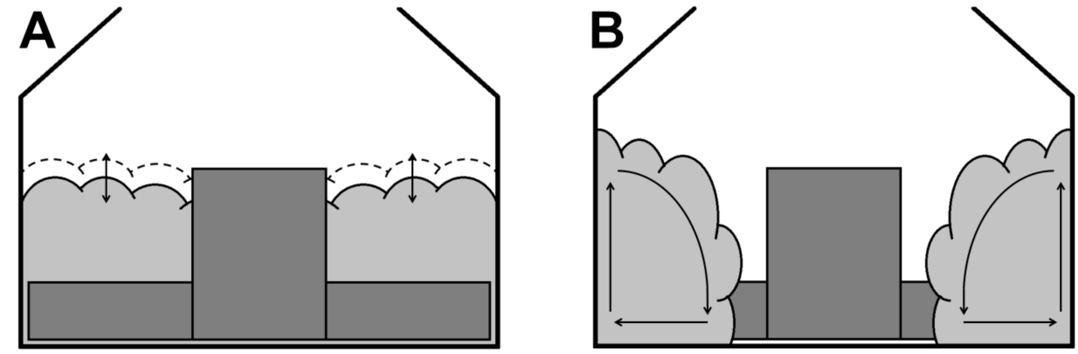


Figure 1.2: The flux regimes assumed by a wet mass in a high-shear mixer: A) the bumping regime achieved at low impeller speeds; B) the roping regime achieved at high impeller speeds. Adapted from Litster et al. [14].

The bumping regime (Fig. 1.2A) generally occurs when the impeller operates at a low speed. The movement of the impeller leads to the rise of the powder which falls right after the blade has passed. In this regime the gravitational force is dominant; thus, it is necessary to increase the speed of the impeller above a critical value in order to win the gravitational forces and achieve the roping regime (Fig. 1.2B). In the roping regime the powders follow a toroidal vortex motion because the force given by the impeller to the mass is enough to win the gravitational resistance of the powders. This peculiar movement is of great importance as it allows an optimal mixing of the formulation components and a correct turnover of the powders during the liquid addition which can be successfully distributed [14]. The critical speed value to switch from a bumping to a roping regime can be influenced by the design of the impeller and the bowl, the powder properties and the operative conditions. The design of the bowl can have an effect on the speed at which the processed powders achieve a toroidal vortex motion [14]. The bowl in fact can be characterized by different designs the most employed are: the rectangular and the tulip shape. A tulip shape bowl improves the motion of the powders promoting the assumption of a roping regime, thus this mixer design is more common and the most preferred. The mixing bowl can have also another important role. In some equipment the bowl can be heated. This can be exploited to perform melt granulation, as the powders mixture is heated up by their flow on the warm wall. This feature can also be used to dry the granules at the end of wet granulation. In this case a vacuum pump is applied on the granulator lid to remove the evaporating solvent. This application gives the possibility to use the HSM as a single pot equipment.

The granulating liquid is generally added to the moving powder using a single fluid nozzle placed on the lid of the HSM. The spray parameters, such the liquid flow and the drops diameter, are generally critical for the resulting granules characteristics as further discussed below.

The phases in a high-shear wet granulation process are generally the following:

1) loading the powder mixture into the mixer bowl;

2) mixing of dry powders, in order to have a uniform distribution of the formulation ingredients. The impeller speed is generally kept low in this phase to avoid the loss of powder due to its adhesion on the bowl wall caused by the high centrifugal forces;

3) addition of granulating liquid on the powder mixture surface while it is fluidized by the impeller. The speed of the impeller is adjusted in order to have a homogeneous distribution of the liquid binder into the powder bed;

4) granulation or wet massing phase in which the impeller speed is increased in order to give the high-shear forces to the wet mass. In this phase there is the granules formation and the following densification caused by the intense forces applied and the movement of the wet mass in the mixing bowl;

5) discharge of granules from the mixer and drying in a fluid bed dryer or in an oven;

6) sieving of dry granules.

1.3 Binding forces involved in granules formation:

Several binding forces are involved in the maintenance of granules structure. The primary particles are in fact bound together due to:

1.3.1 Electrostatic forces:

These attraction forces acts to particles when they are extremely close. They are the forces which generally limit the flowability of the powders. During granulation, Van der Waals forces aid nuclei formation leading to the organization of the primary particles. This makes them more prone for a successful binding. Formation of hydrogen bonds has a key role in wet granules formation [15].

1.3.2 Mechanical interconnections:

Mechanical interconnections are typical of materials with a fibrous structure which can physically interconnect. The strength of these connections is very low but if it is associated to other binding forces, such as hydrogen bonding, it can lead to formation of granules with sufficient resistance properties. This is the case of microcrystalline cellulose which can be granulated with water as liquid binder; the granules are formed of primary particles which are connected through hydrogen bonding and mechanical interconnections [16].

1.3.3 Liquid bridges:

Liquid bridges are generated because of the capillary pressure and interfacial forces which acts between a liquid and the primary particles. These interactions are typical for wet granulation techniques. The amount and the characteristics of the liquid binder employed is of great importance as it will be responsible of the final resistance of the agglomerates once that the solid bridges will form from the liquid interconnections. When the granulating liquid is added to the formulation, it penetrates gradually in the powders bed filling the voids between the primary particles and distributing on the interface between neighboring units. The primary particles are initially connected to each other by the formation of liquid bridges. Further addition of liquid leads to the gradual filling of the pores until forming a slurry. In literature are defined different capillary saturation states which are experienced by the powders when a liquid is gradually added. The liquid saturation states are called: pendular, funicular, capillary and slurry state (Fig. 1.3).

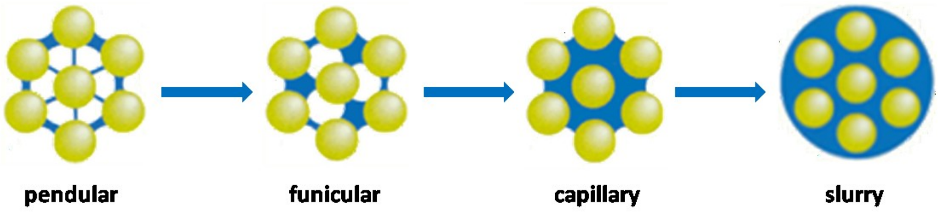


Figure 1.3: Graphical representation of the different liquid saturation states experienced by a powder while it is gradually wetted.

The pendular state occurs at the initial contact between the liquid and the primary particles. In this situation there are still several voids between the particles which are lightly connected to each other for the surface tension of the liquid. The funicular state takes place for further liquid addition. In this condition the liquid bridges increase their presence and the liquid occupy the surface of the primary particles. Voids are still present into the forming agglomerates; the mechanical forces applied and the capillary pressure given by the liquid tends to attract the primary particles reducing the volume of the forming granules. In the capillary state all the voids are filled by the liquid employed. This situation is the one in which the agglomerate has the maximum resistance given by both the capillary pressure and the interfacial interaction. For further liquid addition the formation of slurry occurs. In this state the particles are suspended in the liquid and the interactions between the particles are lost because of the high amount of liquid which is present [15,17].

1.3.4 Solid bridges:

The binding forces described above are important for the initial connection between primary particles; however the solid bridges are responsible for the mechanical resistance of the granules. The re-crystallization of binders dissolved in the granulating liquid employed in the process is responsible for the formation of solid bridges between the primary particles. In this case this role can be played by polymeric binders but also soluble excipients or active ingredients. When the liquid bridges are given by melted binder, the solid connections are generated by cooling the product as the binder solidify [15,18].

1.4 Mechanism of agglomeration

Agglomeration and granules formation have been traditionally divided into three separated phenomena which take place simultaneously, but their division is operated for an easier and deeper study of the process. The three phases in which the granules formation process can be divided are the following:

- Wetting and nucleation, where the liquid binder is added to the powders and distributed through the powder bed leading to nuclei formation;
- Consolidation and growth, where collisions between granules and between granules and the equipment, lead to the agglomerate growth and densification;
- Attrition and breakage, where the impact of the granules between each other or with the equipment lead to their breakage [19].

1.4.1 Wetting and nucleation

Wetting and nucleation is the phase in which there is the first contact between the formulation powder and the granulating liquid.

The liquid interacts with the powder to form the liquid bridges. These will form the solid connections between the particles after solvent evaporation [18]. This initial spread of liquid on the powder bed and the interaction between the liquid and the powder particles have been extensively studied and described in literature. Nucleation zone is the area where the liquid, distributed on the powder bed lead to nuclei formation. These nuclei are identified as the original particles which will lead to granules formation in the following phases because of their coalescence and further consolidation [19]. Thermodynamics of wetting depend on the contact angle (θ) between the liquid binder and the powder bed and on the spreading coefficient λ [20]. Contact angle is used as an assessment of the interaction between the solid and the liquid. A low contact angle (i.e. $\theta < 90°$) is an indication of a positive interaction between the powder and the liquid employed. On the other hand, a high contact angle value (i.e. $\theta > 90°$) suggests a low wettability of the powder by the employed liquid. The spreading coefficient (λ) instead describes the diffusion of a liquid into a solid and is defined as the difference between the work of adhesion ($\mathrm{W_A}$) and cohesion ($\mathrm{W_C}$) Eq. 1 and 2 [20]:

$$\lambda_{\mathrm{LS}} = \mathrm{W_A} - \mathrm{W_{CL}} \tag{1}$$

$$\lambda_{\mathrm{SL}} = \mathrm{W_A} - \mathrm{W_{CS}} \tag{2}$$

For an optimal spreading of the liquid binder, λ should always be positive. When λ is positive, granulation occurs, however two situations might take place:

- When λ_{LS} is positive, the binder forms an adhering film over the powder surface and liquid bridges generates between most contacting particles. This lead to formation of strong and dense granules;
- When λ_{SL} is positive, bonds will form only where the liquid and powder initially touch as the liquid binder does not lead to film formation around the powder particles. Weaker and more porous granules are formed in this case [19,20].

This initial phase is particularly critical also considering the different ways in which the granulation liquid is added to the powder. Several authors pointed out how the nuclei formation might be affected by the dimensions of the liquid binder's drops and by the influence of some process parameters (such as the powder bed renewal and the liquid binder flow rate). These will lead to different nuclei formation which will influence the properties of the final granules, mainly in term of particle size distribution.

Schæfer and Mathiesen proposed two different mechanism of nucleation for melt granulation which depends on the dimensions of the binder particle size compared with the size of the rest of the excipients. These two nuclei formation mechanisms are called: immersion and distribution mechanisms [21]. These mechanisms can be transferred to wet granulation as the behavior of a melted binder is similar to a liquid one.

Immersion mechanism takes place when the powder particles are smaller than the droplets of the employed binder. In this case the powders will be immersed into the binder drop, thus the size of the liquid droplets will determine the size of the forming nuclei. Consequently, a homogeneous distribution of the droplets size will lead to a more controlled size distribution of the formed nuclei which should be associated to a narrow distribution of the final granules diameter.

Distribution mechanism occurs when the diameter of the binder's droplets is smaller or comparable with the powders' particle size. The droplets distribute on the surface of the powder's particles and the nuclei forms due to the coalescence of this wetted primary particles. This mechanism typically leads to a wider granules size distribution.

Similar scenarios were described by Hapgood et al. [22]. In their studies two nucleation regimes were proposed: drop controlled and mechanical dispersion nucleation mechanisms. Nucleation regimes are governed by the different drops interaction with the formulation powders. It is thus of great importance the drop penetration time but also the interaction between the drops which have been spread on the nucleation zone which determine the nucleation regime. The drop penetration time describes the nuclei formation kinetic, it depends on both wetting thermodynamics (affected by the fluid surface tension and the powder liquid contact angle) and the wetting kinetics (strongly affected by the liquid viscosity and effective pore size of the powder bed.) [23]. The situation which takes place in the nucleation zone can be described by the dimensionless number called spray flux number (Ψ_a) reported in the equation 3. It was derived to quantify the effect of the most important process variables acting in the nucleation zone: liquid flow rate, binder drop size, and powder flux under the spray zone [24] and it is a measure of the area wetted by drops from the nozzle compared to the renewal flux of powder surface through the spray zone [24].

$$\Psi_a = \frac{3\dot{V}}{2\dot{A}d_d} \tag{3}$$

Where $\dot{V}$ is the volumetric spray rate, d_d is the droplet diameter, and $\dot{A}$ is the area flux of powder traversing the spray zone. A low value of Ψ_a describes a situation where there are well dispersed droplets, which tend not to overlap. High values of Ψ_a means high spray density and agglomeration of spray drops on the powder surface leading to a broader and more difficult to control nuclei distribution [24]. The dimensionless spray flux can also be applied to situations where the liquid is poured into the granulator. A single stream of liquid can be considered to be a vertical column of drops that are not separated. The “spray area” is then equal to the cross-sectional area of the liquid column. Since the pouring liquid constantly covers this area, the spray flux $\Psi_a \geq 1$.

Hapgood et al. proposed a nucleation map as shown in Figure 1.4 [22] in order to highlight how the different nucleation mechanisms are depending from both the penetration time of the drops in the powder bed and the addition method employed to add the liquid binder.

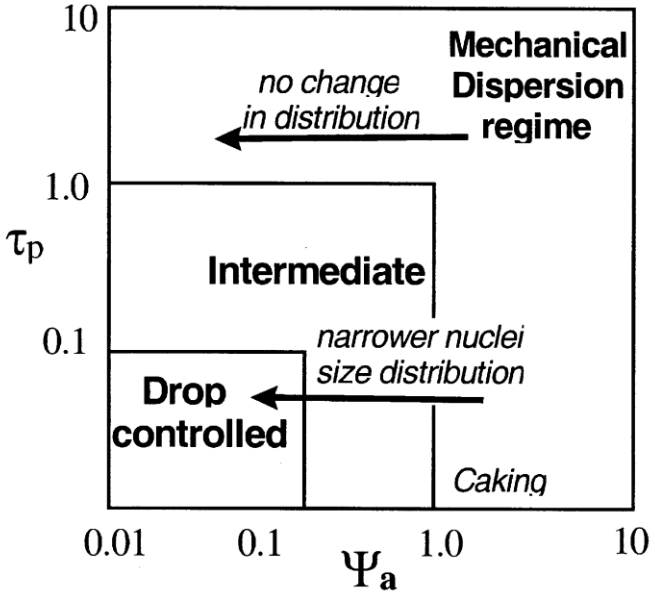


Figure 1.4: Nucleation regime map. On the horizontal axis is present the dimensionless spray flux number, while on the vertical axis there is the dimensionless penetration time. The combination of these two dimensionless numbers leads to the definition of three nucleation regime.

In the vertical axis is presented the penetration time expressed as the dimensionless penetration time τ_p:

$$\tau_p = \frac{t_p}{t_c} \tag{4}$$

Where t_p is the penetration time of a drop in the powder bed and t_c is the circulation time of the particles into the mixer. The procedure by which the binder is added is described in the horizontal axis of the map by the dimensionless spray flux number Ψ_a described in Eq. 3.

Three nucleation regimes are proposed in the map, these determine the characteristics of the formed nuclei:

- Drop control regime: where the dimensions of the forming nuclei is driven by the size of the liquid binder droplet. In order to achieve this regime, the droplet need to penetrate in the powder bed sufficiently fast while the powder is constantly renewed under the spray zone (i.e. for Ψ_a < 1.0). This allows a situation where the single droplets penetrated in the powder bed forms immediately the nuclei without any coalescence with other droplets. This represents an optimal situation where the liquid binder is added efficiently to the formulation powders and is well distributed from the early phase of the granulation process.

- Mechanical dispersion regime: in this case the liquid binder might struggle to penetrate into the powder bed, thus the droplets stack on the surface and coalesce with other droplets before to infiltrate into the powder pores. This situation might happen when a viscous binder is employed, if the liquid is added with a flow rate which does not allow an optimal renewal of the moving powder bed (i.e. for Ψ_a > 1.0). In this regime the nuclei are formed for the mechanical dispersion of the liquid binder due to the mechanical mixing of the wet mass. This case is the typical situation where a liquid binder in not optimally added to the formulation powder, thus it is following spread by the mechanical forces given by the impeller in the high-shear mixer.

- Intermediate regime: is a regime of transition between the situations described above. In this nucleation mechanism the process is extremely sensitive to slight difference in the nucleation zone conditions [22].

Moving from the drop control to the mechanical dispersion regime, a wider nuclei particle size is obtained and a less efficient distribution of the liquid binder is achieved. Thus, this map can be useful to describe the initial phase of the granulation process and the efficiency of the liquid binder distribution. However the characteristics of the final granules are strongly affected by further transformation following described.

1.4.2 Growth and consolidation:

After liquid addition, the formed nuclei experience the growth and consolidation. In this phase coalescence between the formed nuclei takes place leading to formation of bigger agglomerates. Coalescence is due to the deformability of the particles involved given by the presence of liquid which provides the plasticity of the wet mass. This mechanism of growth occurs already during the liquid binder addition but it becomes predominant during the subsequent phase where the mass in kneaded by the impeller movement. Granules grow until the equilibrium between the coalescence and rupture of the agglomerates is reached. Granules consolidate due to the collisions between them and with the wall of the bowl. This consolidation decreases the granule porosity and increases the granule density. In order to describe the growth of granules into a high-shear mixer Iveson and Litster developed a growth regime map which is shown in fig. 1.5 [25].

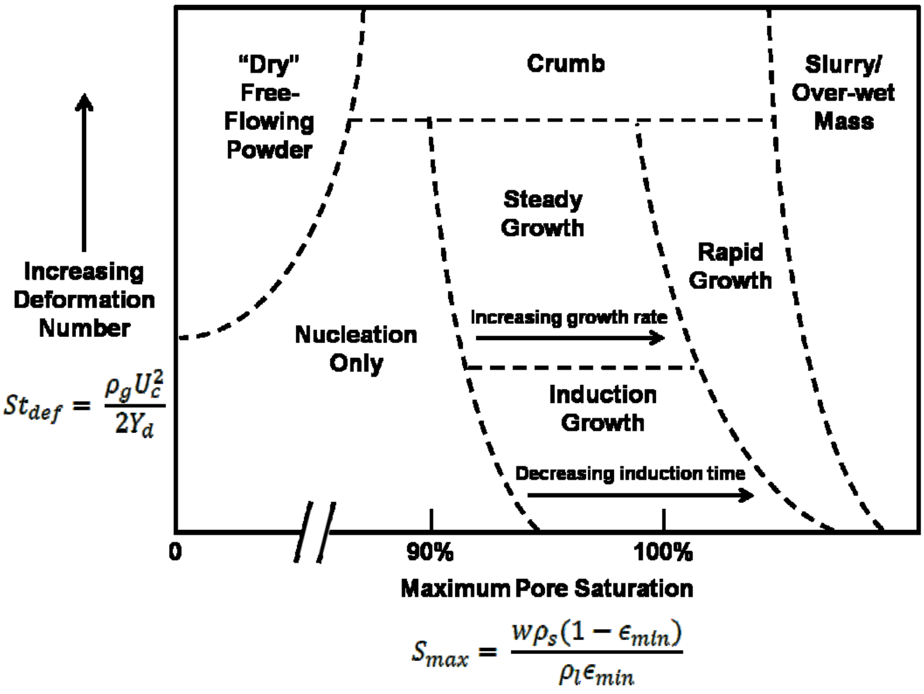


Figure 1.5: Granules growth regime map. This theoretical map combines the deformability of the granules expressed as St_{def} and the maximum pore saturation (S_{max}) and defines different growth regimes depending on these parameters.

The map tries to describe scientifically how granules grow during the process depending on the liquid saturation on the wet mass and the deformability of the granules. As shown in the map, the deformability is expressed by the dimensionless Stokes' deformation number (ordinate axis). Stokes' deformation number (St_{def}) is calculated as:

$$St_{def} = \frac{\rho_g U_c^2}{2Y_d} \quad (5)$$

In the equation ρ_g is the density of the wet granule, U_c is the effective collision velocity into the granulator and Y_d is the dynamic yield stress of the granule matrix. Y_d varies with formulation properties and granule porosity thus need to be assessed at the minimum porosity ϵ_{min}. Y_d which represents the resistance of the wet granules to the impacts can be measured or calculated using the equation proposed by Van den Dries [26] (Eq. 6).

$$Y_d = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\mu\pi V_p}{16d_{3,2}} \quad (6)$$

Where ε is the porosity, μ is the viscosity of the liquid binder, V_p is the tip velocity of the mixer arms and $d_{3,2}$ is the surface mean primary particle size

St_{def} is a measure of the ratio of impact kinetic energy to plastic energy absorbed per unit strain. It takes into account both the process mixing intensity and the granule rheology and indicates the amount of deformation during a typical impact [25]. Deformability is plotted against the liquid saturation of the wet mass expressed as maximum pore saturation (S_{max}) calculated using the Eq. 7.

$$S_{max} = \frac{w\rho_s(1-\epsilon_{min})}{\rho_l\epsilon_{min}} \tag{7}$$

Where w is the liquid to solid ratio employed in the process, ρ_s is the density of the solid particles, ρ_l is the liquid density and ϵ_{min} is the minimum porosity reached by the granules at the particular set of operating condition at which granulation was performed. Map highlights that at very low liquid contents there will be only a dry, free-flowing powder, or else there will be the formation of nuclei due to Van der Waals interactions, but the particles do not grow further. For intermediate values of liquid saturation, the mass will form granules with a growth that follows four possible regimes called: crumb, steady growth, rapid and induction growth.

Crumb regime: in this case the wet mass has the higher deformability. This is related with a very low resistance of the forming granules to the manipulation which are operated in the process. The result is the formation of irregular granules which do not grow due to the low resistance of the wet mass.

Steady growth regime: The material which presents this growth is characterized by an intermediate and optimal deformation. The formed nuclei coalesce together deforming. The optimal deformation of these nuclei leads to a constant growth of the granules until the equilibrium is reached. The diameter achieved at equilibrium depends on the amount of liquid employed, the formulations' components and the impeller speed

Induction regime: This growth mechanism is typical of materials which present a high resistance to the kneading and a low deformability. In this case the growth shows a characteristic trend. Initial nuclei present a lack of growth during the process. The nuclei in this phase consolidate without coalesce to each other. This high consolidation leads to the movement of the liquid binder from the internal pores to the surface of the nuclei. When the liquid reach and cover the surface of the consolidated nuclei, an exponential and uncontrollable growth could occur leading to lump formation [25].

In fig. 1.6 the typical trends of the granule mean diameter as function of the massing time is presented for both the steady and induction growth mechanisms. The picture clearly shows the linear growth of the granules, characteristics of the steady growth regime (Fig. 1.6A). This totally differs from the sigmoid trend presented by the mass undertaking an induction regime (Fig. 1.6B).

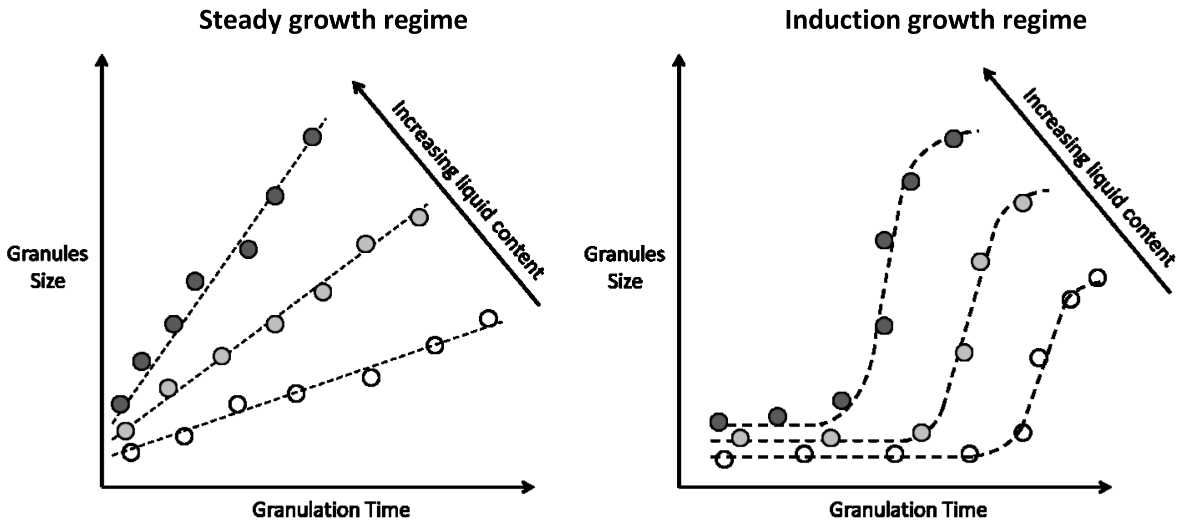


Figure 1.6: Theoretical trend of granules growth is presented for the steady growth regime (A) and the induction regime (B).

Rapid growth regime: in the map this regime is presented at the same condition of the steady growth and induction regimes but at slightly higher liquid saturation values. In this case the high presence of liquid binder lead to a fast coalescence of the granules. The deformability which discriminated the two regimes previously described is overtaken by the plasticity given by the liquid binder amount thus an extremely fast coalescence of the initial nuclei is the characteristics of this regime.

Finally, for very high value of pore saturation, the liquid overcome the ability of the formulation powder to absorb it and a slurry is formed, which can be no longer processed.

1.4.3 Attrition and breakage:

Breakage of wet granules influence the final granule size, it takes place from the very beginning of the process and is due to the shear applied on the granules. Generally at the first stage of granulation the growth and consolidation phenomena overtake the rupture, this lead to the granules growth with the different mechanisms described above. As the granules grow, breakage phenomena gain importance until equilibrate with the growth and consolidation; the granules stop their growth and stabilize their size depending on the formulation characteristics and the process parameters applied. Thus the rupture of wet granules can be a way to control the final granule size. The energy applied during the granulation process can change the extent of the breakage, for instance higher impeller speed are related with more wet granules rupture and smaller granules size [19].

1.5 Material exchange mechanism

Stokes deformation number developed by Iveson and Litster and following employed to build the growth regime map [25] could represent a theoretical tool for the prediction of granules growth and breakage in a HSM. Bouwman et al. studied the possibility to correlate the Stokes deformation number with different mechanism of material exchange during the equilibrium phase of granulation [27]. In the study wet granules behavior was evaluated at the equilibrium between growth and breakage, in order to identify the mechanism by which granules exchange their material. The authors tested different formulations preparing two types of granules: one containing a hydrophobic dye as tracer and a second without the tracing agent. The colored granules were conserved in a sealed container in order to avoid their drying; following they were added to the blank agglomerates and processed together studying how the granules exchanged material during the mixing. This experiment leaded to the identification of three main mechanism of material exchange, depending on the strength and deformability of the wet granules: the disintegration, deformation and distribution mechanisms [27]. The three material exchange mechanisms are presented in Figure 1.7.

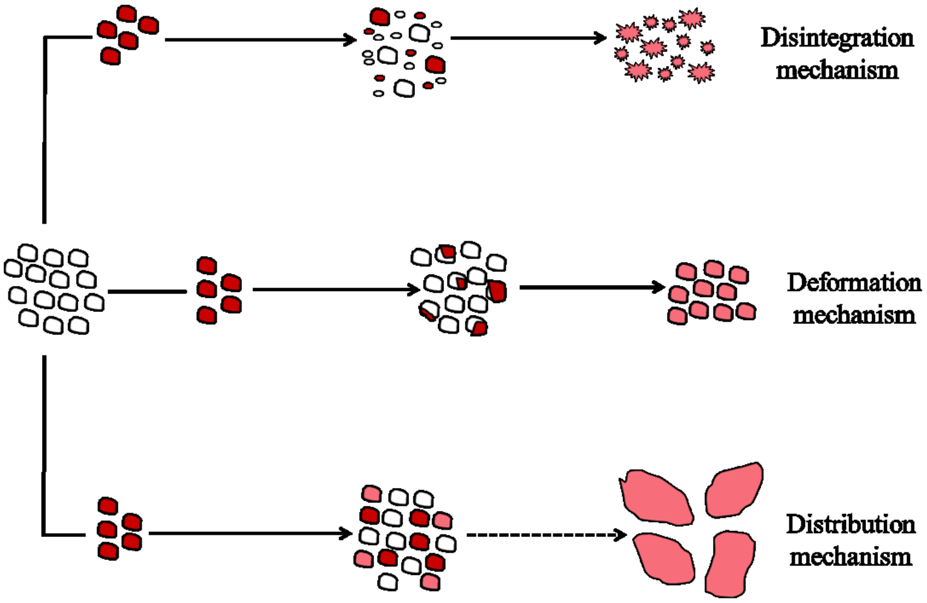


Figure 1.7: Material exchange mechanisms. The picture gives a graphical representation of the different material exchange mechanisms described by Bouwman et al. [27]

For the formulations studied was calculated the Stokes deformation number, this allowed to associate the three mechanisms with the different growth regimes identified by Litster et al [25].

- Disintegration mechanism: it takes place when is processed a material characterized by a high deformability. This mechanism can be associated with the crumb regime proposed in the map in Figure 1.5. When a formulation presents the disintegration mechanism, the granules are crushed to fragments during the process. The resulting fragments re-agglomerate immediately into new granules leading to a rapid distribution of the tracing agent within the mass. The resulting particles are characterized by a rough surface and a wide size distribution.
- Deformation mechanism: in this case the colored granules exchange their material homogeneously with the blanks during the mixing due to the impacts between each other until

a uniform coloration is obtained. This is typical of materials characterized by an optimal deformability and resistance. The mechanism previously described is associated with the steady growth regime.

- Distribution mechanism: it occurs when the granules processed are characterized by a low densification rate. This mechanism is associated with the induction regime. In this case the colored and blank granules present an initial phase where no material is exchanged and the different granules are still separated. After this phase, an incontrollable agglomeration could take place and in this case big lumps are formed. The original granules which coalesced are still visible on the formed lumps at the end of the process because of their low deformability.

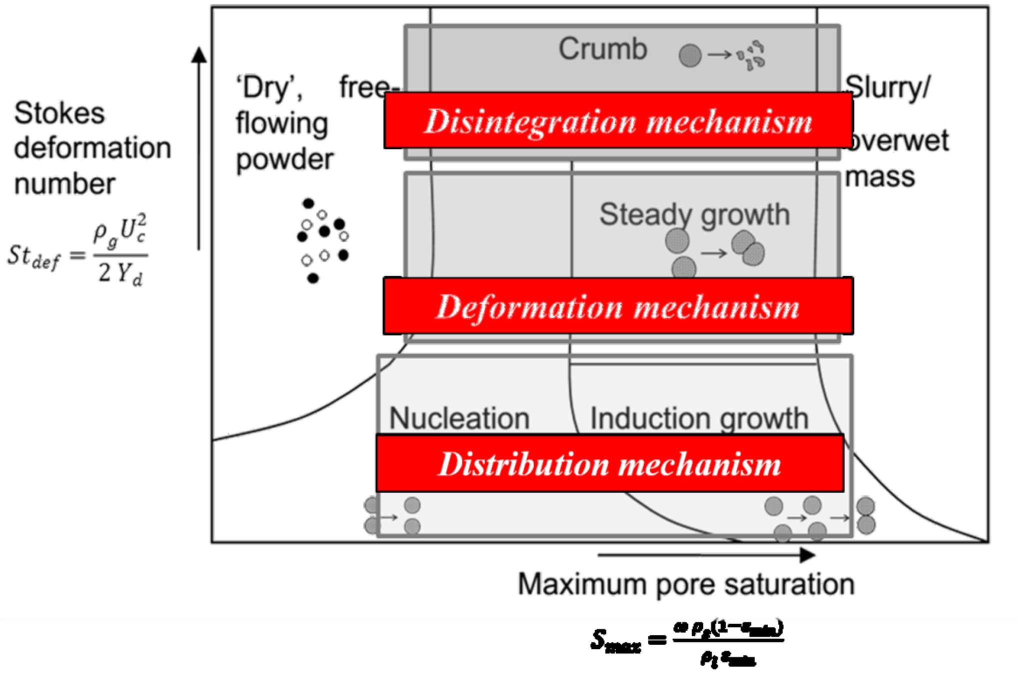


Figure 1.7: The material exchange mechanisms defined using different formulations overlapped with the corresponding granules growth regimes. Adapted from Bouwman et al. [27].

The association of the material exchange mechanism with the different growth regimes allows to identify empirically and with a relatively simple method the growth regime of different formulation [25]. This is of great importance as the parameters necessary for the Stokes deformation number calculation need to be often estimated or measured with techniques which are not common. Moreover the Stokes deformation number calculated for low viscous binder is not accurate and in this case a material exchange mechanism evaluation can solve the issue. The main drawback of this approach is the fact that is based on visual evaluation of the resulting granules which cannot be related with consistent quantitative values [27]. On this purpose, the use of rheological evaluations could be useful to relate the different material exchange mechanisms and growth regime with the wet mass resistance, thus obtaining a quantitative evaluation of the different behaviors.

1.6 Factors which influence the high-shear wet granulation process

Several factors influence the high-shear wet granulation process that can be divided in formulation and experimental variables. The first factor which can influence the process is the composition and the characteristics of the formulation. The formulation is characterized by several material attributes which can be identified as critical (CMA) if they influence significantly the resulting granules. Among these CMA is possible to include solubility, wettability (contact angle), particle size, surface area, pore volume, pre-blend compactability and flow [7,28]. Looking at the attributes previously introduced is possible to identify three main categories which can have great effects on the resulting granules: interaction between the powders and the liquid, initial particle characteristics, bulk properties of the powders. These three characteristics need to be deeply studied before to perform the granulation experiments as minimum variation can lead to complete different results. Solubility of the formulation components for example affects mainly the grow rate of the granules. Indeed materials characterized by a high solubility are associated with a higher tendency to have an uncontrollable growth [28]. In this case the viscosity of the formed solution has an important role as the viscosity of the employed binder. The wettability of the powders is another important characteristic as a high-contact angle affect the wetting phase of the process leading to a wider distribution of the particle size of the obtained granules as previously discussed [7,23]. Particle size distribution of the starting materials has an important role as can lead to powder segregation which can cause a non homogeneous distribution of the active principle ingredient (API) into the manufactured product. Moreover, particle size of starting material can have a strong effect on the densification and compactability of the resulting granules. For instance, a smaller particle size of the starting material is associated with a larger pore volume of the resulting granules [29]. Together with particle size distribution, the surface area and the pore volume of the particles affects the amount of liquid required for the process.

Also the experimental parameters have a crucial role on the properties of the final granules, in fact this process presents several process parameters which need to be controlled and most of them are often considered critical (CPP) as their variation affects significantly the final product quality. The classical critical process parameters for a high-shear wet granulation are: granulator geometry, fill level of the bowl, impeller design, impeller speed, granulating liquid amount, granulating liquid flow rate, wet massing time (i.e. granulation time), and chopper speed. Among the CPP listed the most studied are the granulating liquid amount, the impeller speed, the liquid addition rate, the wet massing time [7]. The liquid amount is often expressed as the ratio between the amount of liquid employed and the powder mass in which it is sprayed or poured (liquid to solid ratio (L/S)) and has often a great impact on the characteristics of the produced granules. Different L/S have an influence on particle size and density of the final granules. Higher values of L/S lead to production of larger and denser granules while lower liquid amount leads to opposite results [30]. Also the rate by which the liquid is added to the powder has a key role. Change in the liquid flow rate might result in a less efficient spread of the liquid binder into the powder bed affecting the properties of the final granules. Impeller speed have an influence on the grow rate and density of the granules because it changes the equilibrium between the growth and breakage phenomenon which characterize the granules. Impeller speed effects depend on the characteristics of the processed wet mass and the granules mechanical properties [31].

Wet massing time effects are formulation dependent, in general it can be stated that an increase in the wet massing time is related with a decrease in porosity and a reduction in compressibility of the produced granules [32].

High-shear wet granulation has thus several parameters which need to be controlled and most of them are formulation dependent. For this reason the process development is particularly difficult using this technique with the risk for this equipment to become the last choice when a new formulation needs to be granulated. Moreover the recent requirements coming from the regulatory authorities ask for a higher knowledge about the influence of the process parameters and material attributes on the final product quality. These requirements are formalized in a new guideline for the development of new pharmaceutical formulations. This guideline is called ICH Q8 and states that the quality of the product need to be built into the process and no more evaluated at the end [33]. In fact often the pharmaceutical industries relay on controls of the final products to assess the quality and assure that the characteristics are within the specification’s limits. In this case the effects of the parameters change during the process are observed only at the end on the batch production. This new guideline have the aim of changing this view, give more importance on the process knowledge in order to predict from an early stage how process variable changes will affect the quality of the final product. This concept is called Quality-by-Design (QbD) as the quality comes from how the product and the process is designed [33]. Moreover, the same guideline asks for a scientific understanding of the process instead of an empirical evaluation of the variables. This novel approach aims to assure a greater and more reliable quality of the final product. QbD thus requires to define a quality target product profile (QTPP) which consists on the characteristics of the final product and the specification limits within which the features of the manufactured good need to be. Following the critical quality attributes (CQA) are evaluated. These CQAs are the final product attribute or the intermediate (e.g. granules) characteristics which affect the safety of the final product and the QTPP [7,33]. CQAs are affected by the characteristics of the raw materials employed and the process parameters applied. Thus the QbD approach requires defining the critical material attributes (CMA) of the starting materials and the critical process parameters (CPP) of the process from a very early stage of the formulation development. Typical CMA and CPP of the high-shear wet granulation process were discussed before and they are identified from the literature and from the experience. Following they are evaluated through a risk assessment, a procedure by which is identified the overall risk of the single attributes and parameters. This risk assessment procedure is highlighted by another guideline named ICH Q9 [34]. The risk is evaluated taking into account the probability that a certain deviation occurs and the impact of this variation on product safety. A full discussion about the risk assessment is out of the aims of the present work. When the CMAs and CPPs are identified, they need to be experimentally evaluated in order to define how their variation will affect the CQAs. This is very important in order to build a solid design space, thus a virtual space defined by the limits of the different CMAs and CPPs in which is granted that the initially delineated QTPP is always met. This long protocol which needs to be applied when a new product is developed is associated with a more flexible regulatory control. Indeed, currently any change in process parameters need to be communicated to regulatory agencies and this lead to a post-approval change of the product registration which is time and cost consuming.

Moreover, this post-approval change needs to be supported by an overwhelming number of data which state how the modified parameters do not affect the quality of the product. With the introduction of this ICH Q8 guideline, the industries are required to evaluate scientifically the effect of the process parameters and the material attributes on the product quality. This more scientific approach can support the building of a design space where the product quality does not change. In other words the application of the QbD allows defining the limits of variation of the different process parameters and material attributes which do not affect the product quality. The design space is the combination of parameters which grant a constant quality of the product. Regulatory agencies allow moving into this design space without the need to communicate any post-approval changes if enough scientific justifications are provided.

1.7 Wet mass rheology

The characteristics of granules produced in a high-shear mixer are strongly affected by the rheology of the wet mass which is processed. In literature are present some works where wet mass rheology has been measured on-line on high-shear mixer for monitoring the process using the power consumption of the engine or the torque experienced by the impeller [5,35]. From those studies is possible to understand how rheology of the wet mass could be a useful tool also to obtain preliminary indications about the critical process parameter of high-shear process. In fact, identifying which parameters have a significant influence on the rheology of the mass might help to predict the critical process parameters and gain a deep knowledge of the process. Mixer torque rheometers can be employed on this purpose. These are tools able to perform off-line measurements of the wet mass rheology. Several studies employed both on-line and off-line rheological measurements to identify the different saturation states of the powder, the correct L/S which needs to be applied for granulation in a high-shear mixer and to evaluate the pseudo viscosity of the processed mass for scale-up studies and end-point determination [36–40].

The optimal L/S for granulation is still often evaluated through an empirical assessment defined as *hand squeeze test.* This assessment consists of squeezing a sample of wet powder into a fist in order to evaluate if the liquid amount added is enough to perform the granulation. The amount of liquid is optimal if the squeezed wet mass maintains a compacted shape after the fist disclosure and presents some breakages. This approach is also used as an in-process control for high-shear wet granulation. It is clear how this method is not reliable as it is hugely affected by the experience and the sensitivity of the operator. Rheology of the wet mass can aid this procedure, in fact on this purpose several studies have been done on the torque recorded by the impeller of the high-shear mixer or on the adsorbed power of the engine during the process [36,37,39,40]. These studies were conducted in order to identify the correct liquid amount which should be employed and the end point of the granulation phase. Leuenberger divided in five sections the power consumption profile, recorded on line in a high-shear mixer (Fig. 1.8).

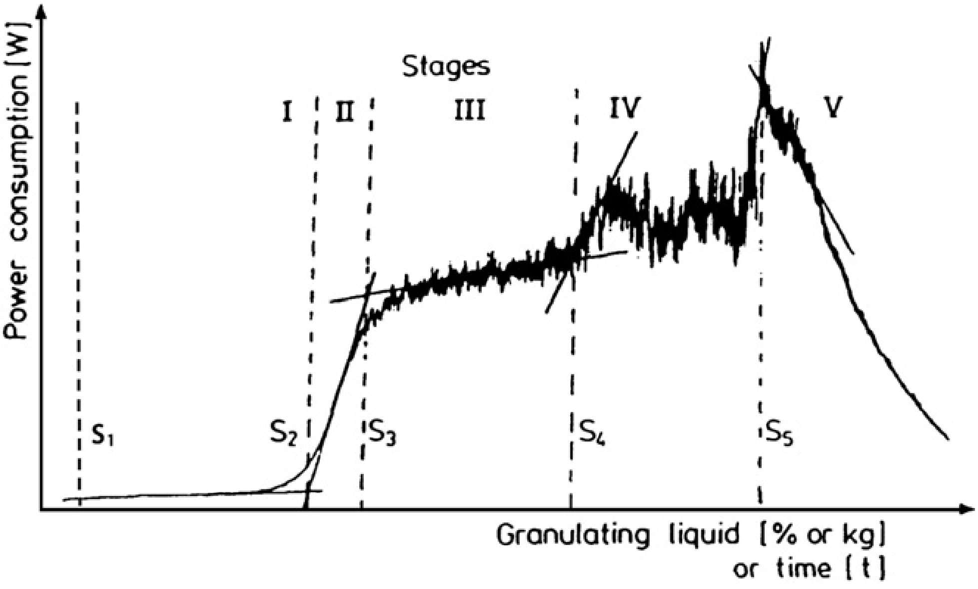


Figure 1.8: Division of the power consumption profile at different liquid saturation of the material according to Leuenberger et al. [35].

This study allowed to identify the different liquid saturation states presented in section 1.3.3 and in Figure 1.3, relying only on the power consumption of a high-shear mixer. In the first part of the profile in Figure 1.8 there is the wetting of the powder. Only the initial capillary bridges between the primary particles are formed in this phase. During the second stage is observed a rapid increment of the power absorbed; this phase corresponds with the achievement of the pendular saturation state and the nuclei formation. In the third section there is the transition between the pendular and funicular saturation states. This transition is represented as a plateau of the power consumption profile. The forth step consists on the filling of the final pores between the particles until achieving the capillary state, identified by the peak of the curve. This transition presents a high oscillation of the signal due to the fact that the particles do not achieve the capillary state at the same moment. The last phase presents a fall of the mass resistance. This is due to the formation of a slurry for the presence of an excessive amount of liquid [35]. This study allowed the identification of the different liquid saturation states of the mass on a high-shear mixer and thus opened the way to the use of the power consumption recorded during the process to identify when the amount of liquid added is sufficient to perform the granulation, thus avoiding the hand squeeze test. For instance the third partition of the curve need to be achieved (the transition between the pendular and funicular saturation state). Further studies were conducted off-line using a mixer torque rheometer by Chitu et al. [36]. These authors aimed to find a relationship between the torque recorded on-line on a high-shear mixer and the torque recorded off-line using a mixer torque rheometer. This study demonstrated how the same liquid saturation previously identified by Leuenberger using the power consumption profile recorded on a high-shear mixer, can be easily recognized through off-line measurement using a mixer torque rheometer [36]. This investigation was conducted on microcrystalline cellulose and on lactose. The results of Chitu et al. highlighted how the transition between the pendular to funicular saturation states can be identified in MCC and lactose by a shoulder on the torque profile. Using this approach is thus possible to predict the liquid to solid ratio

(L/S) required for processing a formulation on a high-shear mixer before performing any granulation experiments. The only restriction of this approach is the identification of the shoulder limits which represent the range of L/S which can be employed for granulation. Moreover when a studied formulation do not present any shoulder on the torque profile recorded, it is not possible to identify the transition between the pendular and funicular saturation state thus limiting the L/S prediction.

1.8 Scale-up of the high-shear wet granulation process

A deep process understanding is very important in several aspect of granulation. Usually a formulation is studied and optimized in lab scale equipments because the limited size of these apparatuses allows performing several experiments employing small amounts of starting ingredients. However it is not possible to produce the amount needed for commercial purposes using the same instruments employed in formulation development. Several studies need to be accomplished to adjust the parameters of commercial scale tools to obtain a product with the same characteristics of the one previously developed. This process accomplished to move the production from a lab to a commercial scale batch production, is called scale-up. Successful scale-up requires that characteristics of the starting materials are fully understood and that detailed knowledge of product-process relations are gained [41]. Moreover, regulatory agencies nowadays require a detailed product and process understanding for approval of a new product and the methods by which scale-up is performed are taken into account during the agency evaluation [7]. In order to achieve a successful scale-up it is necessary to grant a similarity of the process when the different equipments are employed. On this purpose the focus goes to three main aspects: the geometric, kinematic and dynamic similarity. These features of the process need to be maintained constant across the different production scales in order to grant that particles will experience the same pattern of modification at the different levels. This should lead to a successful scale up of the granulation process [7]. Geometric similarity is referred to the shape and geometry of the mixing bowl and impeller. Two equipments are generally similar if the ratio of linear dimension remains constant across scale. The dynamic and kinematic similarities are referred to the forces and velocities experienced by the forming granules into the HSM. The forces and shear experienced by the agglomerates are due to the particle-particle, particle-walls and particle-impeller collisions. In this case the effect of impeller speed and design have an important role [13]. However, a perfect similarity of all the three aspects previously described is extremely difficult, in fact even granulators with related design and dimension ratio showed to have different mixing and material flow patterns [7]. The commonly employed approaches for scale-up the granulation process generally aim to achieve the similarity of one of the previously described aspects (geometric, kinematic, dynamic similarity) even though the similarity is not fulfilled for the others.

1.8.1 Scale-up approaches

Several scale-up approaches have been developed that can be divided in two main types named: attribute-based and parametric-based approaches [7].

1.8.1.1 Attribute-based approaches

The goal of the attribute-based methods is to maintain constant a characteristic, chosen as representative of the final product quality, adjusting the parameters of the process across scale. These approaches focus on the monitoring of the granules attributes during the process and across scale. Granules attributes such as particle size distribution (PSD), pore size distribution, granules hardness, are monitored in-process or at-process using different process analytical technologies (PAT) [7]. Attribute based approaches initially define an endpoint of granulation process monitoring the evolution of the granules attributes on a lab-scale equipment. The same granule attribute is then monitored across the scale in order to identify a scaled up endpoint which grant the same characteristics of the granules achieved in the lab-scale [35]. It is of great importance to focus not only on the granules properties at the end of the process but also monitor the evolution of the agglomerates characteristics along the process. For instance, a successful scale-up following an attribute-based approach aims to achieve across scales, the same granules attributes following the same kinetic of the process. This requirement is important as monitoring the evolution of the process and not only the final quality attributes of the granules, allow obtaining a resulting product which formed following similar transformation across scale. This should be associated to a production of granules at different scales characterized by similar properties. The typical example used to explain this concept is the monitoring of the PSD of granules at different scale as quality attribute. The same PSD can be achieved at different batch sizes applying different process parameters (such as impeller speed and massing time). If the growth kinetic is not monitored the final granules might present the desired PSD but a completely different porosity or granules strength. This result could be potentially associated with a completely different behavior of the granules in terms of tablet formation, dissolution profile or drug release [7].

Wet mass rheology can be monitored along the process to determine the granules evolution and the granulation end-point. On this purpose both in-line or at-line approaches can be used. A mixer torque rheometer, which was discussed above for liquid amount determination, was employed in some studies to monitor the evolution of the rheological behavior of wet mass during the granulation process [40].

Similarly, wet mass rheology can be assessed using the power consumption such as in the dimensionless Newton power number (eq. 8) [42].

$$N_P = \frac{P}{r^5 \omega^3 \rho} \tag{8}$$

Where P is the power consumption, r is the impeller radius, ω is the rotational speed and ρ is the wet mass density [42]. This number relates to the drag force acting on a unit area of the impeller and the inertial stress. It represents the power needed to overcome the frictional force of the mass [5] and it can be calculated from the power consumption of the impeller recorded by the equipment. The main problem of power consumption is that it reflects the load on the motor rather than the load on the impeller, thus it is related to the overall mixer performances i.e. it depends on the motor efficiency [5].

Moreover power consumption can change between different equipments and over time because of loss of performance, regardless of the load.

1.8.1.2 Parametric-based approaches

Parametric-based approaches identify the values of critical process parameters (e.g. powder bed height, impeller speed, etc.) at small scale which provide a product with the desired characteristics. Following, these critical process parameters are scaled-up using certain equations in order to maintain the similarity across scale. The common critical process parameters which need to be considered when a scale-up is operated are discussed in the following sections.

- Powder bed height

The powder bed height needs to be adjusted accordingly to Eq. 9:

$$\frac{h}{D} = constant \tag{9}$$

Where *h* is the bed height and *D* is the impeller or bowl diameter. The height of the powder bed is adjusted in order to keep the same ratio with impeller or bowl diameter across scale. This approach is necessary to achieve a geometrical similarity of the batch size.

- Impeller speed

The stress experienced during the process by the granules, but also their final physical properties are directly related with the impeller speed [43]. Several publications evaluate the effects of different impeller speed related scale-up rules [44–47]. However the main limitation of such studies is the incomplete characterization of the properties of granules obtained at different scales. The speed of the impeller can be scaled in different ways. The more obvious approach is to keep the peripheral speed of the impeller constant across the different scales. This approach is so called constant tip speed (Eq. 10).

$$\omega_1 D_1 = \omega_2 D_2 \tag{10}$$

Where ω_1 and ω_2 are impeller speeds expressed in revolutions per minute and D_1 and D_2 are the impeller diameters of the two granulators to be scaled. The impeller speed is adjusted depending of the batch size with the aim to maintain constant the particle velocity into the different mixers [7].

Another rule commonly used for scale up high-shear wet granulation aims to keep constant the Froude number in equipment with different batch sizes (Eq. 11).

$$Fr = \frac{\omega^2(2r)}{g} \tag{11}$$

Where *g* is the gravitational force; *ω* is the impeller speeds expressed in revolution per minute and *r* is the impeller radius. This is a dimensionless number widely used in fluid mechanics and it represents the ratio of the centrifugal force to the gravitational force. *Fr* is used as criterion for achieve dynamic similarity across scale [46].

These two different approaches to scale up the impeller speed can be resumed in the following general equation derived from the equation 10.

$$\frac{\omega_1}{\omega_2} = \left(\frac{D_2}{D_1}\right)^n \qquad (12)$$

Where ω_1 and ω_2 are the impeller speeds expressed in revolution per minute and D_1 and D_2 are impeller diameters of the two granulators to be scaled. In this case the exponent n can assume different values depending on the scale-up rule which is applied. When $n = 1$ the equation describes the constant tip speed rule. For $n = 0.5$ the relationship allows to calculate the impeller speed which need to be used to apply the constant Froude number rule. A third value of n was derived empirically in order to achieve a constant shear stress in high-shear mixers of different scales. This scale-up approach is described in the work of Tardos et al. [47]. In this study the impeller speed necessary to break test particles with a known rheology was determined in apparatus with different batch sizes. This empirical study leaded to define a novel value of n for equation 12. For instance, a value of $n = 0.85$ is related to a constant shear stress applied to the mass granulated in high-shear mixers of different scales [47].

- Stokes deformation number

This dimensionless number was described in section 1.4.2 it was developed to predict granules growth in the high-shear wet granulation process. Stokes' deformation number (St_{def}) aims to describe the granules deformation as a function of the mechanical properties of the granule matrix and energy of collision [48]. As previously mentioned, this number was used together with the maximum pore saturation (S_{max}) in order to build a granules growth regime map (Fig. 1.5). This map can be also applied for scale-up purposes because it is built using dimensionless numbers, thus it should be able to predict the granules growth regime in equipments of different batch sizes. The main limitation of this approach is that some parameters necessary to calculate those dimensionless numbers cannot be measured but only approximated, thus for some formulation it is not possible to easily predict how the granules will grow [27].

- Wet massing time

Wet massing time refers to the time for which the granulator is operated after the wetting phase. During this stage an optimal distribution of the granulating liquid is achieved and granules forms because of the high forces applied. The granules are consolidated by the effect of the impeller and the degree of the consolidation of the granules is strictly related to massing time and impeller speed. The degree of consolidation strongly affects different properties of final granules such as the granule tensile strength and friability, the tabletability and the hardness of the tablets. [49]. An optimal scale-up of the wet massing time is thus really important. However there are no universal rules to scale up massing time and a limited number of studies are present in literature. Rekhi et al. recommend adjusting the massing time depending on the impeller speed applied [50]. This scale-up rule aims to keep the same number of impeller rotation across scale [7]. The same approach was studied in a more recent study from Tao et al. were this scale-up rule for the granulation time is more clearly defined. The wet massing time, is extended depending on the diameter of the impeller as described in the equation 13.

$$\frac{t_1}{t_2} = \frac{D_1}{D_2} \tag{13}$$

where *t* is the wet massing time in seconds which need to be used at the two employed scales and *D* is the diameter of the impeller of the two equipments with different batch size.

A completely opposite approach would be to keep the wet massing time constant across scale. Sometimes, massing time is extended to achieve the desired end-point; thus the granulation is performed until some of the required properties of the granules are met at different scales. However this approach, while allowing some properties to be successfully matched, it could be detrimental to several other granules characteristics [7].

- Granulating liquid addition

Another important aspect involved in the scale-up is the granulating liquid addition flow. On this purposes it is often applied the dimensionless spray flux number ψ_a discussed in section 1.4.1. The dimensionless spray flux number was developed by Hapgood and Litster to describe the distribution to the binder on the spray zone [22,24]. A constant spray flux number across scales is related to similar nuclei distribution which will lead, after the growth and consolidation phase, to similar size distribution of the final granules. Due to its dimensionless nature, this ψ_a allows to determine the set of process parameters which need to be applied during the granulating liquid addition. The spray flux number can in fact give an indication about the liquid addition flow and the impeller speed which will grant an optimal distribution of the granulating liquid on the powder bed.

1.9 Aim of the project

The aim of the present thesis was to investigate the potential application of the wet mass rheology to study different aspects of the granulation process. High-shear wet granulation is strongly related to the rheology of the wet masses processed. As previously mentioned, in literature are present some studies which focus on wet mass rheology, measured both on-line on high-shear mixers [5,35] and off-line using a Mixer torque rheometer [36–40]. In the present work, rheology of wet mass was studied using a Mixer Torque Rheometer MTR3 (Caleva Process Instruments, UK) presented in Figure 1.9.

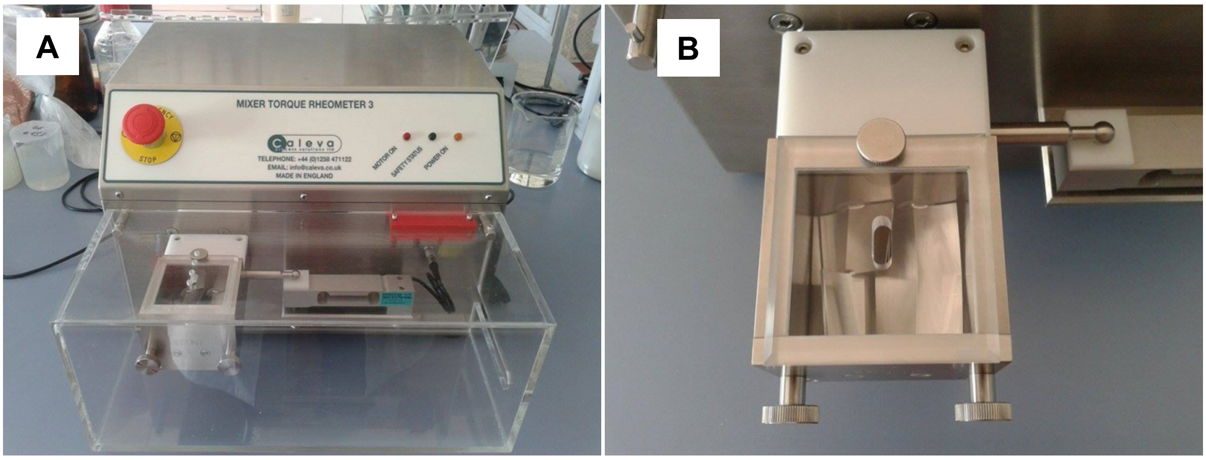


Figure 1.9: Mixer Torque Rheometer (MTR3, Caleva Process Instruments, UK). a) The instrument is composed of a mixing chamber connected to a load cell through a stainless steel arm. b) The mixing chamber contains two contra-rotating shafts.

It is composed of a stainless steel chamber where the sample is placed for the measurement. Into the chamber, two contra-rotating shafts are present for the mixing of the masses (Figure 1.9 b). The drive blade is directly connected to the engine and rotates between 10 and 250 rpm. The second blade is connected to the guide shaft and rotates at the double of its speed. The torque developed by the engine to mix the wet masses into the chamber is measured through a load cell. The stainless steel chamber in fact is free to pivot about the drive shaft and it is kept fixed in its position by the load cell. The cell deflects due to the engine force applied to the mass measuring indirectly the torque. The sample can be a powder which can be wetted while it is kneaded in the chamber and the torque is recorded. Otherwise can be placed a wet mass, such as granules sampled during the granulation process operated in another equipment.

Rheological characterization was operated on several formulations to achieve a deeper knowledge of the granulation process and predict important aspects such as: the optimal liquid amount which should be employed for high-shear wet granulation, the granules growth regimes and the most critical process parameters. On this purpose all the formulations presented in this thesis were characterized using the different procedures following described for the mixer torque rheometer and the results were validated through granulation experiments in lab-scale high-shear mixers.

1.9.1 ‘Multiple addition’ method

In the ‘multiple addition’ procedure the instrument measure the evolution of the torque while a powder is gradually wetted. Initially the instrument measure the torque of the empty chamber in order to eliminate the baseline noise. Following, an amount of powder sufficient to fill the chamber until the shafts are completely covered it is poured into the compartment and the torque for the dry powder is recorded. Subsequently, while the powder is constantly mixed, the equipment add a certain amount of liquid. The liquid addition is operated automatically through a syringe controlled by the instrument software. After any addition the solid-liquid system is left to equilibrate for a predetermined time and subsequently the torque is measured. The measurement is conducted until a slurry is formed into the mixing bowl. This procedure is used to define the different saturation states of the formulation employed in order to define the correct liquid amount which should be employed for granulation purposes.

1.9.2 ‘Variable mix time’ method

In the ‘variable mix time’ procedure, the instrument measure the evolution of the torque for a wet mass while it is mixed for a certain time. Initially the instrument record the torque of the empty chamber in order to eliminate the baseline noise, then an amount of powder, sufficient to fill the chamber until the shafts are completely covered, is poured into the compartment and the torque is measured. After this initial measurement, a liquid amount defined by the operator is added at once to the powder while it is mixed by the shafts. The instrument records the evolution of the torque along time.

1.9.3 ‘Consistency’ method

The ‘consistency’ procedure is a measurement of a single value of torque for a wet mass. For this measurement the instrument records the torque of the empty chamber in order to eliminate the baseline noise. Following an amount of wet mass for which is wanted to be assessed the torque is poured in the chamber. The amount of mass need to be enough to completely cover the shafts of the instruments. The material is mixed for a short time to ensure homogeneity before the torque measurement is taken.

1.10 References:

[1] P. Guigon, O. Simon, K. Saleh, G. Bindhumadhavan, M.J. Adams, J.P.K. Seville, Roll Pressing, in: A.D. Salman, M.J. Hounslow, J.P.K. Seville (Eds.), Handb. Powder Technol., Elsevier B.V., 2007: pp. 255–288.

[2] J. Mosig, P. Kleinebudde, Critical evaluation of root causes of the reduced compactability after roll compaction/dry granulation, J. Pharm. Sci. 104 (2015) 1108–1118. doi:10.1002/jps.24321.

[3] O.-R. Arndt, P. Kleinebudde, Influence of binder properties on dry granules and tablets, Powder Technol. (2017). doi:10.1016/J.POWTEC.2017.04.054.

[4] R. Gokhale, Y. Sun, A.J. Shukla, High-Shear Granulation, in: D.M. Parikh (Ed.), Handb. Pharm. Granulation Technol., Second, Taylor & Francis Group, 2005: pp. 191–228.

[5] M. Levin, Wet granulation: End-point determination and scale-up, Encycl. Pharm. Technol. 1 (2007) 4078–4098. doi:10.1081/E-EPT-120014089.

[6] M. Benali, V. Gerbaud, M. Hemati, Effect of operating conditions and physico–chemical properties on the wet granulation kinetics in high shear mixer, Sel. Pap. from Symp. Powder Sci. Technol. - Powders Sintered Mater. STP-PMF 2007Symposium Powder Sci. Technol. - Powders Sintered Mater. STP-PMF 2007. 190 (2009) 160–169.

doi:http://dx.doi.org/10.1016/j.powtec.2008.04.082.

[7] P. Pandey, S. Badawy, A quality by design approach to scale-up of high-shear wet granulation process, Drug Dev. Ind. Pharm. 42 (2016) 175–189. doi:10.3109/03639045.2015.1100199.

[8] H. Gjelstrup Kristensen & T. Schaefer, Granulation: A Review on Pharmaceutical Wet-Granulation, Drug Dev. Ind. Pharm. 13 (1987) 803–872. doi: 10.3109/03639048709105217.

[9] R. Boerefijn, M.J. Hounslow, Studies of fluid bed granulation in an industrial R&D context, Chem. Eng. Sci. 60 (2005) 3879–3890. doi:10.1016/j.ces.2005.02.021.

[10] T.C. Seem, N.A. Rowson, A. Ingram, Z. Huang, S. Yu, M. de Matas, I. Gabbott, G.K. Reynolds, Twin screw granulation — A literature review, Powder Technol. 276 (2015) 89–102. doi:10.1016/J.POWTEC.2015.01.075.

[11] C. Vervaet, J.P. Remon, Continuous granulation in the pharmaceutical industry, Chem. Eng. Sci. 60 (2005) 3949–3957. doi:10.1016/J.CES.2005.02.028.

[12] G.K. Reynolds, P.K. Le, A.M. Nilpawar, High Shear Granulation, in: A.D. Salman, M.J. Hounslow, J.P.K. Seville (Eds.), Handb. Powder Technol., Elsevier B.V., 2007: pp. 3–19.

[13] M. Börner, M. Michaelis, E. Siegmann, C. Radeke, U. Schmidt, Impact of impeller design on high-shear wet granulation, Powder Technol. 295 (2016) 261–271. doi:10.1016/j.powtec.2016.03.023.

[14] J.D. Litster, K.P. Hapgood, J.N. Michaels, A. Sims, M. Roberts, S.K. Kameneni, Scale-up of mixer granulators for effective liquid distribution, Powder Technol. 124 (2002) 272–280. doi:10.1016/S0032-5910(02)00023-2.

[15] A.D. Salman, G.K. Reynolds, H.S. Tan, I. Gabbott, M.J. Hounslow, Breakage in Granulation, in: A.D. Salman, M.J. Hounslow, J.P.K. Seville (Eds.), Handb. Powder Technol., Elsevier B.V., 2007: pp. 979–1040.

[16] S. Mascia, C. Seiler, S. Fitzpatrick, D.I. Wilson, Extrusion-spheronisation of microcrystalline cellulose pastes using a non-aqueous liquid binder, Int. J. Pharm. 389 (2010) 1–9. doi:10.1016/j.ijpharm.2009.12.058.

[17] C.D. Willet, S.A. Johnson, M.J. Adams, J.P.K. Seville, Pendular Capillary Bridges, in: A.D. Salman, M.J. Hounslow, J.P.K. Seville (Eds.), Handb. Powder Technol., Elsevier B.V., 2007: pp. 1317–1351.

[18] G.I. Tardos, L. Farber, D. Bika, J.N. Michaels, Morphology and Strength Developement in Solid and Solidifying Interparticles Bridges in Granules of Pharmaceutical Powders, in: A.D. Salman, M.J. Hounslow, J.P.K. Seville (Eds.), Handb. Powder Technol., Elsevier B.V., 2007: pp. 1213–1256.

[19] S.M. Iveson, J.D. Litster, K. Hapgood, B.J. Ennis, Nucleation, growth and breakage phenomena in agitated wet granulation processes: A review, Powder Technol. 117 (2001) 3–39. doi:10.1016/S0032-5910(01)00313-8.

[20] R. Rowe, Binder-substrate interactions in granulation: a theoretical approach based on surface free energy and polarity, Int. J. Pharm. 52 (1989) 149–154. doi:10.1016/0378-5173(89)90289-5.

[21] T. Schaefer, C. Mathiesen, Melt pelletization in a high shearmixer. IX. Effects of binder particle size, Int. J. Pharm. 139 (1996) 139–148. doi:10.1016/0378-5173(96)04548-6.

[22] K.P. Hapgood, J.D. Litster, R. Smith, Nucleation regime map for liquid bound granules, AIChE J. 49 (2003) 350–361. doi:10.1002/aic.690490207.

[23] K.P. Hapgood, J.D. Litster, S.R. Biggs, T. Howes, Drop penetration into porous powder beds, J. Colloid Interface Sci. 253 (2002) 353–366. doi:10.1006/jcis.2002.8527.

[24] J.D. Litster, K.P. Hapgood, J.N. Michaels, A. Sims, M. Roberts, S.K. Kameneni, T. Hsu, Liquid distribution in wet granulation: Dimensionless spray flux, Powder Technol. 114 (2001) 32–39. doi:10.1016/S0032-5910(00)00259-X.

[25] S. Iveson, J. Litster, Growth regime map for liquid bound granules, AIChE J. 44 (1998). http://onlinelibrary.wiley.com/doi/10.1002/aic.690440705/full.

[26] K. van den Dries, H. Vromans, Quantitative proof of liquid penetration-involved granule formation in a high shear mixer, Powder Technol. 189 (2009) 165–171. doi:10.1016/j.powtec.2008.04.007.

[27] A.M. Bouwman, M.R. Visser, G.M.H. Meesters, H.W. Frijlink, The use of Stokes deformation number as a predictive tool for material exchange behaviour of granules in the “equilibrium phase” in high shear granulation, Int. J. Pharm. 318 (2006) 78–85. doi:10.1016/j.ijpharm.2006.03.038.

[28] C. Vemavarapu, M. Surapaneni, M. Hussain, S. Badawy, Role of drug substance material properties in the processibility and performance of a wet granulated product, Int. J. Pharm. 374 (2009) 96–105. doi:10.1016/J.IJPHARM.2009.03.014.

[29] S.I.F. Badawy, M. a Hussain, Effect of starting material particle size on its agglomeration behavior in high shear wet granulation., AAPS PharmSciTech. 5 (2004) e38. doi:10.1208/pt050338.

[30] D.M. Parikh, M. Mogavero, Batch Fluid Bed Granulation, in: D.M. Parikh (Ed.), Handb. Pharm. Granulation Technol., 2nd ed., Taylor & Francis Group, 2005: pp. 247–304.

[31] S.I.F. Badawy, A.S. Narang, K. LaMarche, G. Subramanian, S.A. Varia, Mechanistic basis for the effects of process parameters on quality attributes in high shear wet granulation, Int. J.

Pharm. 439 (2012) 324–333. doi:10.1016/J.IJPHARM.2012.09.011.

[32] S.I.F. Badawy, M.M. Menning, M.A. Gorko, D.L. Gilbert, Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer, Int. J. Pharm. 198 (2000) 51–61. doi:10.1016/S0378-5173(99)00445-7.

[33] I. Conference, O.N. Harmonisation, O.F. Technical, R. For, R. Of, P. For, H. Use, Requirements for Registration of Pharmaceuticals for Human Use - Guildlines for Elemental Impurities, ICH Harmon. Guidel. 8 (2014).

[34] ICH Expert Working Group, Quality Risk Management Q9, ICH Harmon. Tripart. Guidel. (2005) 1–23. doi:10.1007/s11095-007-9511-1.

[35] H. Leuenberger, M. Puchkov, E. Krausbauer, G. Betz, Manufacturing pharmaceutical granules: Is the granulation end-point a myth?, Powder Technol. 189 (2009) 141–148. doi:10.1016/j.powtec.2008.04.005.

[36] T.M. Chitu, D. Oulahna, M. Hemati, Rheology, granule growth and granule strength: Application to the wet granulation of lactose-MCC mixtures, Powder Technol. 208 (2011) 441–453. doi:10.1016/j.powtec.2010.08.041.

[37] G. Betz, P.J. Bürgin, H. Leuenberger, Power consumption profile analysis and tensile strength measurements during moist agglomeration, Int. J. Pharm. 252 (2003) 11–25. doi:10.1016/S0378-5173(02)00601-4.

[38] A. Goldszal, J. Bousquet, Wet agglomeration of powders: From physics toward process optimization, Powder Technol. 117 (2001) 221–231. doi:10.1016/S0032-5910(00)00369-7.

[39] R.C. Rowe, G.R. Sadeghnejad, The rheology of microcrystalline cellulose powder/water mixes - measurement using a mixer torque rheometer, Int. J. Pharm. 38 (1987) 227–229. doi:10.1016/0378-5173(87)90118-9.

[40] M. Landin, P. York, M.J. Cliff, R.C. Rowe, A.J. Wigmore, Scale-up of a pharmaceutical granulation in fixed bowl mixer-granulators, Int. J. Pharm. 133 (1996) 127–131. doi:10.1016/0378-5173(95)04427-2.

[41] P.R. Mort, Scale-up of binder agglomeration processes, Powder Technol. 150 (2005) 86–103. doi:10.1016/j.powtec.2004.11.025.

[42] H. Leuenberger, New trends in the production of pharmaceutical granules: The classical batch concept and the problem of scale-up, Eur. J. Pharm. Biopharm. 52 (2001) 279–288. doi:10.1016/S0939-6411(01)00200-4.

[43] S. Watano, T. Okamoto, Y. Sato, Y. Osako, Scale-up of high shear granulation based on the internal stress measurement., Chem. Pharm. Bull. (Tokyo). 53 (2005) 351–4. doi:10.1248/cpb.53.1547.

[44] J. Tao, P. Pandey, D.S. Bindra, J.Z. Gao, A.S. Narang, Evaluating Scale-Up Rules of a High-Shear Wet Granulation Process, J. Pharm. Sci. 104 (2015) 2323–2333. doi:10.1002/jps.24504.

[45] N. Rahmanian, B.H. Ng, A. Hassanpour, M. Ghadiri, Y. Ding, X. Jia, J. Antony, Scale-up of high shear mixer granulators, KONA Powder Part. 26 (2008) 190–204. doi:10.13140/RG.2.1.1034.0883.

[46] G.J.B. Horsthuis, J.A.H. van Laarhoven, R.C.B.M. van Rooij, H. Vromans, Studies on upscaling parameters of the Gral high shear granulation process, Int. J. Pharm. 92 (1993) 143–150. doi:10.1016/0378-5173(93)90273-I.

[47] G.I. Tardos, K.P. Hapgood, O.O. Ipadeola, J.N. Michaels, Stress measurements in high-shear granulators using calibrated “test” particles: Application to scale-up, Powder Technol. 140 (2004) 217–227. doi:10.1016/j.powtec.2004.01.015.

[48] J.D. Litster, Scaleup of wet granulation processes: Science not art, Powder Technol. 130 (2003) 35–40. doi:10.1016/S0032-5910(02)00222-X.

[49] S. van den Ban, D.J. Goodwin, The Impact of Granule Density on Tabletting and Pharmaceutical Product Performance, Pharm. Res. 34 (2017) 1002–1011. doi:10.1007/s11095-017-2115-5.

[50] G.S. Rekhi, R. Caricofe, D.M. Parikh, L.L. Ausburger, A new approach to scale-up of a high shear granulation process used in the manufacture of metoprolol tartrate tablet formulations, Pharm. Technol. 20 (1996) 2–10.

Chapter 2

Liquid amount prediction for high-shear wet granulation

2.1 Introduction

High-shear wet granulation (HSWG) has been one of the most commonly used methods to enlarge particle size in different fields such as agrochemical and pharmaceutical industries since the early 1980s [1]. Common ingredients used in both the food and pharmaceutical industries are sweeteners, often associated with the functional use of sucrose, which has traditionally been referred to as ‘sugar’. Sucrose is not only the basic ingredient for traditional sugar confectionery but it is also used as diluent, binder, taste masking agent, sweetener and agent for drug controlled release (e.g. sugar beads) in pharmaceutical field. However, in order to reduce the amount of energy, the exposure to factors which are known to cause dental decay, etc. many other products could be used as sweeteners (e.g. polyols). The use of sugar and sweeteners in the wet granulation process nevertheless poses some important issues. They are indeed soluble and sticky ingredients [2,3]. Consequently, their manipulation and processing in high-shear granulators may be difficult because, after the addition of water: they may adhere to the mixer walls, cause encrustation, hinder cleaning and ultimately lead to loss of product. Control of the granulation process can also be difficult due to the uncontrolled growth of the granules may result in final products with non-optimal functional properties. Generally the correct amount of liquid binder to use in the HSWG falls within a narrow range, indeed if an incorrect amount of binder solution is used, lack of growth or over-granulation with the formation of large lumps can occur. In both cases, significant loss of product and longer production time may again result, thus it would therefore be highly desirable to predict the required amount of liquid binder based on the formulation composition [4]. This is a difficult task since the amount of liquid binder depends on several formulation variables (e.g. physicochemical properties of the raw ingredients, interactions between solid and liquid binder) and on numerous process variables (e.g. impeller speed, wet massing time, binder addition rate) [1,5].

The purpose of this research was to develop an easy and reliable method to predict the correct amount of liquid binder required to produce granules with acceptable technological properties with the high-shear wet granulation process.

2.2 Materials and methods

2.2.1 Materials

Confectionary sucrose, sorbitol, mannitol, xanthan gum, and microcrystalline cellulose (MCC, type T1) were all purchased from Acef (Acef SpA, Italy). Mannitol and sorbitol were purchased as direct compression grade to avoid the influx of the different particle size of the sweeteners.

Sucrose is a disaccharide compound characterized by a sweet taste and a great solubility in water (1:0.5 at 20°C). It finds several applications in oral pharmaceutical formulations. Sucrose syrup, containing 50-67% w/w sucrose, is used as a binding agent for wet granulation. In the powdered form it is employed as a dry binder where it is granulated using water or hydroalcoholic solution; it can be found also as a bulking agent or sweetener for tablet and capsules manufacturing [6].

Sorbitol is a polyol, a hexahydric alcohol related to mannose and isomeric with mannitol. It is highly hygroscopic at relative humidity (RH) > 65% and becomes deliquescent at RH higher than 70% producing supersaturated solutions. This characteristic of forming supersaturated solutions makes the solubility assessment difficult. Sorbitol is extensively used as excipient in pharmaceutical formulations, in cosmetic and food products. It is used as a bulking agent for tablet formulation and wet granulation; it finds an application as plasticizer for gelatin in capsules [6].

Mannitol is a hexahydric alcohol related to mannose as sorbitol which is its isomer. It occurs as a white, odorless, crystalline powder, or free flowing granules. Mannitol is widely used in pharmaceutical formulations as diluents for tablets production because of the favorable tabletability. In the tablet, mannitol can assumes a particular value associated with moisture-sensitive active ingredients because it is not hygroscopic. It can be employed also for granulation, as bulking agent in lyophilized preparations, as carrier in dry powder inhalers and as plasticizer in soft-gelatin capsules [6].

Cellulose is a polysaccharide built by several units of glucose bound through β(1-4) glucosidic connections. Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is widely used in the pharmaceutical industry as excipient of choice for several applications because of its peculiar characteristics. It is employed as binder/diluents in tablets, capsules and granules as it can be used both in dry and wet granulation moreover it has also some lubricant and disintegrant properties. Microcrystalline cellulose is practically insoluble in water but it is hydrophilic and hygroscopic [6].

2.2.2 Characterization of the raw materials

The sweeteners were sieved in order to have a similar mean diameter; in particular particles in the size range between 63 and 300μm were selected for the study. The raw materials were characterized in terms of particle size distribution (PSD) using a laser light scattering (Malvern Hydro 2000 Malvern, UK) using as liquid medium silicon oil.

Aqueous solutions containing increasing amount of the sweeteners were characterized by a viscosimetric analysis using a Rotovisco RV 20 viscometer (Haake, Germany) equipped with a rheocontroller RC 20 with M5 sensor system. Measurements were taken at shear rates ranging from 0 to 700s^{-1} at 20°C using the NV equipment. Results are the average of three independent experiments.

Sugars and other food powders (e.g. fat and milk proteins) lead to sticking and caking phenomena. Sticking has been defined as the stage when liquid bridges between particles have formed. These liquid bridges may be constituted of molten fats, plasticized amorphous materials or concentrated viscous solutions. Two main mechanisms for sticking have been identified and can also play a role in the caking of sugar powders: amorphous caking and moisture driven caking [7].

Amorphous caking is due to the powder being exposed to conditions where the amorphous material undergoes a transition to a rubbery state. As a result rubbery bridges between adjacent particles are formed. The transition from glass to rubbery state occurs at a particular temperature called glass transition temperature (Tg), which is peculiar to each amorphous material but can decrease as a function of the water absorbed by the material. Moisture driven caking occurs instead when the powder is exposed to conditions which produce moisture adsorption on the particle surface. If the material is soluble (as in the case of crystalline sweeteners) this mechanism can trigger deliquescence and the formation of viscous liquid bridges which cause sticky behavior of the wet mass [7].

In order to determine which binding mechanism (amorphous caking or moisture driven bridging) was dominant the solid state of the three selected sweeteners was investigated by means of the X-ray powder diffraction technique (XRPD) using a X'Pert Pro diffractometer (PANalytical B.V., the Netherlands) in transmission geometry equipped with Cu X-ray tube (setting 40 kV and 40 mA), focusing mirror, capillary spinner and PixCel Detector. Experiments were performed in the 3°–70° of 2θ, range steps were of 0.013° and the counting time of 60s/step. Powder samples were mounted in boron glass capillaries with 0.7 mm inner diameter.

2.2.3 Evaluation of the interaction between powders and liquid binder

The interaction between the powders and the liquid binder is characterized in terms of wettability and drop penetration time. The water affinity of the powders was evaluated through contact angle measurement carried out on compacts of the sugars, according to the sessile drop method [8] using the drop shape analyzer DSA 30 (Kruss, Germany). Drop penetration time was evaluated on tapped bed of powders. The different sweeteners were blended with microcrystalline cellulose (MCC) in the percentages reported in Table 2.3. Following, a sample from each formulation previously presented, was placed in a 25ml cylindrical container, tapped in standard conditions in order to remove any bed imperfections, then magnified videos of water drops falling from a tube and lying on dry powder mixture were filmed using the drop shape analyzer DSA 30 (Kruss, Germany). The time for complete sinking of the droplet was then precisely measured and referred to as drop penetration time [8].

2.2.4 Determination of the optimal liquid binder amount for high-shear wet granulation

A mixer torque rheometer (MTR3, Caleva, UK) was employed in order to evaluate the different states of liquid saturation using the multiple addition method. Briefly, an amount of powder mixture corresponding to 50ml was poured into the empty bowl, mixed at a shafts speed of 50 or 150 rpm and the baseline was measured for 30s. Afterwards, multiple additions of 0.5ml of water were performed, the wet mass was mixed for 15s and the torque value was measured for 15s. Water was added until slurry was formed and the over-wetting reached. Experiments were conducted three times and the data report the average values of the three determinations.

2.2.5 Granulation experiments

Granulation experiments were conducted in both a 1.0l lab scale high-shear mixer (Eirich EL1, Maschinenfabrick Gustav Eirich, Germany) and a 1.5l lab-scale high-shear a Rotolab (IMA Zanchetta, Italy). In Figure 2.1 are shown the two equipments employed in the present study.

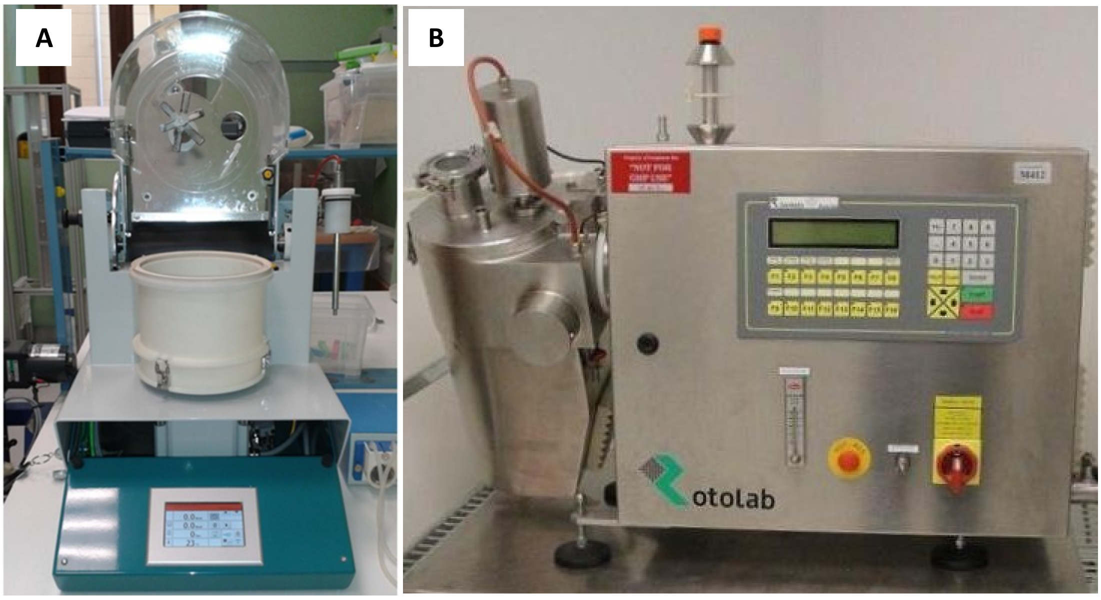


Figure 2.1: The two equipments employed in the study. a) Eirich EL1 equipped with the PTFE rotating bowl, the impeller is visible on the open led; b) Zanchetta Rotolab is showed on the right. The closed stainless steel bowl contains the bottom-driven impeller.

The two granulators have different layouts. The Eirich EL1 high-shear mixer is composed of a rotating pan made of PTFE and an eccentric vertical top-driven impeller (Figure 2.1a). The Rotolab is a classical high-shear mixer with a fixed stainless steel bowl and a centered bottom-driven impeller (Figure 2.1b). The granulation procedures on both the granulators were determined through preliminary experiments. Briefly, powders were dry mixed in the high-shear granulator, then the liquid binder (i.e. deionized water) was dropped into the dry powders using a peristaltic pump. At the end of the wetting time impeller speed was increased for 180s. Experimental variables selected for the two instruments are resumed in Table 2.1. At the end of granulation procedure granules were dried at 40°C in a ventilated oven until constant weight was achieved.

Table 2.1: Parameters of the high-shear mixers.

	Einrich EL1*	Rotolab
Dry mixing:		
Impeller speed	300rpm	120rpm
Time	200s	120s
Wetting phase:		
Flow rate:	0.65ml/s	0.17ml/s
Massing phase:		
Impeller speed	2000rpm	800rpm
Time	180s	180s

* In all the experiments the bowl rotated at a fixed velocity of 85 rpm in opposite direction with respect to the impeller.

2.2.6 Granules size distribution

Granules size distribution (GSD) was characterized by sieve analysis. A set of sieves (63, 300, 400, 500, 600, 800, 1000, 1250, 2000, and 3150µm) was placed on a vibrating apparatus (AS 20, Retsch, Germany) operated at a medium vibrating level for 10min. The fractions from each sieve were collected and weighted; the resulting cumulated distribution of the particle size was used to evaluate the median diameter (d_{50}). Granules with a d_{50} between 500µm and 2000µm were considered and indicated in the results as successfully granulated; instead granules having a d_{50} higher than 2000 µm were considered over-granulated.

2.3 Results and discussion

2.3.1 Characteristics of the starting ingredients

In order to compare formulations containing sweeteners having different solubility and viscosity but similar particle size distribution, raw materials were sieved and only sweeteners in the size range 63-300µm were used. PSD was then evaluated by laser light scattering (Table 2.2).

Table 2.2: Properties of the raw materials employed.

Ingredient	d_{10} [μm]	d_{50} [μm]	d_{90} [μm]
Sorbitol	83.24	286.84	426.90
Mannitol	230.68	341.85	504.11
Sucrose	168.97	338.34	579.87
MCC	36.18	98.82	213.65

Sweetener	Solid state	Water solubility [g/100g solution]	Viscosity (at saturation) [mPa s]	Contact Angle [°]
Sorbitol	Crystalline (γ form)	75	219±14	25 ± 4
Mannitol	Crystalline (β form)	18	3.5±1.3	34 ± 4
Sucrose	Crystalline	66	205±6.1	24 ± 2

The wettability was evaluated through contact angle measurements which are an assessment of the interaction between a solid and a liquid, as discussed in section 1.4.1. Contact angle values were always lower than 90°, this represent a great affinity between the ingredients employed in the study and the granulating liquid employed (i.e. deionized water). Results from contact angle measurements match with those obtained for water solubility of the sweeteners. Sucrose and sorbitol present similar values, while mannitol shows the lower water affinity and solubility among the studied sweeteners.

Solid state of the three sweeteners was investigated by means of the X-ray powder diffraction technique (XRPD). The X-ray patterns obtained for all the sugars (Figure 2.2) showed narrow peaks, indicative of the crystalline solid presence. In addition, the comparison between patterns and database has allowed to correctly identify the crystalline state reported in Table 2.2. It was possible to conclude that the selected sugars in dry condition were in their crystalline state and thus the addition of water was responsible for the sticking behavior of the sugars according to the moisture driven mechanism.

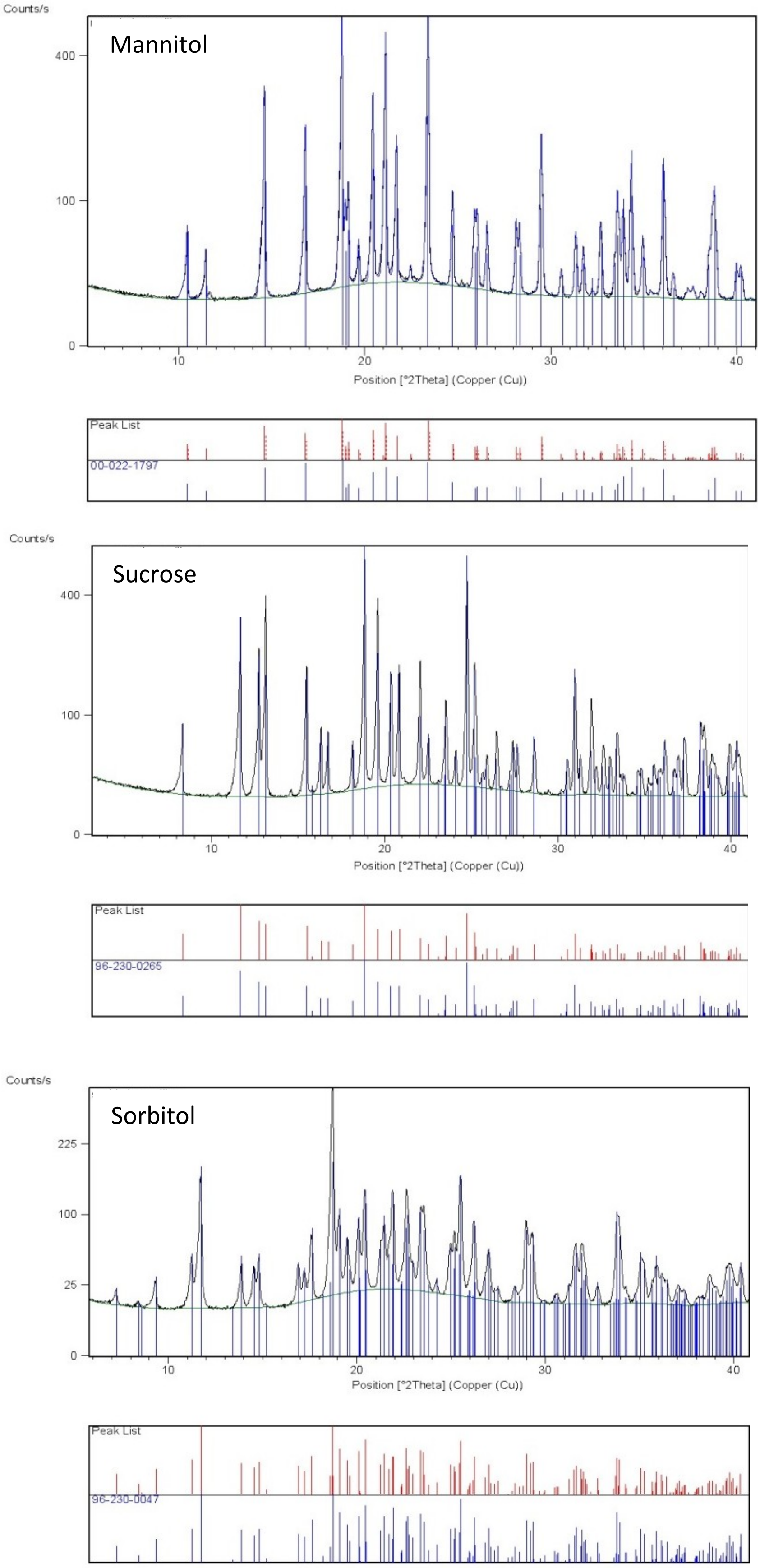


Figure 2.2: X-ray powder diffraction patterns for the studied sweeteners. The narrow peaks showed by the XRPD patterns are indicative of the sweeteners crystallinity.

In order to evaluate the thickening power of the different sweeteners, the viscosity of saturated water solutions was evaluated and results are reported in Table 2.2. Results highlight that sorbitol and sucrose present the higher water solubility, 75 g/L and 66 g/L respectively, and the highest thickening power, therefore it is possible to hypothesize that they will have a similar behavior in granulation. Sweeteners were then mixed with MCC and the formulations prepared are listed in Table 2.3.

Table 2.3: The composition of the formulations containing sweeteners employed in the study.

Name	Sucrose [% (w/w)]	MCC [% (w/w)]	Name	Mannitol [% (w/w)]	MCC [% (w/w)]
SUCR25	25%	75%	MANN25	25%	75%
SUCR50	50%	50%	MANN50	50%	50%
SUCR75	75%	25%	MANN75	75%	25%
SUCR100	100%	0%	MANN100	100%	0%
Name	Sorbitol [% (w/w)]	MCC [% (w/w)]			
SORB25	25%	75%			
SORB50	50%	50%			
SORB75	75%	25%			
SORB100	100%	0%			

Literature reports that final granule size distribution can retain a memory about the initial nuclei size distribution. Therefore, initial wetting represents a critical step towards uniform nuclei formation and enhanced product quality [9]. On this purpose the drop penetration time is an important evaluation which allows to characterize the interaction between the formulations powders and the granulating liquid. From the penetration time reported in Table 2.4 it is clear that the water drops penetrate rapidly the powder bed.

Table 2.4: Drop penetration time for the different formulations evaluated in the study.

Formulation	Tp [s]	Formulation	Tp [s]
SUCR25	0.18±0.01	MANN25	0.18±0.02
SUCR50	0.20±0.02	MANN50	0.20±0.01
SUCR75	0.20±0.04	MANN75	0.15±0.03
SUCR100	0.21±0.29	MANN100	0.11±0.02
SORB25	0.18±0.02	MCC100	0.09±0.01
SORB50	0.22±0.02		
SORB75	0.60±0.13		
SORB100	0.84±0.17		

The drop penetration time recorded for MCC100 is the lowest among the different formulations. It can be observed a tendency of the drop penetration time to increase when higher amount of sweeteners are included. In particular the longest penetration time was recorded for SORB100. This is probably due to the rapid formation of a viscous solution when the water drop is added to the powder bed. The viscous solution thus struggle to penetrate between the pores of the powder.

2.3.2 Wet mass characterization and L/S prediction

The possibility to predict the correct L/S to process a formulation in high-shear mixer is of great importance as it is one of the most critical parameter for the granulation process. Liquid amount added to a formulation determine the granules size and the kinetic of granules growth [10]. Several publications aim to solve this issue using the wet mass rheology. The use of a mixer-torque rheometer (MTR) to characterize the rheological properties of the wet masses and to predict the optimal liquid amount for granulation experiments was first investigated by Rowe and colleagues [11,12]. Some authors compared the torque measured on-line on a high-shear mixer and off-line using a mixer torque rheometer. From this comparison was possible to establish that the optimal amount of liquid which should be used for a successful granulation corresponds to the transition from the pendular to the funicular state of the powder capillary saturation. Moreover, this transition corresponds to a shoulder in the MTR profile [13]. Torque profiles using the multiple addition method were recorder using the MTR3 and results are reported in Figure 2.3.

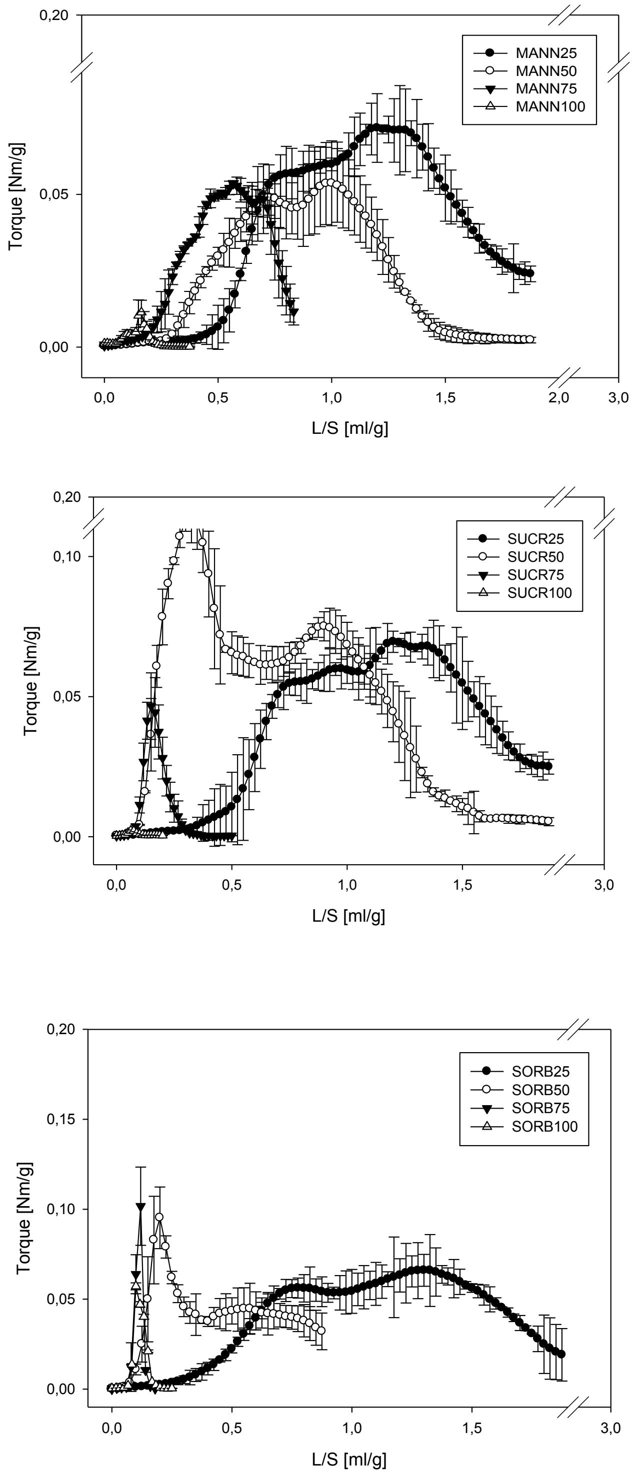


Figure 2.3: Multiple addition profiles for the different formulations.

In particular for this set of experiments, a standard shafts speed of 50rpm was used as indicated in the operation manual of the instrument.

From the torque profiles obtained it is possible to note that the torque recorded is generally very low for the pure sweeteners (with the exception of sorbitol) and it increase when MCC is added to the mixture. The graphs obtained are sharp when high amount of soluble materials are present, this is caused by the rapid achievement of the capillary state due to the dissolution of the sweeteners. From Figure 2.3 it is possible to note a clear effect of MCC on the mixture rheology. In particular the amount of liquid required to reach the torque peak and corresponding to the capillary state decreased with the decrease of the MCC amount. Moreover the characteristic shoulder on the torque profile, which is indicative of the transition between pendular to funicular saturation states, is gradually lost as the sweeteners gain importance in mixture. For an amount of sweeteners above 50% the shoulder, is no longer present. Thus, the shoulder on the torque profile is not reliable to identify the optimal liquid amount to be used in HSWG, especially when soluble materials need to be used in the formulation. Consequently, a mathematical approach was employed to define a general and reliable method which can be used both in presence or absence of the characteristic shoulder. The analysis of the second derivative of the torque profiles was adopted. In particular two typical cases are shown in Figure 2.4 to clarify this approach.

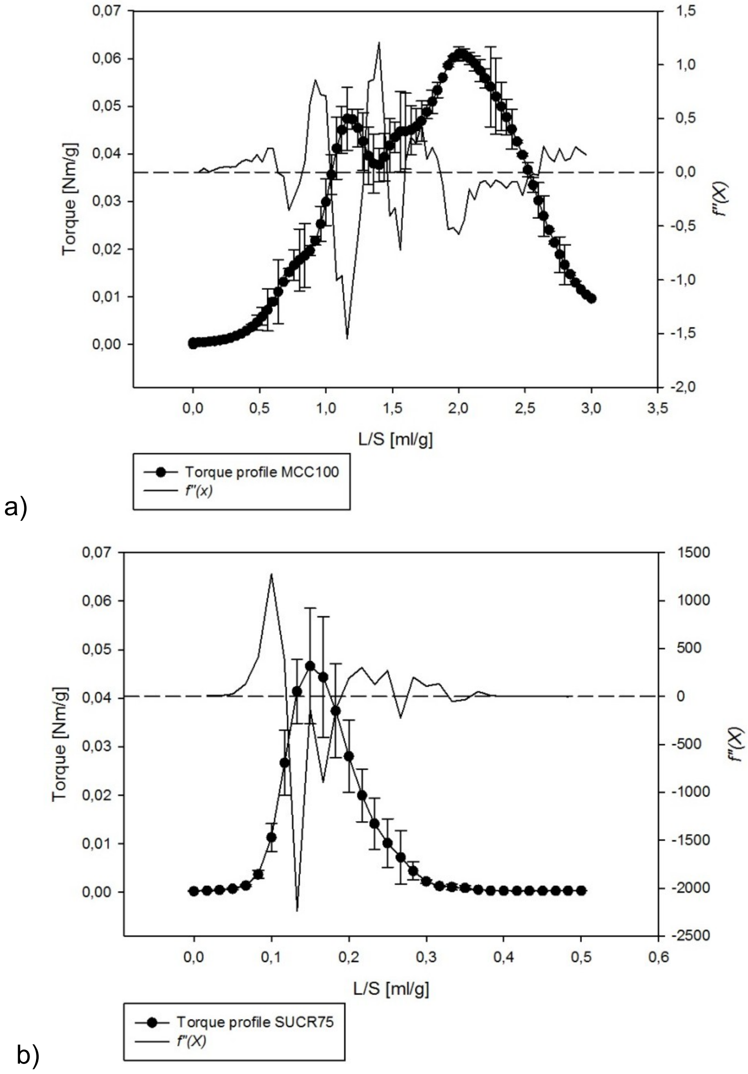


Figure 2.4: Torque profiles recorded for (a) MCC100 and (b) SUCR75 and their second derivative.

In the presence of a shoulder, the second derivative identifies two inflection points (where the second derivative assumes a value of zero) which enclose the shoulder. These two points define a range of L/S which could be used to perform the granulation experiments and the midpoint between the two inflection points was considered as the optimal L/S ratio. In the second case (Figure 2.4b), where no shoulder is present, can be identified a single inflection point before the torque peak. The inflection point is considered as corresponding to the optimal L/S ratio. Torque of this type of formulations is very sensitive to small variation in liquid amount and consequently the process may be less robust or more difficult to control. This type of analysis was conducted for all the formulations and the L/S ratios determined using this method are resumed in Table 2.5.

Table 2.5: Liquid to solid ratios identified for the different formulations using the second derivative of the torque profile recorded with the MTR3.

Formulation	**L/S [ml/g]**	**Formulation**	**L/S [ml/g]**	**Formulation**	**L/S [ml/g]**
SORB100	0,09	MANN100	0,10	SUCR100	0,05
SORB75	0,12	MANN75	0,37	SUCR75	0,10
SORB50	0,23	MANN50	0,65	SUCR50	0,25
SORB25	0,70	MANN25	0,70	SUCR25	0,70
MCC100	1,20	-	-	-	-

Results highlight that the higher is the amount of the sweeteners present in the formulation and the lower is the amount of water necessary for the granulation process (Figure 2.5). Moreover, the amount of liquid binder necessary for the HSWG depends on thickening power and solubility of the sweeteners; indeed the predicted L/S values are lower for those formulations containing sweeteners having the higher thickening power and water solubility (sucrose and sorbitol).

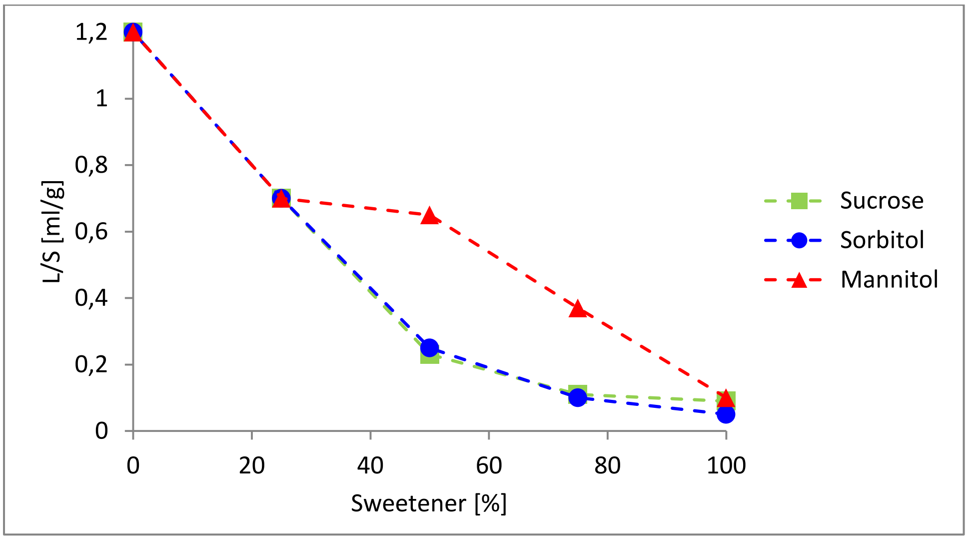


Figure 2.5: Relationship between the amount of sweeteners and the amount of liquid binder necessary for the HSWG expressed in terms of L/S.

The ability of the MTR3 to predict the optimal liquid amount was evaluated through granulation experiments performed using a lab scale high-shear mixer Eirich EL1. Granules were dried and sieved in order to evaluate the mean diameter (d_{50}). Data are resumed in Figure 2.6.

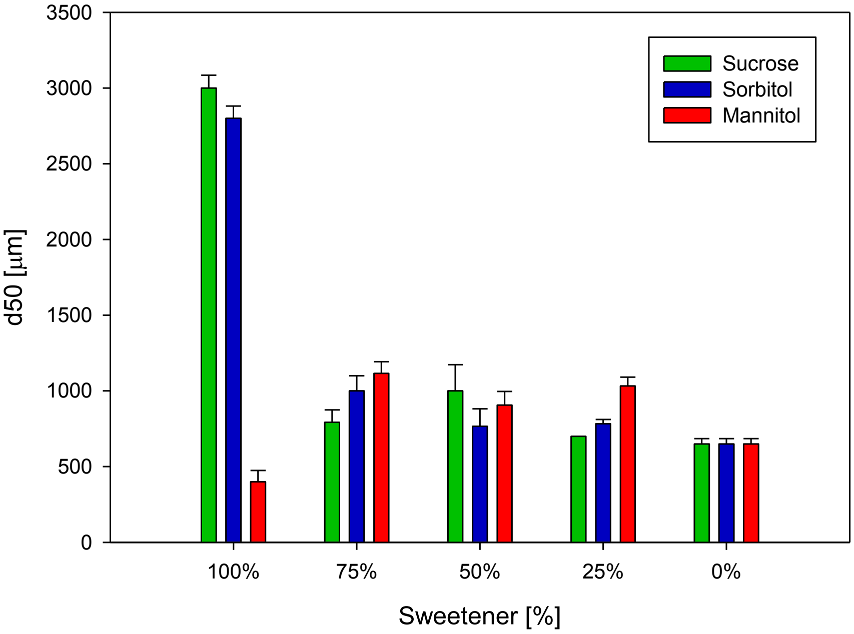


Figure 2.6: Mean diameter (d_{50}) of the granules produced with the Eirich EL1 high-shear mixer using the predicted L/S.

The granules produced using the L/S determined with the second derivative approach presented an acceptable particle size distribution. The mean diameter (d_{50}) of the produced granules using the formulations MCC100 and those containing a percentage of sweeteners up to 75% ranged between 500 and 1500, thus their PSD can be defined as acceptable for most of the application which generally involves the granules. On the other hand for formulations containing 100% (w/w) of sorbitol or sucrose an over-granulation was observed. This behavior it is probably connected to the higher sensitivity of these formulations, as observed with the torque profiles, due to the higher water solubility and thickening power. However it is possible to assume that, for general granulation purposes, the L/S employed was correct for granules production in high-shear equipment. In conclusion it can reasonably assume that MTR3 is a useful tool to predict optimal liquid amount for high-shear wet granulation.

2.3.3. Validation of the L/S prediction method using a different high-shear mixer

In order to further validate this method, granulation experiments were conducted also in a different high-shear mixer, a bottom driven lab scale 1.5l Rotolab Zanchetta, using the same formulations previously discussed and a standard procedure as reported in section 2.2.5.

At the end of the granulation process, granules were dried and sieved and mean diameter was calculated. Results of the formulations containing 100% (w/w) of sorbitol and sucrose are not reported because an over-granulation was observed after few minutes (Figure 2.7); instead the results of formulation containing 100% (w/w) of mannitol are not reported due to the high adhesion of the material to the mixer walls which did not allow the process to be carried out blocking the instrument.

Figure 2.7: Ball growth of and over-granulation of the formulation containing 100% (w/w) of sorbitol.

Data regarding the other formulations are resumed in Figure 2.8.

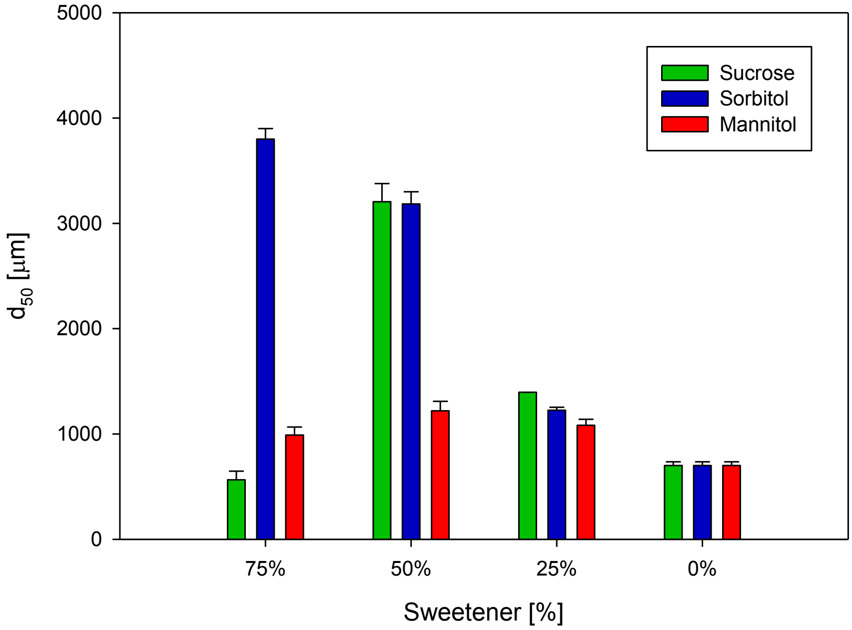
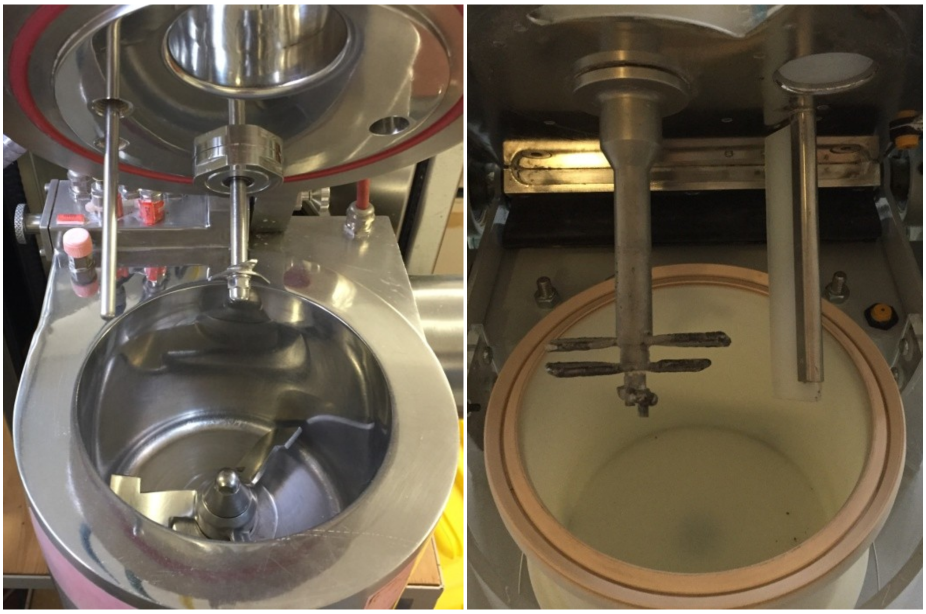


Figure 2.8: mean diameters of the granules produced by 1.5l high-shear mixer Rotolab.

Figure 2.8 highlights that the granulation process of formulations containing more than 25% of sorbitol and sucrose are difficult to control using the high-shear mixer Rotolab and the experimental conditions selected for this study; in fact, an uncontrollable growth is observed in 180s. These results could be due to the different material of the bowl or to the different instrument layout. In particular 1l high-shear mixer Eirich EL1 presents a bowl made of PTFE, a hydrophobic polymer which can reduce the adhesion of sticking materials. Moreover the counter-rotating movement of the pan can promote the detachment of adhered material. The two granulators present also completely different impeller geometry and impeller position (Figure 2.9) producing different flux regimes and shear stress which play an important role in the granules growth.



a) b)

Figure 2.9: Details of the different bowl conformation of Rotolab Zanchetta (a) and Eirich EL1 (b). The bottom driven impeller of the Rotolab Zanchetta have a completely different diameter and shape compared with the eccentric, top-drive impeller of the Eirich EL1.

This rapid growth could be associate to an increase in the sweetener dissolution kinetic due to the higher shear applied. In order to evaluate if the shafts speed of the rheometer could influence the sweetener dissolution kinetic and thus the prediction of the water amount request for the granulation, multiple addition experiments were repeated using the maximum shafts speed (150rpm) and the optimal liquid amount has been recalculated (Table 2.6).

Table 2.6: Comparison between L/S evaluated using the MTR3 at 50 and 150rpm.

Formulation	**L/S [ml/g] 50rpm**	**L/S [ml/g] 150rpm**	**Formulation**	**L/S [ml/g] 50rpm**	**L/S [ml/g] 150rpm**
SORB75	0.12	0.10	MANN75	0.37	0.37
SORB50	0.23	0.16	MANN50	0.65	0.65
SORB25	0.70	0.70	MANN25	0.70	0.70
Formulation	**L/S [ml/g] 50rpm**	**L/S [ml/g] 150rpm**	**Formulation**	**L/S [ml/g] 50rpm**	**L/S [ml/g] 150rpm**
SUCR75	0.10	0.10	MCC100	1.20	1.20
SUCR50	0.25	0.20			
SUCR25	0.70	0.70			

Results highlight that for formulations containing high amount of sweeteners presenting a high thickening power (sucrose and sorbitol), the increase in shafts speed reduces the water amount necessary to reach the pendular-to-funicular transition and thus the liquid amount which is required for the granulation process. When the torque profile is recorded at a low shafts speed, the powders and the added water do not reach the equilibrium before a following liquid addition is performed. The higher shafts speed instead promotes the sweetener solubilization and a better equilibration of the solid and liquid phase before a further water addition is operated. Consequently, this leads to a more accurate assessment of the optimal L/S ratio. In order to verify if the new value of L/S are correct, granulation experiments using Rotolab were repeated. The mean diameters of these new granules are reported in Figure 2.10.

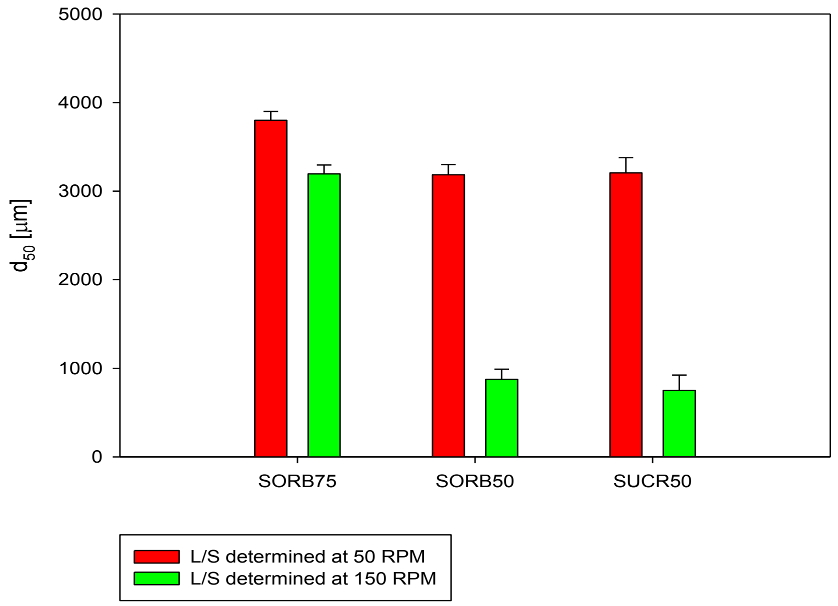


Figure 2.10: Comparison between the mean diameter (d_{50}) of the granules produced with the L/S predicted at different shafts speed.

The L/S predicted at 150rpm appeared to be more accurate as the granules presented an acceptable diameter. The only exception was shown by SORB75 which still present an over-granulation. However, this is probably due to a peculiar granules growth kinetic rather than a non-optimal L/S, thus further investigations need to be conducted focusing on the granules growth kinetic.

Granules produced using the L/S predicted using a higher shafts speed in the MTR3 showed lower mean diameter values and thus acceptable characteristics in terms of PSD which ranged between 500 and 1500µm. This result indicates that the use of a shafts speed of 150rpm allowed to predict more precisely the correct amount of water. The reason of the initial overestimation of the L/S can be due to the competition between MCC and sweeteners to interact with the added water and the solubilization of the sweeteners during the process. When the torque profile is recorded at high shafts speed, the sweeteners solubilization is promoted.

2.4. Conclusions

The correct amount of liquid binder to be used for HSWG falls within a narrow range and if an incorrect amount of binder solution is used, lack of growth or over-granulation can occur. Thus to make the process development easier, it would be highly desirable to develop a method to predict the amount of liquid binder necessary for a successful process. Results have shown that an easy and fast prediction of the optimal liquid amount (deionized water in this case) required to provide granules with acceptable technological properties can be carried out by a rheological characterization using a mixer torque rheometer. Moreover the application of the second derivative to the torque profile have permitted to develop a reliable method to identify the optimal value of L/S. Granulation experiments have confirmed the ability of the MTR to predict optimal liquid amount.

Furthermore, this instrument showed the great possibilities of measuring the rheology of the wet masses to predict important parameters for the granulation process. The applications of this instrument should be fully investigated. In particular it would be interesting to study how the rheology of the wet masses evolves after the optimal liquid amount is added. This measurement could be useful to understand the granulation process progression.

2.5 References

[1] R. Gokhale, Y. Sun, A.J. Shukla, High-Shear Granulation, in: D.M. Parikh (Ed.), Handb. Pharm. Granulation Technol., Second, Taylor & Francis Group, 2005: pp. 191–228.

[2] B. Adhikari, T. Howes, B.R. Bhandari, V. Truong, Stickiness in foods: A review of mechanisms and test methods, Int. J. Food Prop. 4 (2001) 1–33. doi:10.1081/JFP-100002186.

[3] P. Boonyai, B. Bhandari, T. Howes, Stickiness measurement techniques for food powders: A review, Powder Technol. 145 (2004) 34–46. doi:10.1016/j.powtec.2004.04.039.

[4] M. Cavinato, E. Andreato, M. Bresciani, I. Pignatone, G. Bellazzi, E. Franceschinis, N. Realdon, P. Canu, A.C. Santomaso, Combining formulation and process aspects for optimizing the high-shear wet granulation of common drugs, Int. J. Pharm. 416 (2011) 229–241. doi:10.1016/j.ijpharm.2011.06.051.

[5] S. Nalesso, C. Codemo, E. Franceschinis, N. Realdon, R. Artoni, A.C. Santomaso, Texture analysis as a tool to study the kinetics of wet agglomeration processes, Int. J. Pharm. 485 (2015) 61–69. doi:10.1016/j.ijpharm.2015.03.007.

[6] R. Rowe, P. Sheskey, M. Quinn, Handbook of Pharmaceutical Excipients, Handb. Pharm. Excipients, Sixth Ed. (2009) 549–553. doi:10.1016/S0168-3659(01)00243-7.

[7] K.D. Foster, The prediction of sticking in dairy powders, Massey University, 2002.

[8] L. Susana, F. Campaci, A.C. Santomaso, Wettability of mineral and metallic powders: Applicability and limitations of sessile drop method and Washburn’s technique, Powder Technol. 226 (2012) 68–77. doi:10.1016/j.powtec.2012.04.016.

[9] W.F. Sakr, M.A. Ibrahim, F.K. Alanazi, A.A. Sakr, Upgrading wet granulation monitoring from hand squeeze test to mixing torque rheometry, Saudi Pharm. J. 20 (2012) 9–19. doi:10.1016/j.jsps.2011.04.007.

[10] S. Iveson, J. Litster, Growth regime map for liquid bound granules, AIChE J. 44 (1998). http://onlinelibrary.wiley.com/doi/10.1002/aic.690440705/full.

[11] R.C. Rowe, G.R. Sadeghnejad, The rheology of microcrystalline cellulose powder/water mixes - measurement using a mixer torque rheometer, Int. J. Pharm. 38 (1987) 227–229. doi:10.1016/0378-5173(87)90118-9.

[12] M. Kuhs, J. Moore, G. Kollamaram, G. Walker, D. Croker, Predicting optimal wet granulation parameters for extrusion-spheronisation of pharmaceutical pellets using a mixer torque rheometer, Int. J. Pharm. 517 (2017) 19–24. doi:10.1016/J.IJPHARM.2016.11.057.

[13] T.M. Chitu, D. Oulahna, M. Hemati, Rheology, granule growth and granule strength: Application to the wet granulation of lactose-MCC mixtures, Powder Technol. 208 (2011) 441–453. doi:10.1016/j.powtec.2010.08.041.

Chapter 3

Rheology of wet masses as a useful tool to predict the evolution of the granulation process

3.1 Introduction

High-shear wet granulation (HSWG) has been one of the most commonly used method for the pharmaceutical particle size enlargement. Although HSWG has been used for several decades, the process is still not completely understood [1,2]. In HSWG the liquid binder is added to powder mixtures while constantly mixed by an impeller which provides high-shear forces. The process can be divided in different stages: the first consists in wetting and nucleation, followed by consolidation and coalescence and, finally, attrition and breakage. Some authors have demonstrated that during this last stage an equilibrium between granule growth and breakage is obtained and thus a material exchange between granules is possible. In particular, literature reports three different material exchange mechanisms named disintegration, deformation and distribution mechanisms. The type of the mechanism that occurs depends on wet granule deformability and strength [3–5]. These two properties could be described in terms of Stokes deformation number (St_{def}) which represents the ratio of initial collisional kinetic energy to the energy dissipated by viscous lubrication forces, and it is one measure of normalized bed agitation energy [3]. This number can be used to predict wet granules breakage (at the critical Stokes deformation number) but also in growth regime map in which the maximum pore saturation of granules is plotted against Stokes deformation number [5]. Although the use of St_{def} represents a useful conceptual tool to describe the evolution of a granulation process, its practical use can be difficult since numerous parameters need to be estimated (e.g. particle collision velocity) or complex characterizations need to be performed (e.g. measure the wet granule strength in dynamic conditions at high levels of shear) to calculate its value. Consequently, the St_{def} cannot be estimated unambiguously and thus the growth regime map can be used as guidance only, not for the exact prediction of the different growth regimes occurring during granulation [6]. Since the material exchange mechanisms and the growth regimes depend on the same properties it is possible to highlight a correlation between them. This correlation was investigated by Bouwman et al. by performing different experiments with a tracer [6]. They observed that the disintegration mechanism is associated to the ‘crumb behaviour’, the deformation mechanism corresponds to the ‘steady growth regime’, and finally the distribution mechanism is associated to ‘nucleation’ and ‘induction growth’. Since, in the regime map, the exchange mechanisms match to the granule growth mechanisms, the use of tracers with different colours might be used to indirectly reveal the granulation regime [6]. However the approach proposed by Bouwman et al. requires to perform a large number of granulation experiments, which is time and material consuming. The purpose of this study was therefore to propose an alternative method for the description and prediction of the wet granulation process evolution, based on easy and fast rheological characterizations requiring the analysis of limited amounts of wet powder mixture.

3.2 Materials and methods

3.2.1 Materials

Confectionary sucrose, sorbitol (direct compression grade), mannitol (direct compression grade), xanthan gum, and microcrystalline cellulose (MCC, type T1) were all purchased from Acef (Acef SpA, Italy). The formulations used in this study are collected in Table 3.1.

Table 3.1: Compositions of the formulations selected for the study.

Formulation	XG [% (w/w)]	MCC [% (w/w)]
MCC100	0%	100%
XG1	1%	99%
XG5	5%	95%
Formulation	Mannitol [% (w/w)]	MCC [% (w/w)]
MANN25	25%	75%
MANN50	50%	50%
MANN75	75%	25%
Formulation	Sucrose [% (w/w)]	MCC [% (w/w)]
SUCR25	25%	75%
SUCR50	50%	50%
SUCR75	75%	25%
Formulation	Sorbitol [% (w/w)]	MCC [% (w/w)]
SORB25	25%	75%
SORB50	50%	50%
SORB75	75%	25%

3.2.2 Evaluation of the thickening power of the solid binders

In order to evaluate the thickening power of the different solid binders added to the cellulose microcrystalline, aqueous solutions containing increasing amount of the sweeteners and aqueous dispersion containing increasing amount of xanthan gum were characterized by a viscosimetric analysis using a Rotovisco RV 20 viscometer (Haake, Karlsruhe, Germany) equipped with a rheocontroller RC 20 with M5 sensor system. Measurements were taken at shear rates ranging from 0 to 700 s^{-1} at 20°C using NV equipment. Results are the average of three independent experiments.

3.2.3 Determination of the optimal liquid binder amount for high-shear wet granulation

A mixer torque rheometer MTR3 (Caleva, UK) was employed in order to predict the optimal liquid amount for the HSWG using the ‘multiple addition’ method. The instrument and the employed procedures are described in detail in section 1.9.1. Briefly, an amount of powder mixture corresponding to 50ml was poured into the empty bowl, mixed at a shafts speed of 150rpm and the baseline was measured for 30s. Afterwards, multiple additions of 0.5ml of water were performed; the wet mass was mixed for 15s and the torque value was measured for 15s. The water was added until a slurry was formed and the over-wetting reached. Experiments were conducted three times for each formulation and the data report the average values of the determinations.

3.2.4 Granulation experiments

Granules were produced in a 1.5l high-shear mixer Rotolab (IMA Zanchetta s.r.l., Italy). Granulation standard procedure was standardized on the basis of preliminary trials. Briefly, approximately 500ml of powder mixture was initially dry mixed at an impeller speed of 120rpm for 2min. Then liquid binder was dripped on dry powders at a flow rate of 10 ml/min. The liquid amount necessary for the granulation of the different formulations was calculated through rheological studies using the second derivative approach discussed in section 2.3.2. At the end of the wetting phase the impeller speed was increased as reported in Table 3.2. The wet massing time was conducted until the desired characteristics were achieved. At the end of the massing phase, a small sample of 25g of wet granules was taken for consistency measurement while the remaining granules were dried at 40°C in a ventilated oven until constant weight was achieved and then kept in sealed plastic bags.

Table 3.2: Amount of liquid binder expressed in terms of liquid to solid ratio (L/S) calculate for all the formulations and experimental conditions applied for the granulation experiments.

Formulation	L/S [ml/g]	Impeller speed during the massing phase [rpm]	Massing time [min]
SUCR25	0.70	850 rpm	5 min
SUCR50	0.20	850 rpm	2 min
SUCR75	0.10	850 rpm	2 min
SORB25	0.70	850 rpm	5 min
SORB50	0.16	850 rpm	1 min
SORB75	0.11	850 rpm	1 min
SORB75	0.11	400 rpm	2 min
MANN25	0.70	850 rpm	5 min
MANN50	0.65	850 rpm	5 min
MANN75	0.37	850 rpm	5 min
MCC100	1.10	1200 rpm	5 min
XG1	1.10	1200 rpm	5 min
XG5	0.65	1200 rpm	5 min

3.2.5 Prolonged granulation experiments

Additional granulation experiments were executed in order evaluate the growth kinetics. In particular prolonged granulation experiments were performed. During the process, small samples (about 10g) of wet granules were collected at time intervals of 1min and dried at 40°C in a ventilated oven until constant weight was achieved. Samples were kept in sealed plastic bags before the evaluation of the particle size distribution.

3.2.6 Characterization of wet granules

In order to evaluate the resistance of the wet granules to the deformation, a mixer torque rheometer MTR3 (Caleva, UK) was used. MTR3 was used in the consistency modality, described in detail in section 1.9.3. For the measurement, the following procedure was used: a sample of granules was collected directly from the high-shear mixer bowl at the end of the process and conserved in a sealed plastic bag at maximum for 15min in order to avoid their drying. Torque of the empty mixing bowl of the MTR3 was initially measured for 30s, then an amount of wet granules corresponding to 50ml was placed in the bowl and mixed at 50 rpm while the torque was recorded for 30s. The final value of consistency is expressed as the ratio between the torque measured and the granule weight. The results are presented as the average of three independent measurements.

3.2.7 Characterization of dried granules

3.2.7.1 Granule size distribution by sieve analysis

For the size distribution analysis, 100g of granules were poured over a set of sieves (4000, 3360, 2830, 2000, 1410, 1180,1000, 800, 600, 500, 400, 300, 200 and 112μm). A vibrating apparatus AS 200 (Retsch, Germany) was used at medium vibration level for 10min. The fractions were then collected and weighted. The results of the particle size analysis were presented as cumulated distribution [7].

3.2.7.2 Granule size distribution by image analysis

Pictures of granules collected at different time intervals were taken using a scanner Epson perfection 1250, Seiko Epson Corporation, Japan). Images were analyzed using the open source image processing software ImageTool® (Copyright 2008, A Division of Evans Technology, Inc.), to evaluate the granule Feret diameter and then the particle size distributions of samples were presented as cumulated distribution [7].

3.2.8 Material exchange experiments

The material exchange mechanisms were studied using the procedure developed by Bouwman et al. [6]. Briefly, two different granules batches were produced for each formulation. First the tracer granules (called “red granules”) were produced by dry mixing 1% (w/w) of water insoluble Sudan III to the powder mixture. Sudan III was chosen as tracing agent because of its water insolubility; this allows to grant that the movement of the dye between the granules during the experiment is due to the actual exchange of material between the agglomerates and not because of the dye migration in the employed liquid binder. Liquid binder was then added following the granulation procedure reported in Table 3.2 and the resulting red granules were stored in a closed plastic bags for maximum one hour. The high-shear mixer was cleaned and a second batch without tracer (called “blank granules”) was produced. 50g of red granules were then mixed with 150g of blank granules in the granulator and processed together for 9 min at the impeller speed which was employed for their production. Samples of granules were collected at time intervals until the end of the experiment in order to monitor the material exchange during the massing time. Picture of the granules sampled during the material exchange experiment were taken using a digital microscopy (Celestron, USA). The picture were following studied to determine the material exchange mechanism.

3.2.9 Evaluation of the torque evolution of wet masses

The mixer torque rheometer MTR3 (Caleva, UK) was employed in order to evaluate the torque evolution over the time of wet masses using the ‘variable mix time’ method described in detail in section 1.9.2. Briefly, an amount of powders corresponding to 40 ml was poured into the empty bowl and mixed at a shafts speed of 50 rpm then an amount of liquid binder corresponding to the optimal L/S ratio was added in a single step and torque was measured for 10 minutes. All the reported data are the average of three determinations.

3.3 Results and discussion

Although HSWG offers several advantages over the other granulation processes and it is one of the most commonly used methods for the pharmaceutical particle size enlargement, some issues like the end point determination and the prediction of the process evolution are still present [3]. Indeed, even if the growth regime map developed by Litster and coworkers represents a useful tool to describe the process evolution, it cannot be used for prediction of the growth regimes due to the difficulties to estimate unambiguously the Stokes deformation number appearing in the map [6]. Consequently, the purpose of this study was to find an easy and reliable method able to describe and predict the high-shear wet granulation process evolution based on the rheological characterization of the wet mass behaviour. To pursuit this purpose mixtures containing MCC and different amount of xanthan gum or MCC and different amount of sweeteners (mannitol, sorbitol and sucrose) were studied.

3.3.1 Thickening power of the employed ingredients

In order to identify the thickening power of the different solid binders added to the MCC, the viscosity of sweeteners water solution and polymer water dispersions was evaluated and the results are reported in Figure 3.1. On the basis of viscosity of water solutions or dispersions solid binders it is possible to note that mannitol presents a low thickening power, sorbitol and sucrose have similar thickening power which increases significantly at concentrations above 50% (w/V) instead xanthan gum presents a high thickening power even at low percentages.

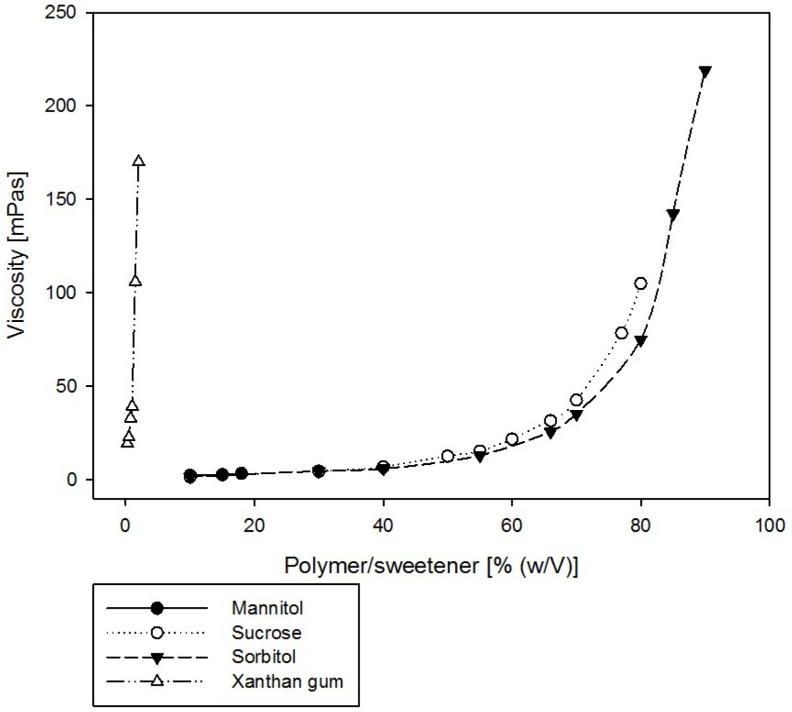
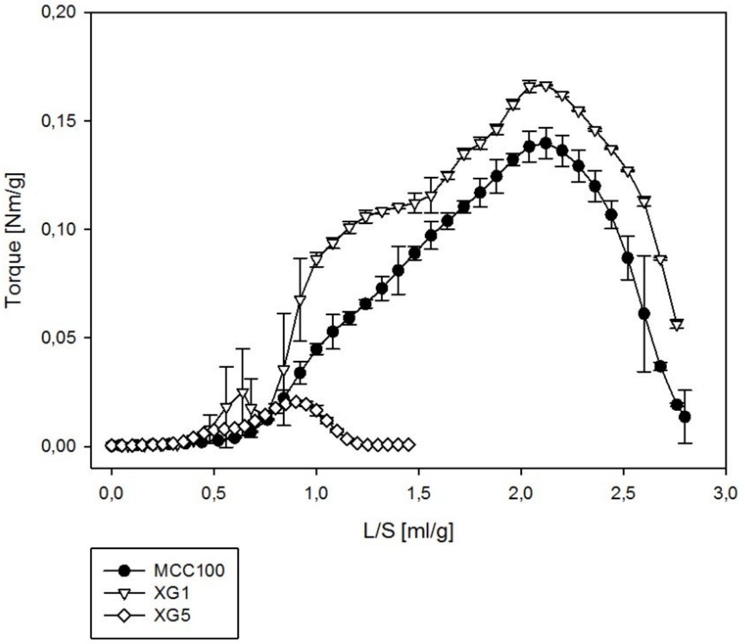


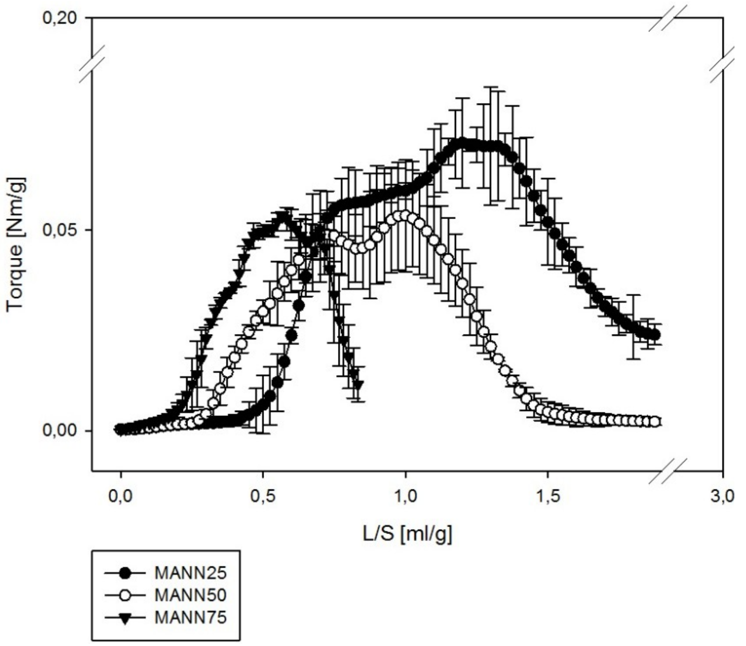
Figure 3.1: Viscosity of sweeteners water solutions and xanthan gum water dispersions.

3.3.2 Determination of the optimal liquid binder amount for high-shear wet granulation

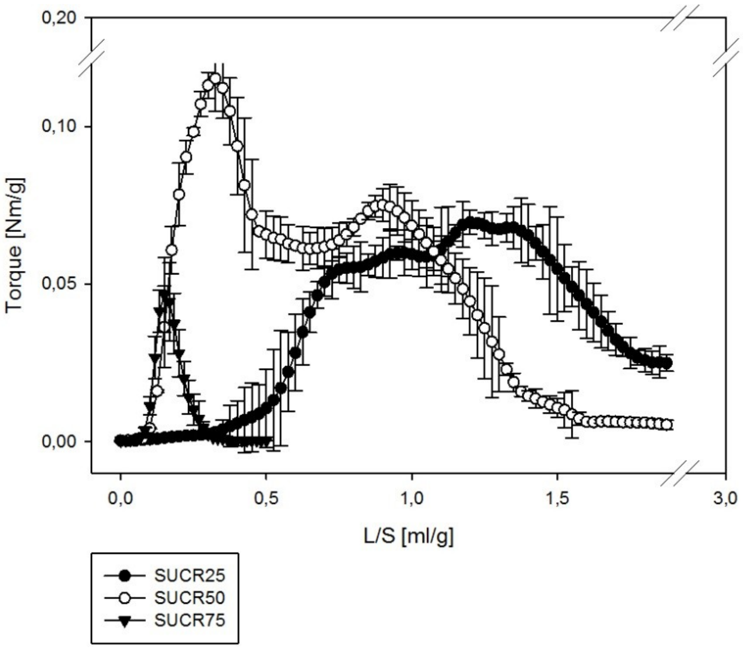
The water amount necessary for the granulation process was determined using the mixer torque rheometer. ‘Multiple addition’ experiments performed using a shafts speed of 150rpm (Figure 3.2) have permitted to predict the optimal liquid amount for the granulation experiments, expressed in terms of liquid to solid ratio and reported in Table 3.3.


0,20
0,15
0,10
0,05
0,00
Torque [Nm/g]
0,0
0,5
1,0
1,5
2,0
2,5
3,0
L/S [ml/g]
MCC100
XG1
XG5

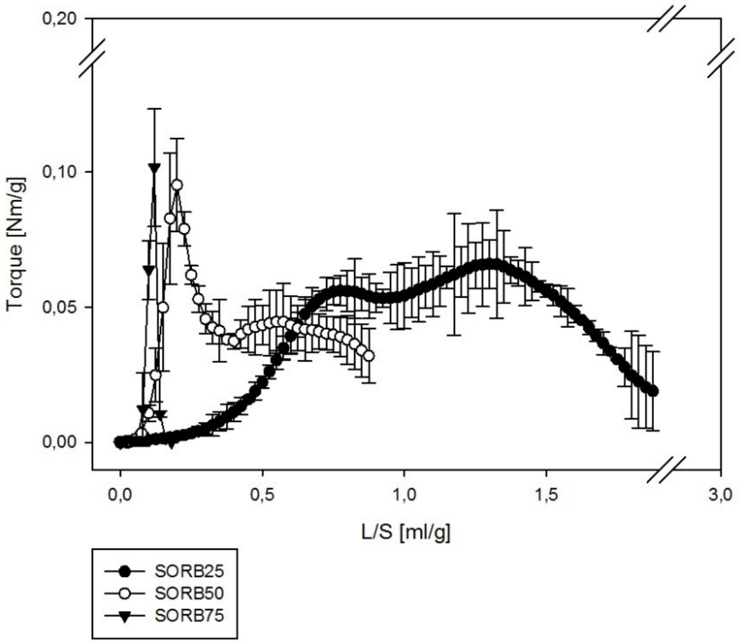
a)


0,20
0,05
0,00
Torque [Nm/g]
0,0
0,5
1,0
1,5
3,0
L/S [ml/g]
MANN25
MANN50
MANN75

b)



c)



d)

Figure 3.2: ‘Multiple addition’ profiles obtained using a shafts speed of 150rpm for formulations containing XG (a), mannitol (b), sucrose (c) and sorbitol (d).

In order to confirm the ability of the MTR3 to predict the optimal liquid amount, granulation experiments were performed using the experimental conditions reported in Table 3.2. At the end of the process, granules were dried and the mean diameter was evaluated by sieve analysis.

Results presented in Table 3.3 show that granules with acceptable mean diameter were obtained. This is a further confirmation that the developed rheological method is a fast and reliable approach to predict the optimal liquid amount for high-shear wet granulation. However this method does not provide information on the kinetics and granule growth mechanism.

Table 3.3: Amount of liquid binder (L/S) for the granulation experiments and mean diameter of the granules obtained.

Formulation	XG [% (w/w)]	MCC [% (w/w)]	L/S [ml/g]	d_{50} [µm]
MCC100	0%	100%	1.1	685.00
XG1	1%	99%	1.1	1520.00
XG5	5%	95%	0.65	710.00
Formulation	Mannitol [% (w/w)]	MCC [% (w/w)]	L/S [ml/g]	d_{50} [µm]
MANN25	25%	75%	0.70	1080.00
MANN50	50%	50%	0.65	1220.00
MANN75	75%	25%	0.37	990.00
Formulation	Sucrose [% (w/w)]	MCC [% (w/w)]	L/S [ml/g]	d_{50} [µm]
SUCR25	25%	75%	0.70	1396.00
SUCR50	50%	50%	0.20	750.00
SUCR75	75%	25%	0.10	565.00
Formulation	Sorbitol [% (w/w)]	MCC [% (w/w)]	L/S [ml/g]	d_{50} [µm]
SORB25	25%	75%	0.70	1225.00
SORB50	50%	50%	0.16	875.00
SORB75	75%	25%	0.11	3195.00

Ivenson et al. in their map expressed the granules growth regimes in terms of liquid saturation of the agglomerates and wet granules properties, such as strength and plastic deformation. These two properties are described by the Stokes deformation number (St_{def}) [5]. Nevertheless, given the difficulty of calculating its value, growth regime map can be used as guidance only, not for prediction of different growth regimes. Moreover, when water or low viscosity binders are used, St_{def} cannot be used as a predictive tool for the granulation regime because the method to calculate wet granule strength is not accurate [6].

3.3.3 Material exchange mechanism and granules growth regime assessment

During the last phase of granulation the equilibrium between growth and breakage is obtained and material exchange between wet granules can occurs. The type of the exchange mechanism depends on wet granule properties such as strength and plastic deformation [6], which are the same properties described by St_{def} and employed by Ivenson et al. to define the different granules growth regimes. Consequently, the granulation regime can be evaluated by performing exchange mechanism experiments as proposed by Bouwman et al. [6]. Since both the granulation regimes and the exchange mechanisms are determined by the granule plastic deformation, a correlation between the growth regimes and the exchange mechanisms is expected. This correlation was investigated by

Bouwman et al. [6] (Figure 3.3) which defined three different mechanisms of material exchange named: disintegration, deformation and distribution mechanisms [6] presented in detail in section 1.5.

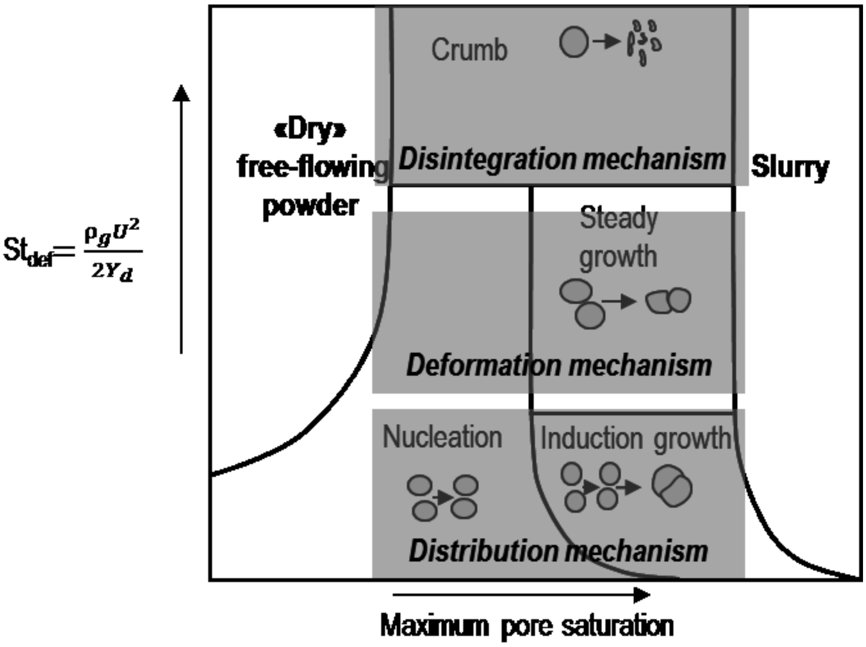


Figure 3.3: Relationship between growth regime map and the exchange material mechanisms. Adapted from Bouwman et al. [4].

The mechanisms of material exchange of the formulations involved in this study was investigated using the approach developed by Bouwman and co-workers [6]. Experiments were performed using Sudan III as tracing agent and the most representative images of the resulting granules are reported in figures 3.4, 3.7, 3.9. Moreover, additional granulation experiments were conducted to validate the correlation between the material exchange mechanisms and the granules growth regime presented in literature [6]. In particular prolonged granulation experiments were done in order to evaluate the granule growth kinetic. On this purpose, during the process samples of granules were withdraw, dried and evaluated to assess the evolution of the mean diameter of the forming agglomerates. The comparison of images obtained from the material exchange experiments and data achieved from the prolonged granulation experiments, allowed to identify the mechanisms of material exchange and granule growth of the studied formulations. In particular three different material exchange and growth mechanisms were identified as resumed in Table 3.4.

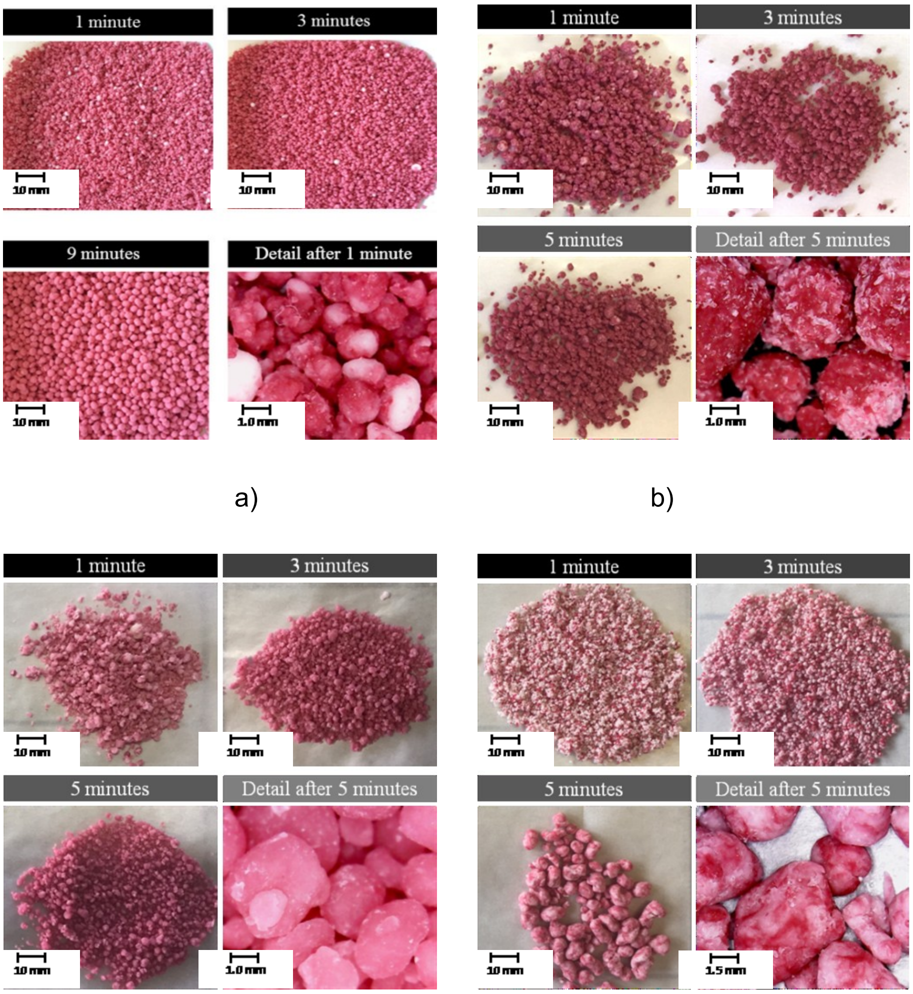
Table 3.4: Material exchange mechanism and growth regime identified for the formulations.

Formulation	Material exchange mechanism	Growth regime
MCC100	Deformation	Steady growth
XG1	Deformation	Steady growth
XG5	Disintegration	Crumb behavior
Formulation	Exchange mechanism	Corresponding growth regime
MANN25	Deformation	Steady growth
MANN50	Deformation	Steady growth
MANN75	Deformation	Steady growth
Formulation	Exchange mechanism	Corresponding growth regime
SUCR25	Deformation	Steady growth
SUCR50	Deformation	Steady growth
SUCR75	Deformation	Steady growth
Formulation	Exchange mechanism	Corresponding growth regime
SORB25	Deformation	Steady growth
SORB50	Deformation	Steady growth
SORB75	Distribution	Induction growth

Formulations MCC100, XG1, MANN25, MANN50, MANN75, SUCR25, SUCR50, SUCR75, SORB25 and SORB50 presented a deformation mechanism (Figure 3.4). This mechanism is typical of deformable granules and it is characterized by a fast exchange of material between granules due to the shear applied and the impact between the agglomerates.

For MCC100 the material exchanged rapidly, leading to the homogeneous spread of the tracer and the formation of spherical granules. Similar scenarios could be observed for all the formulations containing mannitol and also for XG1, SUCR25, and SORB25.

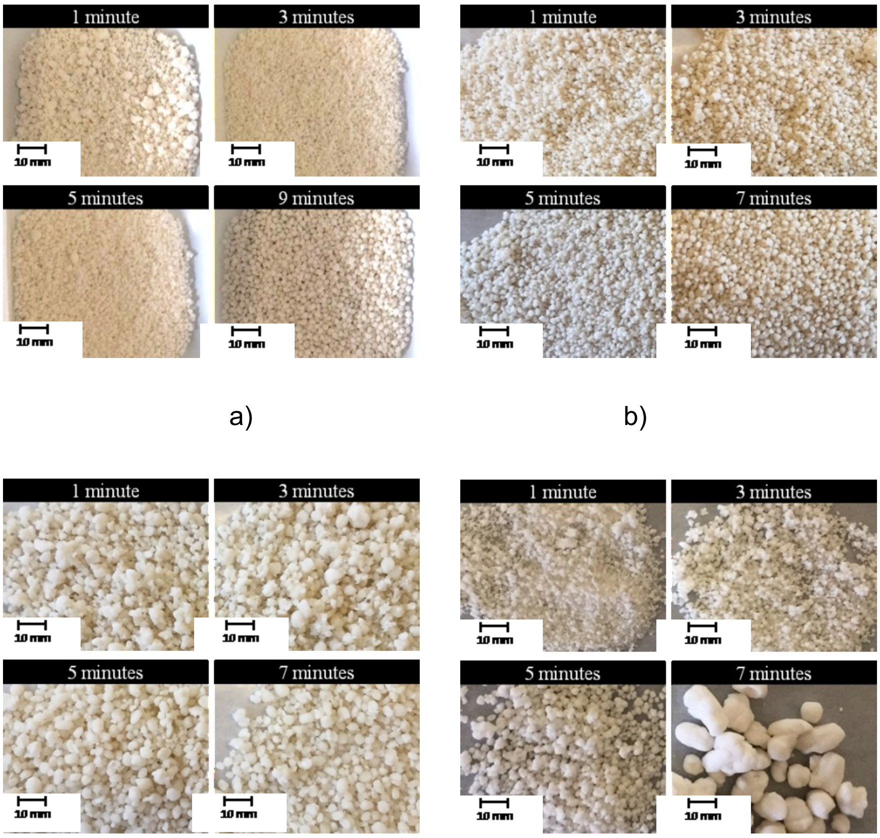
MCC100 and all the formulations containing mannitol, share low thickening power of the liquid binder solution which is produced during the process (Figure 3.1), thus the liquid is free to move within the internal structure of the agglomerates promoting the deformability of the granules. A similar behavior occurs for those formulations containing limited amount of excipients which can confer a high viscosity to the granulating liquid (xanthan gum, sorbitol and sucrose). However, when the amount of xanthan gum, sucrose and sorbitol is increased in mixture, it can be observed a decrease in the wet granule deformability. This is highlighted by material exchange which becomes slower as showed in Figure 3.4d for SUCR50.



a) b) c) d)

Figure 3.4: Digital microscope images of samples withdraw during exchange materials experiments: a) MCC100; b) MANN25; c) SUCR25; d) SUCR50.

Consequently it is possible to state that the kinetic of the material exchange is strongly affected by the formulation employed and in particular it seems to be related with the thickening power of the liquid binder: the lower the binder thickening power and the faster is the material exchange.



a) b)

c) d)

Figure 3.5: Digital microscope images of samples withdraw during prolonged granulation experiments: a) MCC100; b) MANN25; c) SUCR25; d) SUCR50.

Deformation mechanism is associated to the steady growth regime, thus the granules mean diameter is expected to increases linearly with the massing time for the formulations which present this material exchange mechanism. Data obtained with the prolonged granulation experiments confirmed this hypothesis (Figures 3.5, 3.6). In fact, the formulations which presented the deformation mechanism are characterized by a linear growth of the granules mean diameter. Moreover it is possible to note that the growth kinetic appears to be affected by the thickening power of the liquid binder.

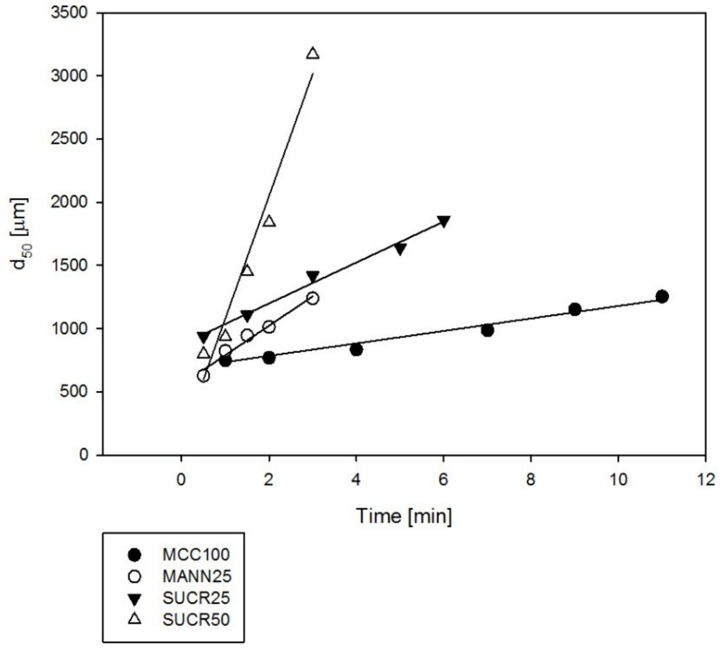


Figure 3.6: Growth kinetics evaluated by image analysis of samples withdraw during prolonged granulation experiments: MCC100; MANN25; SUCR25; SUCR50.

Formulation XG5 presents the disintegration mechanism that takes place when the material is characterized by a high deformability. During the granulation process, granules are crushed to fragments which re-agglomerate immediately leading to a rapid distribution of the tracing agent within the mass. The resulting granules are characterized by a rough surface and a wide size distribution as can be seen in Figure 3.7.

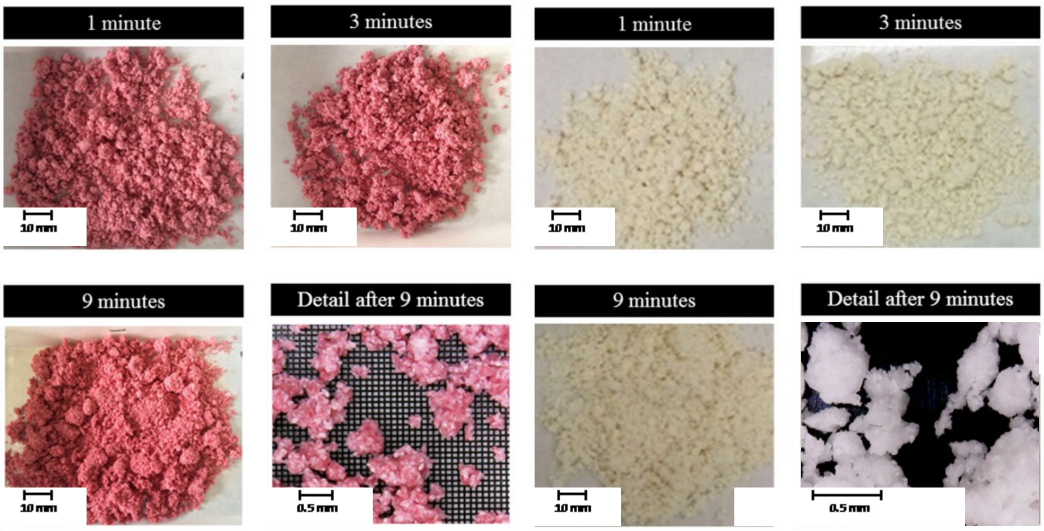


Figure 3.7: images with digital microscope of samples withdraw during exchange materials experiments (a) and during prolonged granulation experiments (b) for the formulation XG5.

Formulations which present the disintegration mechanism should be characterized by the crumb regime in terms of granules growth. In this case, the result is the formation of irregular granules which do not grow due to the low resistance of the wet mass. The extended granulation experiment (Figure 3.8) confirmed the result obtained from the material exchange test.

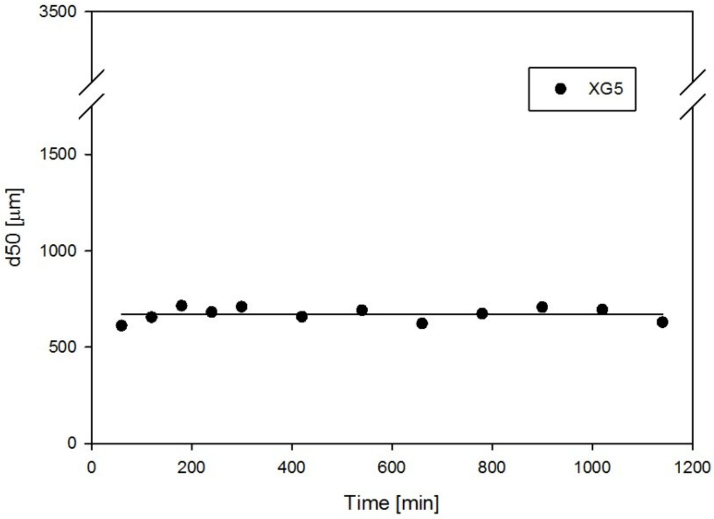


Figure 3.8: Growth kinetic evaluated by image analysis of samples withdraw during prolonged granulation experiments with the formulation XG5.

The study of the material exchange was not possible for SORB75 because an uncontrollable growth of the granules was observed during the first minute of granulation, thus the granules did not present a stable mean diameter for a period suitable to perform this type of experiments. The rapid and uncontrollable growth of the granules could be associated with both the distribution and deformation mechanisms. Since the growth kinetic depends on the impeller speed, the prolonged granulation experiment was repeated using an impeller speed of 400rpm instead of 850rpm. This was accomplished to clarify which mechanism is responsible for the uncontrollable growth of the granules produced with SORB75, Result of the prolonged granulation experiments reported in Figure 3.9 highlights a sigmoidal growth kinetics of the granules. This is characteristic of the induction growth regime, thus the material exchange is expected to follow the distribution mechanism. This mechanism occurs with granules having a low deformability. The granules which present this characteristics are consolidated by the impacts in the granulator but no material is exchanged. Generally, the consolidation leads the liquid present into the granular structure to move on the granule surface, this is associated with a rapid granule coalescence.

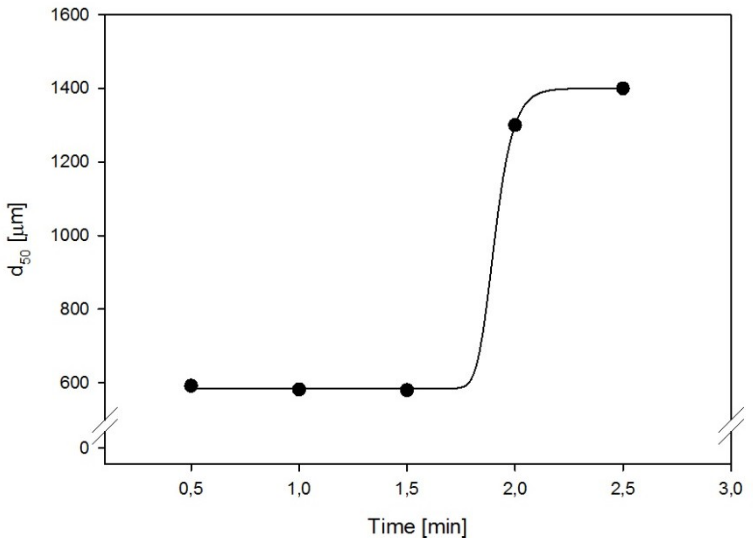


Figure 3.9: Growth kinetic evaluated by image analysis of samples withdraw during prolonged granulation experiments for the formulation SORB75 at 400 rpm.

3.3.4 Consistency evaluation

Material exchange mechanisms and growth mechanisms that occur depend on the deformability and the resistance of the wet granule [6]; therefore to find a fast method able to measure these two wet granule properties, consistency measurements were performed at the end of the granulation process. Consistency represents a measure of the wet granules cohesiveness and hence an assessment of wet granules strength [8].

The resulting values of wet mass consistency measured on the granules produced are shown in Figure 3.10.

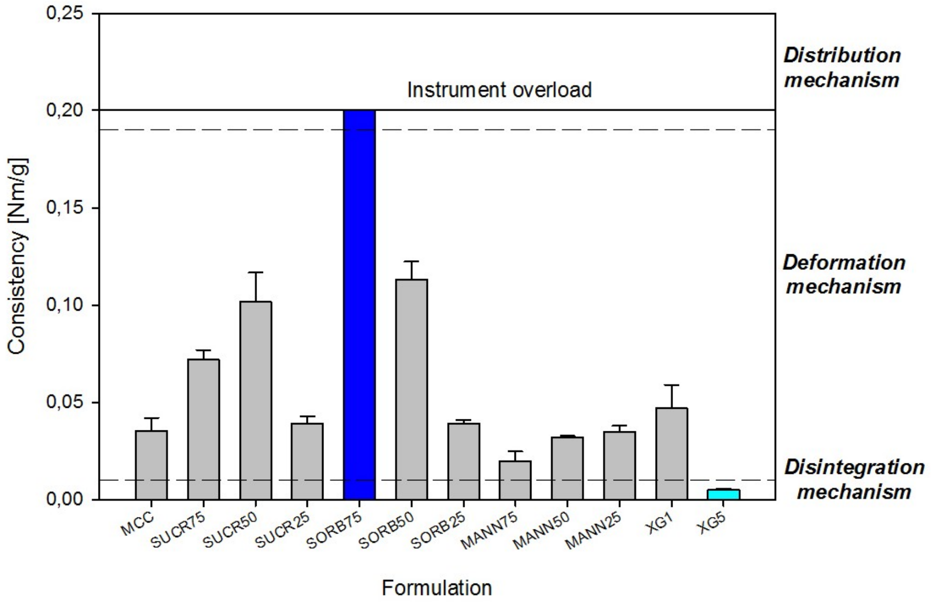


Figure 3.10: Wet mass consistency measured on the granules produced and classification of the material exchange mechanisms based on the results obtained.

In general it is possible to state that wet granules consistency is affected by the formulation employed and in particular depends on the amount and thickening power of the solid binder (in this case the sweeteners or the xanthan gum). The higher is the amount of solid binder, or its thickening power, and the higher is the consistency value and thus the wet granules strength.

Distribution mechanism occurs with granules having a low deformability and hence with granules having high strength, this means that this type of exchange mechanism is expected for granules having high consistency values. Results shown in Figure 3.10 match with these considerations, indeed the formulation SORB75 which present the highest consistency values is the only one that presents the distribution mechanism and hence the induction growth.

Formulations presenting the deformation mechanism were characterized by similar consistency values ranging from 0.020 to 0.122 Nm/g. Moreover among these formulations, consistency values depends on the amount and the thickening power of the binder added to the formulation.

Finally formulation XG5 is characterized by very low consistency value and hence low wet granules strength and this matches with the disintegration mechanism and crumb behavior observed.

Although it is necessary to perform further experiments to fully validate these data, it is possible to define a preliminary correlation between the wet granules consistency and the different material exchange mechanisms observed. In Figure 3.10 a classification of the material exchange mechanisms based on the wet consistency values obtained is proposed. This correlation between the consistency of the wet granules and the material exchange mechanisms could be of great interest. The wet granules consistency assessment can give information about the material exchange mechanism and growth regime without performing the tests with the tracing agent and the prolonged granulation experiments, thus reducing the development time of a new product. Moreover the consistency measurements are more reliable than the material exchange experiments because this approach do not require a visual assessment of the material exchange mechanism which can be subjective. However, the main limitation of the consistency method is due to the fact that this approach can only be descriptive because it requires the preparation and characterization of granules.

In order to overcome these issues and develop a method able to predict the process evolution, further experiments with the MTR3 were conducted. In particular the torque evolution was measured over the time for all the formulations using the 'variable mix time' method described in detail in section 1.10.2. Typical torque profiles obtained with this method are shown in Figure 3.11.

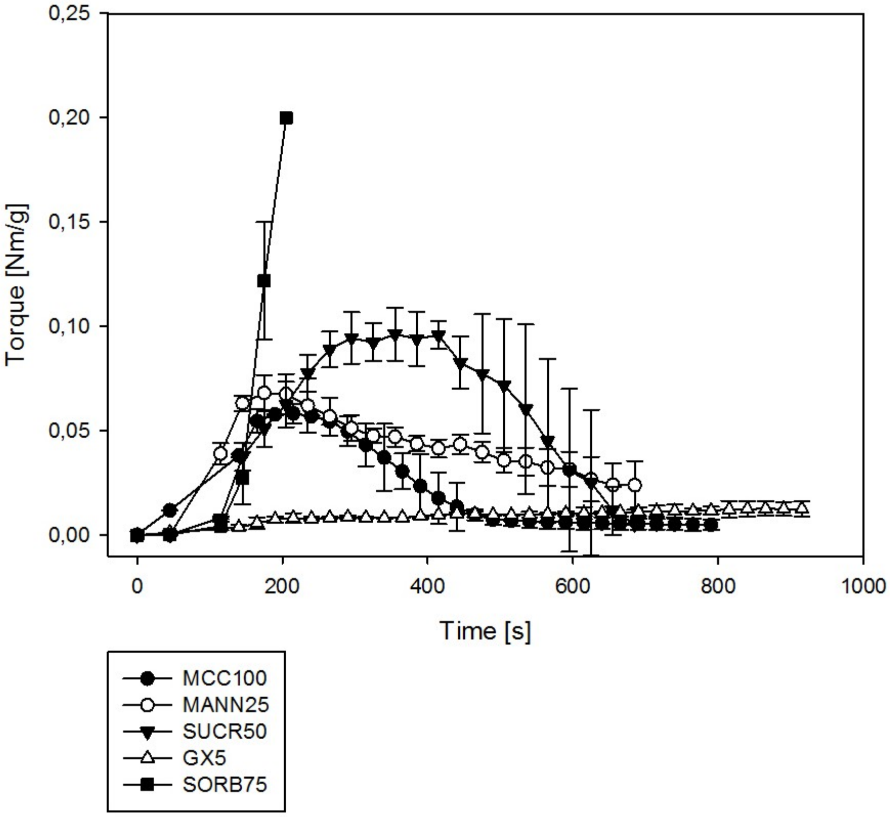


Figure 3.11: 'Variable mix time' profiles obtained with the formulations MCC100; MANN25; SUCR50; GX5 and SORB75.

From the resulting profiles it is possible to observe that torque values increase over the time until a maximum is reached, then torque values can remain constant or decrease. The maximum value of the torque profile recorded using this approach (named Torque peak) could represent a measure of the maximum cohesiveness of the wet mass.

Table 3.5: Torque peak obtained in the ‘variable mix time’ experiments.

Formulation	Torque peak [Nm/g]
MCC	0.052±0.002
SUCR75	0.092±0.005
SUCR50	0.096±0.013
SUCR25	0.064±0.003
SORB75	0.20 (overload)
SORB50	0.109±0.028
SORB25	0.069±0.008
MANN75	0.042±0.001
MANN50	0.044±0.003
MANN25	0.068±0.009
XG1	0.085±0.011
XG5	0.010±0.001

Only for formulation SORB75 the torque reach the maximum value of the instrument producing an overload. In this case the torque peak was assumed to be 0.20 Nm/g.

Torque peaks were evaluated for all the formulations (Table 3.5) and compared with the consistency values of the corresponding granules (Figure 3.12).

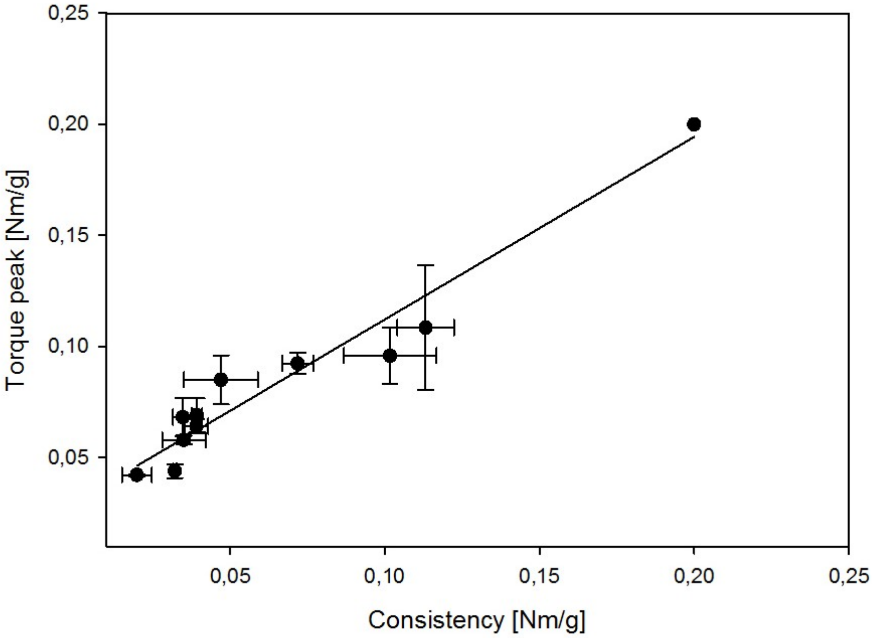


Figure 3.12: Comparison between wet granule consistency and Torque peak obtained using ‘variable mix time’ method.

A roughly linear relationship between the Torque peak and the wet granule consistency emerged from the comparison shown in Figure 3.12. This is probably due to fact that both these parameters represent a measure of the cohesiveness, the first refers to the wet mass and the second to the wet granules. This result is of great importance as the 'variable mix time' procedure is a rheological study of the wet mass which can be performed for a formulation before to conduct any granulation experiments and consequently it permits to predict the cohesiveness of the wet granule. Moreover, since there is a correlation between the cohesiveness of the wet granules, the material exchange and the growth mechanisms, the developed method could be used to predict the process evolution.

On the basis of the results obtained in this study a classification of the different growth regimes and material exchange mechanism is proposed in Figure 3.13.

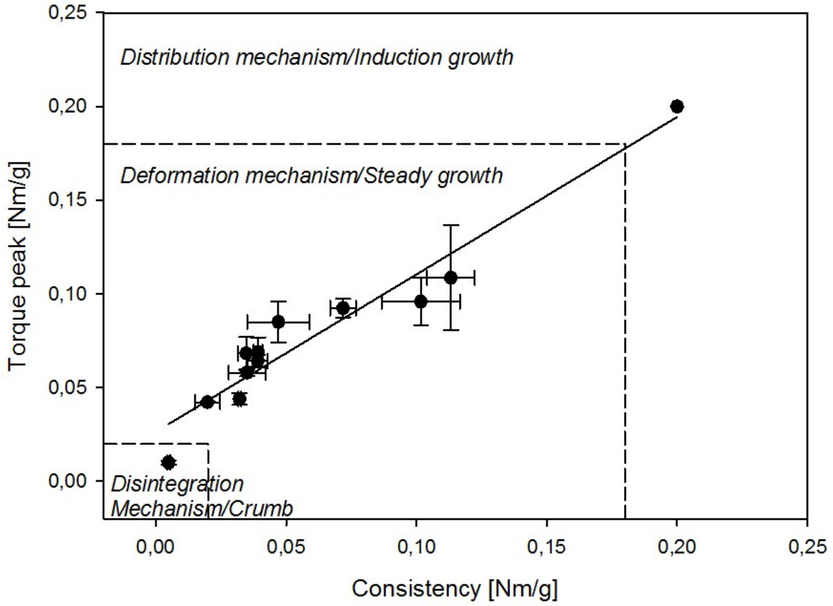


Figure 3.13: Relationship between torque peak and consistency. The dashed lines highlight the experimentally values of torque peak and consistency that characterize the different mechanisms

3.4 Conclusions

The results obtained highlighted the possibility to employ the rheological studies as a potential tool to gain several information about the granulation process. In particular, the rheological characterization performed by a mixer torque rheometer has proved to be useful for:

- predict the optimal liquid amount for the granulation;
- evaluate the wet granules strength and wet mass cohesion;
- predict the material exchange mechanisms and growth regimes.

However, further studies need to be conducted in order to delineate more precisely the limits of the presented ranges of torque peak and consistency and to validate the predictive potential of this approach.

3.5 References

[1] M.E. Aulton, K.M.G. Taylor, Aulton’s Pharmaceutics: The Design and Manufacture of Medicines, Fifth Edit, Elsevier, 2018.

[2] M. Kuhs, J. Moore, G. Kollamaram, G. Walker, D. Croker, Predicting optimal wet granulation parameters for extrusion-spheronisation of pharmaceutical pellets using a mixer torque rheometer, Int. J. Pharm. 517 (2017) 19–24. doi:10.1016/J.IJPHARM.2016.11.057.

[3] B.J. Ennis, Theory of Granulation: An Engineering Perspective, in: D.M. Parikh (Ed.), Handb. Pharm. Granulation Technol., Second Edi, Taylor & Francis Group, 2005: pp. 7–78.

[4] P. Vonk, C.P.. Guillaume, J.. Ramaker, H. Vromans, N.W.. Kossen, Growth mechanisms of high-shear pelletisation, Int. J. Pharm. 157 (1997) 93–102. doi:10.1016/S0378-5173(97)00232-9.

[5] S.M. Iveson, P.A.L. Wauters, S. Forrest, J.D. Litster, G.M.H. Meesters, B. Scarlett, Growth regime map for liquid-bound granules: Further development and experimental validation, Powder Technol. 117 (2001) 83–97. doi:10.1016/S0032-5910(01)00317-5.

[6] A.M. Bouwman, M.R. Visser, G.M.H. Meesters, H.W. Frijlink, The use of Stokes deformation number as a predictive tool for material exchange behaviour of granules in the “equilibrium phase” in high shear granulation, Int. J. Pharm. 318 (2006) 78–85. doi:10.1016/j.ijpharm.2006.03.038.

[7] T. Allen, Particle Size Measurement Volume 1: Powder sampling and particle size measurement, Fifith Edi, Springer Netherlands, 1996.

[8] T.M. Chitu, D. Oulahna, M. Hemati, Wet granulation in laboratory scale high shear mixers: Effect of binder properties, Powder Technol. 206 (2011) 25–33. doi:10.1016/j.powtec.2010.07.012.

Chapter 4

Rheological characterization of powders: a useful tool to predict the influence of different process parameters on granules growth

4.1. Introduction

High-shear wet granulation is one of the most employed technologies for particle size enlargement in the pharmaceutical industry. Despite its widespread application, the complete understanding of high-shear wet granulation process is far to be achieved; in fact it presents several process parameters which need to be controlled and most of them are often considered critical (C*ritical Process Parameters*-CPPs) because their variation affects significantly the final product quality. The classical CPPs for high-shear wet granulation are: the amount of granulating liquid employed, the liquid addition rate, the impeller speed, and the wet massing time [1]. The liquid amount is often expressed as the ratio between the amount of liquid employed and the powder mass in which it is sprayed or poured (liquid to solid ratio (L/S)) and has often a great impact on the characteristics of the produced granules such as the particle size and the density of the final granules [2]. Impeller speed have an influence on the growth rate and density of the granules because it changes the equilibrium between the growth and breakage phenomenon which characterize the granules [3]. Wet massing time effects are formulation dependent, in general it can be stated that an increase in the wet massing time is related with a decrease in porosity and a reduction in compressibility of the produced granules [4]. High-shear wet granulation has thus several parameters which need to be controlled and most of them are formulation dependent. For this reason the process development is particularly difficult, with the risk for this equipment to become the last choice when a new formulation needs to be granulated. Moreover the recent requirements from the regulatory authorities, formalized in the guideline ICH Q8, states that a scientific understanding of the process, about the influence of the process parameters and material attributes on the final product, need to be achieved and the quality of the product need to be built into the process and no more evaluated at the end [5]. This concept is called Quality-by-Design (QbD) as the quality comes from how the product and the process is designed [5]. On this purpose, QbD requires the definition of a quality target product profile (QTPP) which consists on the characteristics of the final product. Following, the critical quality attributes (CQAs) are evaluated. These CQAs are the final product attributes or the intermediate (e.g. granules) characteristics which affect the safety of the final product and the QTPP [1,5]. CQAs are affected by the characteristics of the raw materials employed and the process parameters applied. Thus the QbD approach requires defining the critical material attributes (CMAs) of the starting materials and the critical process parameters (CPPs) from a very early stage of the formulation development. The aim of the present work was to evaluate the possibility of predict the CPPs for the high-shear wet granulation process from rheological studies. In particular was investigated the possibility of exploiting a Mixer Torque Rheometer to predict the CPPs of the process such as: L/S, impeller speed, granulating liquid flow rate. Moreover the instrument was used to define the growth regimes and the granules growth kinetic of different formulations which can be useful information during process development.

4.2. Materials and methods

4.2.1 Materials

Confectionary sucrose and xanthan gum were purchased by ACEF (Acef SpA, Italy). Microcrystalline cellulose (MCC, Vivapur 101) was purchased by a different manufacturer compared with that used in the previously presented studies. For instance MCC was kindly donated by JRS Pharma (Germany). In Table 4.1 are collected the formulation employed in this study.

Table 4.1: Composition of the formulations evaluated in this study.

Formulation	Composition
MCC100	- Microcrystalline cellulose 100%
SUCR50	- Sucrose 50% - Microcrystalline Cellulose 50%
XG5	- Xanthan gum 5% - Microcrystalline Cellulose 95%

4.2.2 Determination of the optimal liquid binder amount for high-shear wet granulation

Due to the change in the MCC manufacturer all the rheological characterizations for the correct L/S determination were repeated. The mixer torque rheometer MTR3 (Caleva, UK) was employed using the ‘multiple addition’ method described in detail in section 1.10.1. Briefly, an amount of powder mixture corresponding to 50ml was poured into the empty bowl, mixed at a shafts speed of 150rpm and the baseline was measured for 30s. Afterwards, multiple additions of 0.5ml of water were performed, the wet mass was mixed for 15s and the torque value was measured for 15s. The water was added until a slurry was formed and the over-wetting reached. Experiments were conducted three times for each formulation and the data report the average values of the determinations. The second derivative approach, as described in section 2.3.2, was applied to identify the amount of liquid, expressed in terms of liquid to solid ratio (L/S), corresponding to the transition between the pendular and funicular capillary states [6], which represent the optimal amount of liquid to perform granulation in high-shear mixer [7].

4.2.3 Evaluation of the torque evolution for wet masses

The mixer torque rheometer MTR3 (Caleva, UK) was employed in order to evaluate the torque evolution over the time of wet masses using the 'variable mix time' method described in detail in section 1.10.2. The torque of the empty bowl of MTR3 is recorded for 30s to eliminate the baseline noise. Then an amount of powders corresponding to 50ml were placed in the mixing bowl of the MTR3 and the torque is recorded for 30s. An amount of liquid binder corresponding to the optimal L/S ratio was then added in a single step and torque was measured for 15-20min depending on the studied formulation. From the obtained graphs it was possible to collect the value of maximum torque (defined as Torque peak) which showed interesting potential applications for the prediction of the granules growth regimes in third chapter of this thesis (section 3.3.4). In order to evaluate the possibility to use the wet mass rheology for the prediction of the high-shear wet granulation CPPs, these type of experiments were conducted using different experimental parameters. In particular the effect of the amount of liquid binder (L/S), shafts speed and binder flow rate on the value of Torque peak was investigated. Each formulation was studied at two different binder flow rates (X1), two different shafts speeds (X2) and three different L/S (X3). On this purpose a Design of Experiments (DoE) technique was applied and in particular a screening design was used. With the study of screening it may be possible to identify the variables able to influence the system since they determine a significant variation of the experimental responses [9]. In order to compare different variables characterized by different units and levels of variation, it is necessary convert all the variables in codified dimensionless variables using the following equation:

$$X_i = \frac{U_i - U_i^0}{\Delta U_i} \qquad \text{(eq. 4.1)}$$

Where X_i is the value of the codified variable, U_i is the value of the original process parameter, U_i^0 is the value of the process parameter in the center of the experimental domain.

The experimental variables and the corresponding codified variables are collected in Table 4.2.

Table 4.2: Experimental parameters evaluated in the 'variable mix time' study. The experimental values and the codified levels are tabulated

Experimental variables	Studied levels	Codified variable	Codified level
Binder flow rate [ml/h]	300 1800	X1	1; 2
Shafts speed [rpm]	50 150	X2	1; 2
Amount of liquid binder (L/S) [ml/g]	Lower value* Optimal value* Upper value*	X3	1;2;3

In the screening technique it is assumed that exists a linear relationship between the variables and responses, and the model employed is a polynomial equation of first order. The mathematical model postulated for the screening of the three experimental variables is:

$$Y = b_0 + b_1 x_1 + b_2 x_2 + b_{3A} x_3 + b_{3B} x_3 + b_{3C} x_3 \quad \text{(eq. 4.2)}$$

The experiments necessary to estimate the coefficients (*bi*) of the mathematical model were designed by employing a full factorial $2^2 3^1$//12 experimental matrix using the software Nemrodw (Version 2015, D. Mathieu, J. Nany, R. Phan-Tan-Luu, Marseille, France). The experimental matrix is showed in Table 4.3

Table 4.3: Full factorial $2^2 3^1$//12 experimental matrix.

Exp	X1	X2	X3
1	1	1	1
2	1	2	1
3	2	1	1
4	2	2	1
5	1	1	2
6	1	2	2
7	2	1	2
8	2	2	2
9	1	1	3
10	1	2	3
11	2	1	3
12	2	2	3

Encoded variables were following converted to natural variables with the creation of the experimental plan which collects the required experiments. For each experiment of the plan will be obtained an experimental response (y_i) necessary for the calculation of the coefficients associated with each variable. An example of the experimental plan used for the MCC100 is reported in Table 4.4.

Table 4.4: Example of the experimental plan used for formulation MCC100.

Exp	Binder flow rate [ml/h]	Shafts speed [rpm]	L/S [ml/g]
1	300	50	1.04
2	300	150	1.04
3	1800	50	1.04
4	1800	150	1.04
5	300	50	1.16
6	300	150	1.16
7	1800	50	1.16
8	1800	150	1.16
9	300	50	1.24
10	300	150	1.24
11	1800	50	1.24
12	1800	150	1.24

All the experiments were performed in triplicate in order to evaluate the standard deviation and the error associated. The Pareto approach was applied on the calculated coefficients to determine which experimental variables had the most important impact on the Torque peak value. The Pareto principle is based on the assumption that the 20% of the inputs produce the 80% of the outputs. The responses are presented as the percent and cumulative distribution referred to the single variables in study. The variables which lead to the 80% of the response are those considered as most critical for the chosen output (Figure 4.1).

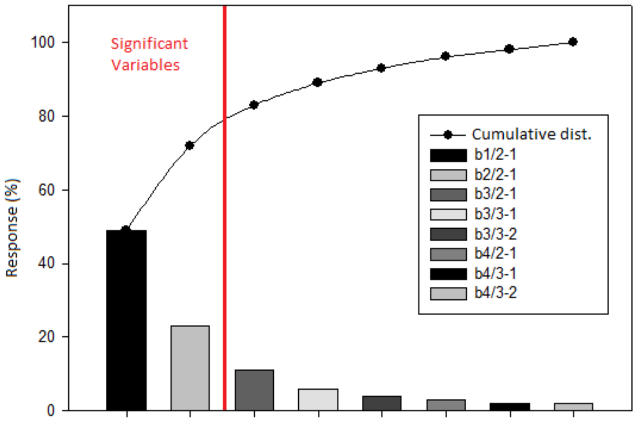


Figure 4.1: Example of the Pareto chart.

4.2.4 Granulation experiments

4.2.4.1 Extended granulation experiments

The formulations were processed using a lab scale high-shear mixer Rotolab (IMA Zanchetta, Italy) with a batch size of 1.5l. Granulation procedure was standardized on the basis of preliminary trials. Briefly, an amount of powders corresponding to approximately 500ml were dry mixed for 2min at an impeller speed of 120rpm. Liquid binder (water) was then added on dry powders at a flow rate of 3240ml/h. The liquid amount necessary for the granulation of the different formulations was calculated through rheological studies using the second derivative approach discussed in section 2.3.2. At the end of the liquid addition, impeller speed was increased at 400 or 1000rpm, corresponding to 3.14m/s and 7.85m/s respectively. In order to evaluate the granule growth kinetic, the massing time was prolonged for up to 20min and samples of granules were collected at time intervals during this phase. At the end of the process, final granules and samples were dried at 40°C in a ventilated oven until constant weight was achieved.

4.2.4.2 Material exchange mechanism experiments

The granules material exchange mechanism was studied using the procedure developed by Bouwman et al. [8]. Two different granules batches were produced for each formulation and operative conditions. Initially, tracer granules were produced with the addition of 1% (w/w) of Sudan III to the powder mixture. The dye was dry mixed with the other formulation components and following the colored powders were granulated. 50g of the resulting red granules were collected and stored in a sealed plastic bag to prevent them for drying. The high-shear mixer was cleaned and a second batch without tracer was produced (blank granules). At the end of the procedure the high-shear mixer was stopped and 50g of the blank granules were substituted by the same amount of red granules and processed together. Samples of granules were collected at time intervals in order to monitor the material exchange. The granulation time applied to the granules during the material exchange procedure was adjusted depending on the formulation and the process condition applied. Sudan III was chosen as tracing agent because of its water insolubility. This allows to state that the movement of the dye between the granules during the experiment is due to the material exchange between the agglomerates and not to the dye migration through the granulating liquid. Pictures of the collected samples were taken using a digital microscopy (Celestron, USA) and studied to determine the material exchange mechanism which characterized each formulation.

4.2.4.3 Evaluation of granulation CPPs through a Design of Experiment

Among the different potential process parameters (pCPPs), impeller speed (X1), binder flow rate (X2), massing time (X3) and amount of liquid binder (X4) were investigated. In particular impeller speed and binder flow rate were studied at two levels, while the wet massing time and the liquid binder amount were studied at three levels. The list of the pCPPs investigated, their experimental values and codified levels are reported in Table 4.5.

Table 4.5: pCPPs investigated, their experimental values and their codified levels.

pCPPs	**Studied levels**			**Codified variable**	**Codified level**
Impeller speed [rpm]	400 1000			X1	1 2
Binder flow rate [ml/h]	2200 3240			X2	1 2
Massing time [min]	1 3 5			X3	1 2 3
L/S [ml/g]	MCC100	SUCR50	XG5	X4	1 2 3
	1.04 1.16 1.28	0.16 0.20 0.24	0.64 0.69 0.74		

In order to evaluated which pCPPs significantly affect the granule critical quality attributes (CQAs) considered in this study (particle size distribution, roundness and granules strength), a Design of Experiments (DoE) technique was applied and in particular a screening design was used. The first order mathematical model postulated for the screening of the four experimental variables was:

$$Y = b_0 + b_1 x_1 + b_2 x_2 + b_{3A} x_3 + b_{3B} x_3 + b_{3C} x_3 + b_{4A} x_4 + b_{4B} x_4 + b_{4C} x_4 \quad \text{(eq 4.2)}$$

The experiments necessary to estimate the coefficients (*bi*) of the mathematical model were designed by employing a reduced asymmetric factorial matrix $2^2*3^2//9$, which is reported in Table 4.6, using the Nemrodw software (Version 2015, D. Mathieu, J. Nany, R. Phan-Tan-Luu, Marseille, France).

Table 4.6: Reduced asymmetric factorial matrix $2^2*3^2//9$ employed for this study.

Exp	X1	X2	X3	X4
1	1	1	1	1
2	1	2	2	2
3	1	1	3	3
4	2	1	2	3
5	2	2	3	1
6	2	1	1	2
7	1	1	3	2
8	1	2	1	3
9	1	1	2	1

Encoded variables were following converted to natural variables with the creation of the experimental plan that describes the experiments required. For each experiment of the plan will be obtained an experimental response (y_i) necessary for the calculation of the coefficients associated with each variable. An example of the experimental plan used for MCC100 is reported in Table 4.7.

Table 4.7: Experimental plan for the MCC100.

Experiment	Impeller speed [rpm]	Binder flow rate [ml/h]	Massing time [min]	L/S [ml/g]
1	400	2200	1	1.04
2	400	3240	3	1.16
3	400	2200	5	1.28
4	1000	2200	3	1.28
5	1000	3240	5	1.04
6	1000	2200	1	1.16
7	400	2200	5	1.16
8	400	3240	1	1.28
9	400	2200	3	1.04

Experiments were executed and the repetitions of some experiments were performed in order to accurately calculate the coefficients estimating the experimental error associated. The experimental responses (CQAs) considered, as previously mentioned, were the granules PSD, roundness and crushing strength. Pareto principle was then employed to evaluate which of the pCPPs had the most important impact on the CQAs of the granules.

4.2.5 Granules characterization

4.2.5.1 Particle size distribution through sieve analysis

For the size distribution analysis, 100g of granules were poured over a set of sieves (4000, 3360, 2830, 2000, 1410, 1180,1000, 800, 600, 500, 400, 300, 200 and 112μm). A vibrating apparatus AS 200 (Retsch, Germany) was used at medium vibration level for 10min. The fractions were then collected and weighted. The results of the particle size analysis were presented as cumulated distribution [9].

4.2.5.2 Granule size distribution by image analysis

Pictures of granules collected at different time intervals were taken using a scanner (Epson perfection 1250, Seiko Epson Corporation, Japan). Images were analyzed using the open source image processing software ImageTool® (Copyright 2008, A Division of Evans Technology, Inc.), to evaluate the granules Feret diameter and then the particle size distributions of samples were presented as cumulated distribution [9].

4.2.5.3 Roundness

Fifty granules, randomly selected from the modal size fraction of each batch of granules, were used for shape characterization using a digital microscope (Celestron, Torrance, CA, USA). Imagines were analyzed using the open source image processing software ImageTool® (Copyright 2008, A Division of Evans Technology, Inc.) to evaluate the shape of the granules in terms of roundness (Φ_R) which was defined as:

$$Roundness, \Phi_R = \frac{4\pi A_P}{P^2} \quad \text{(eq. 4.3)}$$

Where A_P is the projected area and P the perimeter. Particle roundness values range from 0 to 1 and the greater is the value, the rounder is the granule[10]

4.2.5.4 Granules crushing strength

The failure load of the granules was evaluated for each batch of the different formulations. On this purpose, the most represented fraction was selected after the granules were sieved for the PSD evaluation. The reason for using the most represented fraction for each batch was to reduce the influence of the particle size during the comparison of batches obtained from the different formulations and process conditions applied [11]. The failure load of granules was evaluated through a uniaxial confined compression analysis [12] using a Texture Analyser (Stable microsystem, UK). For the test, granules were placed on a die of 28,3 mm^2 base area and 26,6 mm of height. The granules were compressed uniaxially at an upper punch speed of 0,1 mm/s until reaching a final height between 30% and 70% of the total die depth in order to obtain homogeneously compacts of granules. The test was repeated 5 times in order to get reliable data [13].

The value of the cohesive strength of the agglomerates τ was derived from eq. 4.4

$$\ln \mathrm{P} = \ln \left[\frac{\tau}{\alpha}\right] + \alpha\epsilon + \ln\left(1 - e^{-\alpha\epsilon}\right) \quad \text{(eq. 4.4)}$$

where P is the applied pressure, α is the friction coefficient and ϵ is the natural strain. Values of τ and α were obtained by fitting the force and displacement data from the compression test into Eq. 4.4 [12]. At large values of ϵ, the plot is linear; the slope of this linear part corresponds to α, while the intercept with the y axis corresponds to $\ln\left[\frac{\tau}{\alpha}\right]$ [12]. Average crushing strength of granules (F_{calc}) was estimated using eq. 2 for the different sieve classes employed [12].

$$\mathrm{F}_{\mathrm{calc}} = \frac{\pi\, d_a^2}{4}\, \tau \quad \text{(eq. 4.5)}$$

where d_a is the average agglomerate diameter (equal to the mean value of the sieve class).

4.3 Results and discussion

4.3.1 Rheological characterization

The MCC used in this study was purchased from a different manufacturer thus the correct liquid amount needed to be assessed for all the formulations.

The optimal liquid amount for the granulation experiments were determined using the mixer torque rheometer using the ‘multiple addition’ method. The second derivative approach was then applied to torque profile. Results showed that, despite the different manufacturer and appearance of the MCC, the optimal liquid amount resulted coherent with that predicted in the previous chapters. Granulation experiments confirmed the correctness of the predicted L/S thus supporting the results obtained with the MTR3. In section 2.3.2 was described the method of the second derivative of the torque profile for the prediction of the optimal L/S for high-shear wet granulation. For instance is stated that in presence of a shoulder, the second derivative identify two inflection points (where the second derivative assume a value of zero) which enclose the shoulder. These two points define a range of L/S which could be used to perform the granulation experiments. As it is possible to observe in Figure 4.2, a shoulder is present on the torque profiles of all the three formulation studied.

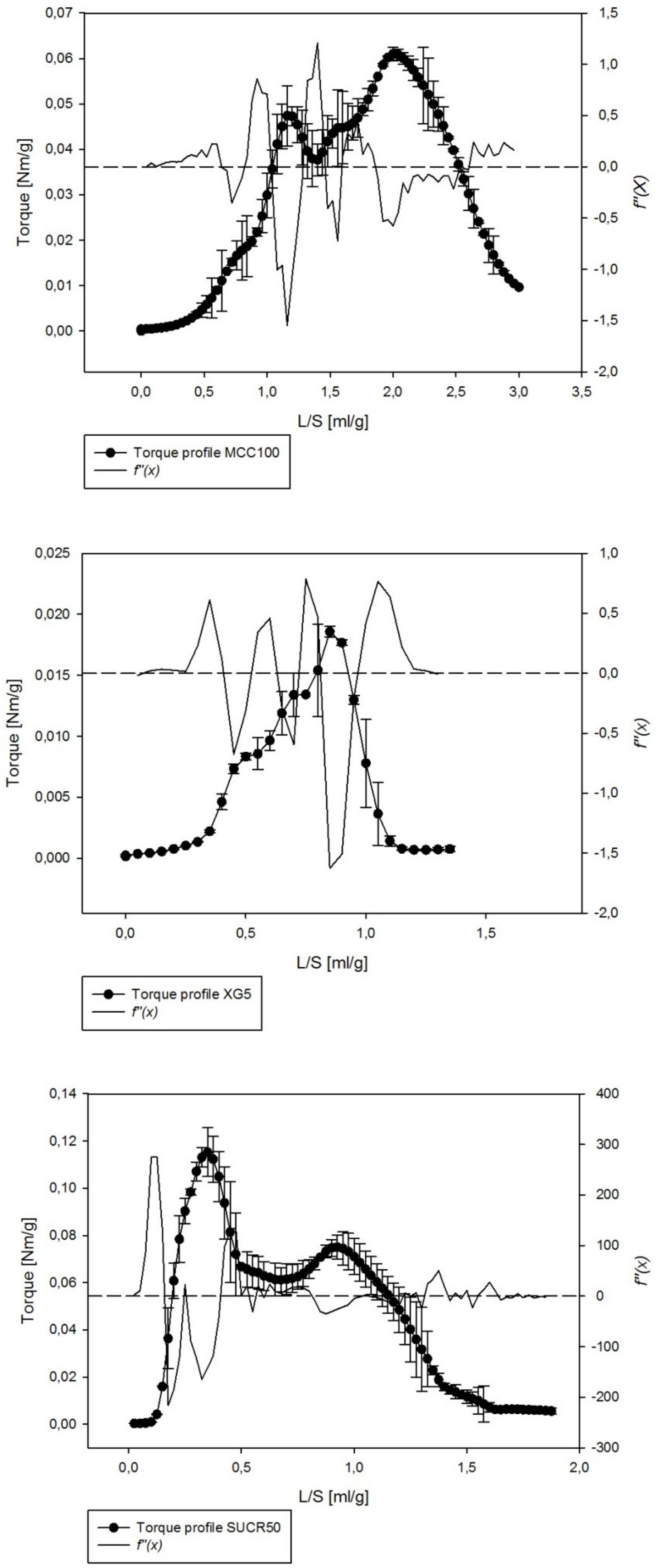


Figure 4.2: ‘Multiple addition’ torque profiles obtained for the three formulations.

In order to evaluate the influence of the amount of liquid on the granulation process, three values of L/S within the range identified by the second derivative approach were selected for further investigations. The L/S values are collected in Table 4.8

Table 4.8: L/S values identified for the three formulations.

Formulation	**L/S**		
	Lower limit [ml/g]	**Optimal value [ml/g]**	**Upper limit [ml/g]**
MCC100	1.04	1.16	1.28
SUCR50	0.16	0.20	0.24
XG5	0.64	0.69	0.74

In Chapter 3 was investigated the possibility to employ the maximum value of torque recorded during 'variable mix time' experiments in the MTR3 to predict the granules growth regime of a certain formulation. In that study were defined the limits of maximum torque which are predictive of different granules growth mechanisms, these are reported below in Table 4.9.

Table 4.9: Range of the Torque peak values corresponding to the different growth mechanism.

Torque peak (Nm/g)	**Granules growth regime**
< 0.025	*Crumb regime*
0.025 – 0.18	*Steady growth regime*
> 0.18	*Induction growth regime*

In the present study was further investigated the possible application of these rheological measurements to identify the CPPs of the granulation process. On this purpose torque profiles were recorded using the 'variable mix time' method. Torque peak values were calculated at different experimental conditions including: shafts speed, binder flow rate and amount of liquid binder as reported in Table 4.2. Results obtained with the different formulations are reported in the following sections.

4.3.1.1 MCC100

Torque peak values recorded using different condition with the 'variable mix time' method are resumed in Table 4.10 together with the operative conditions applied.

Table 4.10: Torque peak values obtained in ‘variable mix time’ experiments for the formulation MCC100.

L/S [ml/g]	Binder flow rate [ml/h]	Shafts speed [rpm]	Torque peak [Nm/g]	Predicted growth regime
1.04	1800	50	0.039 ± 0.004	Steady Growth
	1800	150	0.053 ± 0.001	
	300	50	0.043 ± 0.003	
	300	150	0.053 ± 0.003	
1.16	1800	50	0.050 ± 0.006	Steady Growth
	1800	150	0.056 ± 0.008	
	300	50	0.055 ± 0.007	
	300	150	0.064 ± 0.006	
1.28	1800	50	0.061 ± 0.004	Steady Growth
	1800	150	0.054 ± 0.003	
	300	50	0.067 ± 0.013	
	300	150	0.060 ± 0.002	

As can be observed from Figure 4.3, for higher shafts speeds the maximum value of torque is achieved faster but there are not significant changes on its value (Table 4.10). The values range between 0.039 and 0.067Nm/g which are included between the thresholds predicting a steady growth regime.

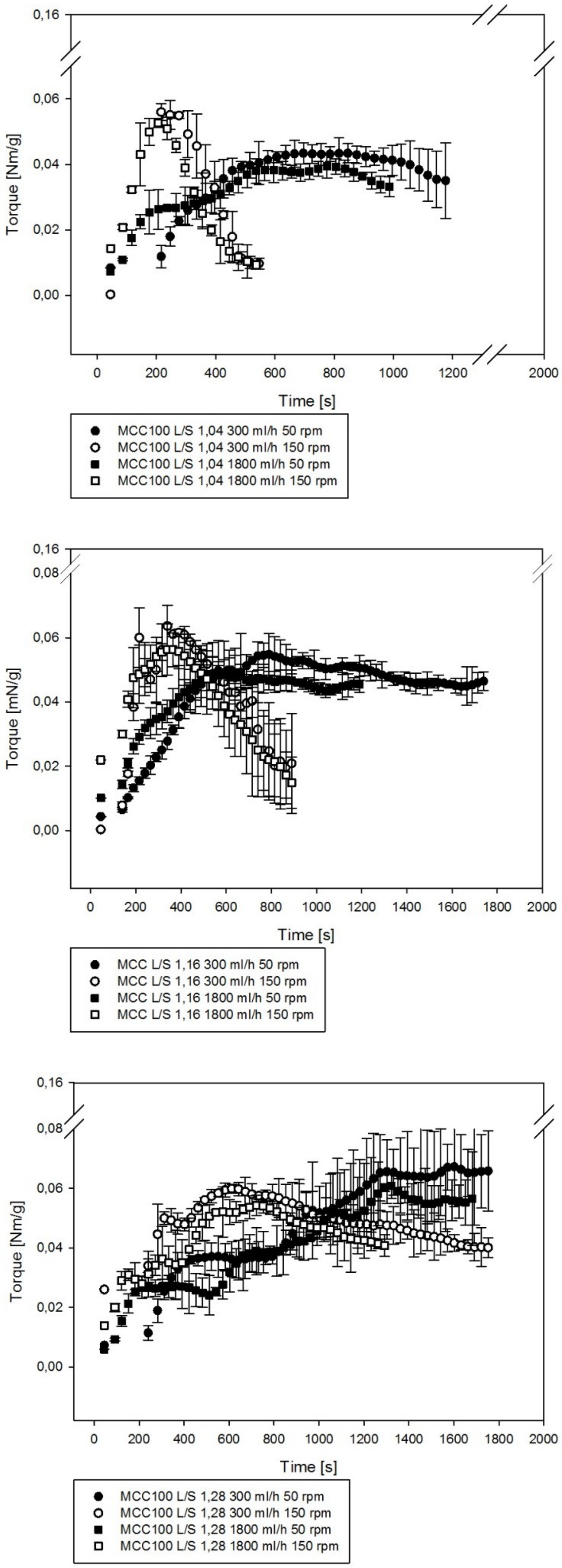


Figure 4.3: ‘Variable mix time’ torque profiles obtained with the formulation MCC100.

In order to validate this prediction, extended granulation and material exchange experiments were performed using a standard procedure. Briefly, powders were dry mixed for 2min at 120rpm, then an amount of liquid binder (water) corresponding to the lower, the upper or the optimal L/S ratio was added using a flow rate of 3240ml/h. At the end of the wetting time, impeller speed was increased at 400 or 1000rpm in order to evaluate the effect on growth kinetics.

The results of these granulation experiments are shown in Figures 4.4 and 4.5.

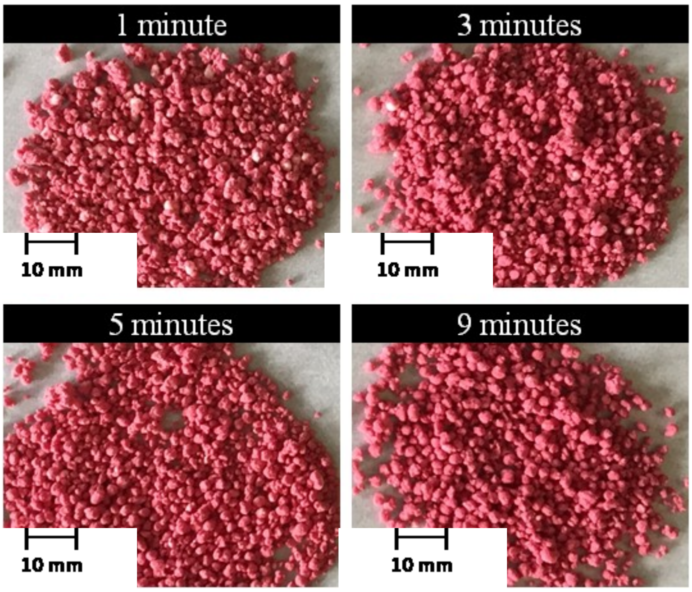


Figure 4.4: Digital microscope images of samples withdraw during exchange materials experiments for formulation MCC100 using L/S of 1.16 and an impeller speed of 400rpm.

Images of the samples withdrawn during the material exchange experiments highlight the presence of the deformation mechanism, correlated to the steady growth regime. This result is further validated by the extended granulation experiments. The growth kinetics profiles obtained are reported in Figure 4.5 where it is possible to note the typical linear trend of the granules growth. Moreover, Figure 4.5 highlights that an increase in the impeller speed produce a slight increase in the growth kinetic.

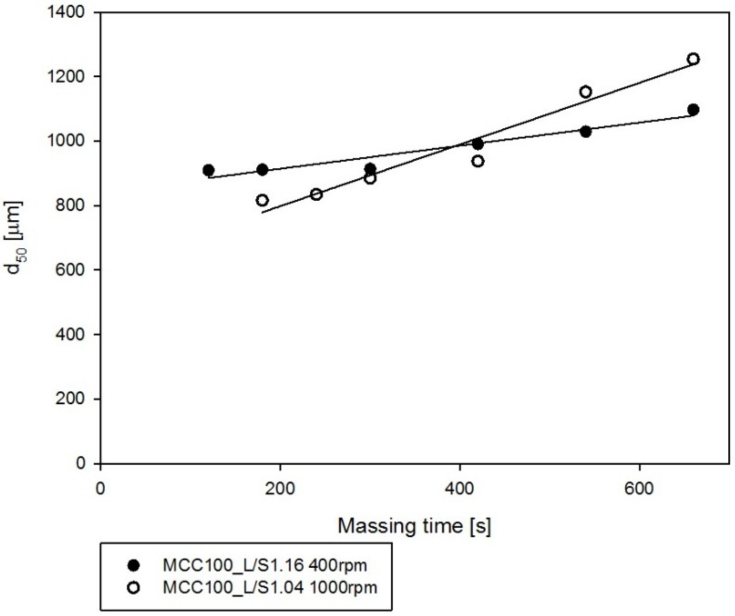


Figure 4.5: Growth kinetics evaluated by image analysis of samples withdraw during prolonged granulation experiments: MCC100 using L/S of 1.16 and an impeller speed of 400rpm and using L/S of 1.04 and an impeller speed of 1000rpm.

4.3.1.2 SUCR50

Torque profiles obtained with the ‘variable mix time’ experiments for the formulation SUCR50 are presented in Figure 4.6.

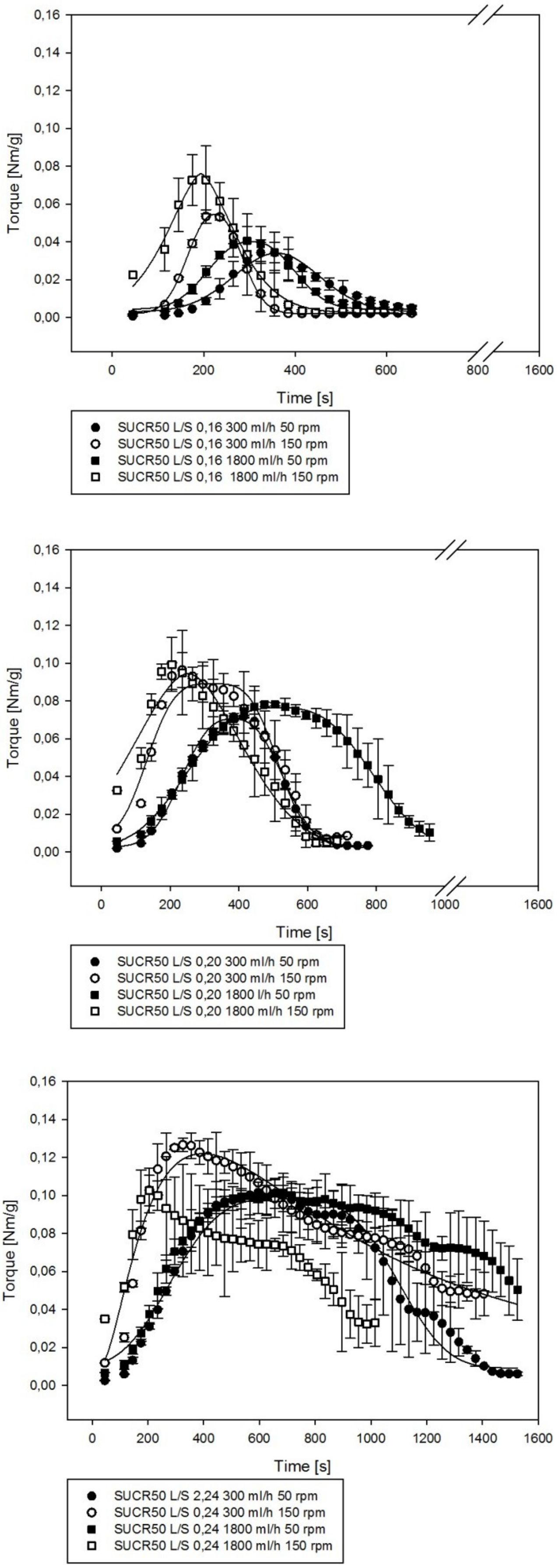


Figure 4.6: ‘Variable mix time’ torque profiles obtained with the formulation SUCR50.

The torque profiles recorded showed to be affected by the L/S and the shafts speed employed, while the influence of the binder flow rate is not straightforward. Moreover Torque peak values range between 0.034 and 0.127Nm/g and hence are within the thresholds which predict a steady growth (Table 4.11).

Table 4.11: Torque peak values obtained in 'variable mix time' experiments for the formulation SUCR50.

L/S [ml/g]	Binder flow rate [ml/h]	Shafts speed [rpm]	Torque peak [Nm/g]	Predicted growth regime
0.16	1800	50	0.041 ± 0.008	Steady Growth
	1800	150	0.073 ± 0.018	
	300	50	0.034 ± 0.005	
	300	150	0.065 ± 0.021	
0.20	1800	50	0.078 ± 0.001	Steady Growth
	1800	150	0.099 ± 0.012	
	300	50	0.059 ± 0.010	
	300	150	0.096 ± 0.009	
0.24	1800	50	0.102 ± 0.010	Steady Growth
	1800	150	0.103 ± 0.008	
	300	50	0.092 ± 0.017	
	300	150	0.127 ± 0.004	

However, the differences on the Torque peak values are considerable, thus is expected a different behavior of the granules when different parameters are applied for their production.

Material Exchange experiments conducted following the procedure proposed by Bouwman et al. confirmed the results previously discussed. The material is exchanged between granules following a deformation mechanism. As can be appreciated in Figure 4.7, the speed of this material exchange is lower compared to that observed for MCC100. This is due to the lower deformability of the granules as highlighted by the rheological studies.

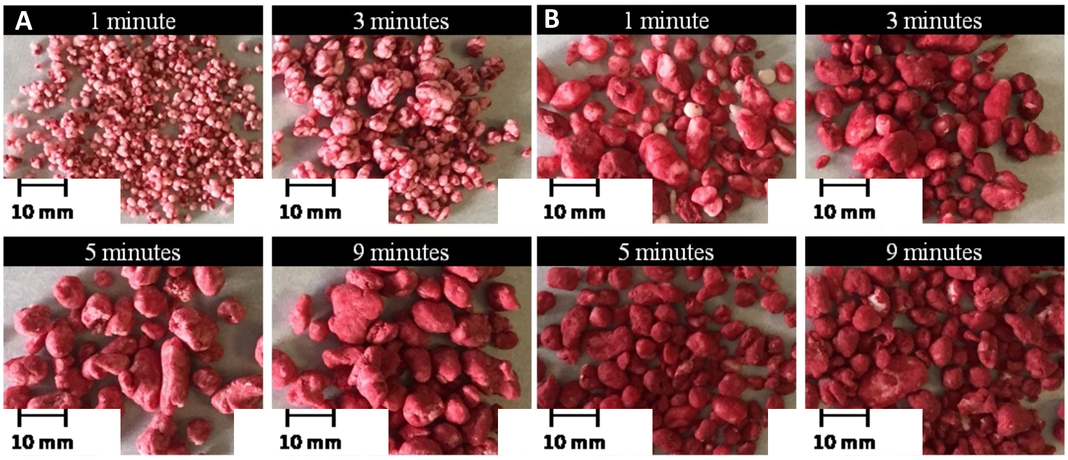


Figure 4.7: Digital microscope images of samples withdraw during exchange materials experiments for formulation SUCR50 using L/S of 0.20 and an impeller speed of 400rpm (A) and 1000rpm (B).

The extended granulation experiments further confirmed the linear growth of the granule size supporting the steady growth regime prediction obtained by the rheological characterization (Figure 4.8).

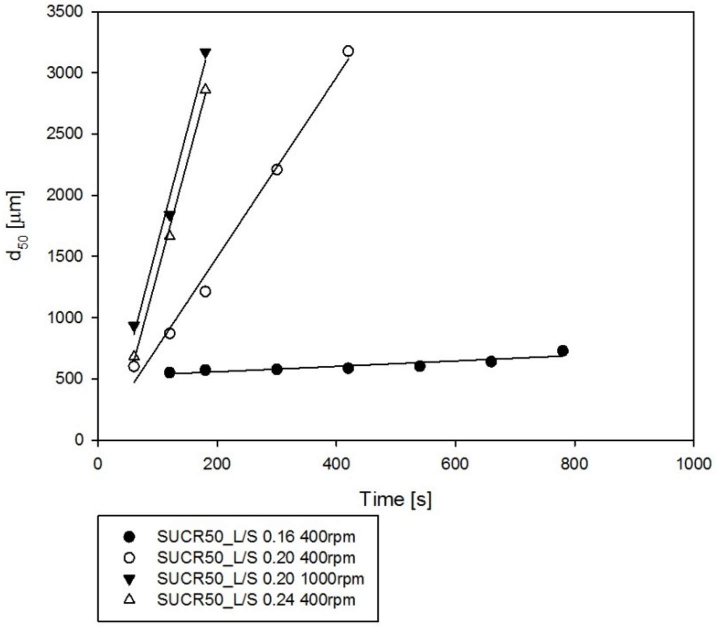


Figure 4.8: Growth kinetics evaluated by image analysis of samples withdraw during prolonged granulation experiments of formulation SUCR50 in different experimental conditions.

In Figure 4.8 it is possible to observe that granule growth kinetic is strongly dependent on the experimental conditions and in particular increases in the amount of liquid binder or impeller speed enhance the growth kinetic. Moreover using a L/S value higher than 0.20ml/g the granules increment rapidly their diameter also at a low impeller speed, thus it is expected that the process control could be difficult.

A good agreement between the results obtained with the MTR3 and those achieved with the granulation experiments can be underlined for the formulations MCC100 and SUCR50. In order to evaluate if existed a correlation between the granule growth kinetic and the Torque peak values a comparison was performed (Figure 4.9). In particular the growth kinetic was calculated as the slope of the linear regression between the granulation time and mean diameter of the granules (Figures 4.5 and 4.8).

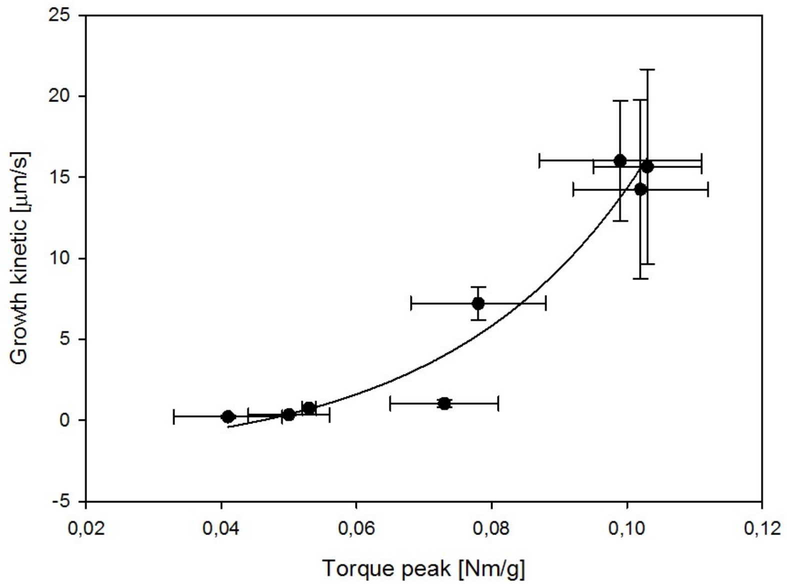


Figure 4.9: Relationship between Torque peak values and the growth kinetic.

Figure 4.9 highlights an exponential relationship between the two variables. This indicates that for Torque peak values higher than 0.07-0.08Nm/g the growth kinetic becomes rapid and the process could be difficult to control. In this case the granules growth could be represented by a rapid growth regime due to an increase in the maximum pore saturation; this is in agreement with the growth regime map proposed by Ivenson and Litster (Figure 4.10) [14].

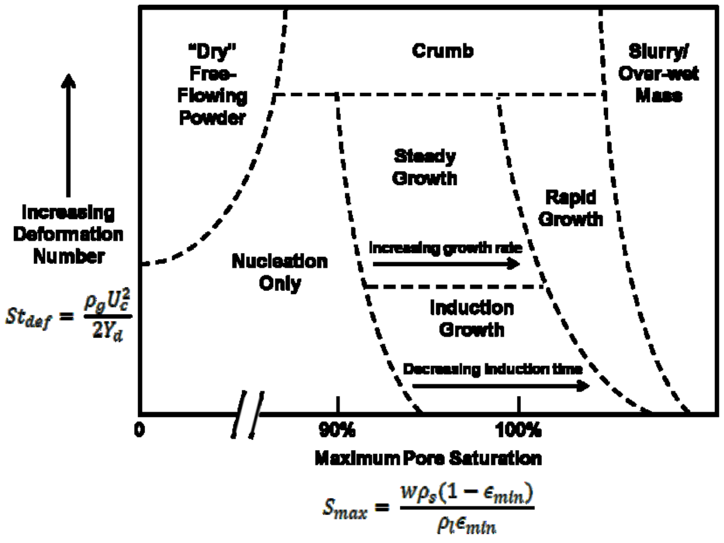


Figure 4.10: Growth regime map adapted from Ivenson et al. [14]. Rapid growth regime is presented at the same condition of the steady growth and induction regimes but at higher pore saturation values.

4.3.1.3 XG5

Torque profile obtained with the ‘variable mix time’ experiments for the formulation XG5 are reported in Figure 4.11.

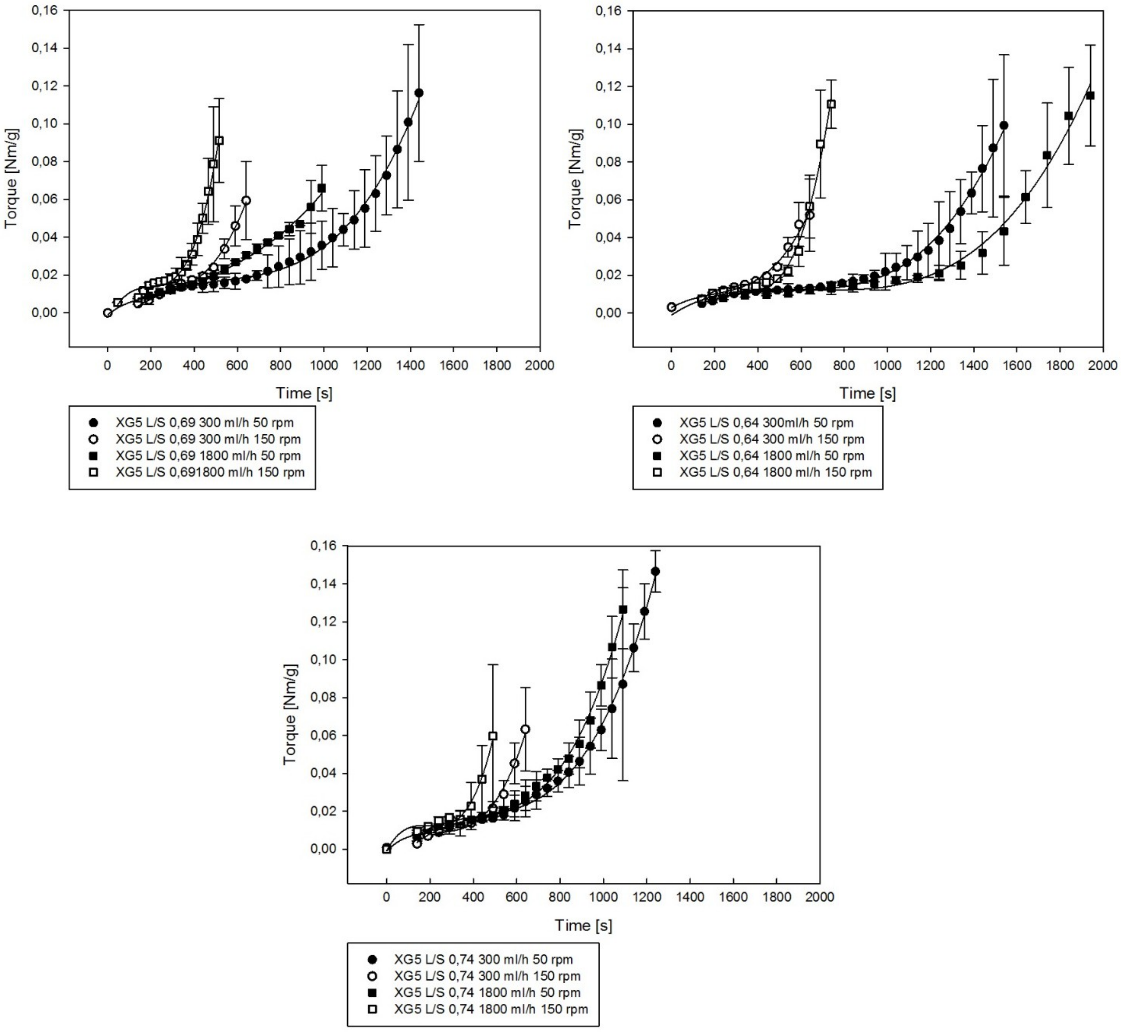


Figure 4.11: ‘Variable mix time’ torque profiles obtained with the formulation XG5. The data shown are those recorded until the instrument overload.

The formulation XG5 presented completely different results compared to those observed for the other formulations; this because was always achieved the instrument overload after an induction period characterized by a low resistance of the wet mass. Moreover the behavior of this formulation significantly differed from that observed for the same mixture in Chapter 3. This was probably due to the different MCC employed which could present a different interaction with the polymer.

Instrument overload is associated to a torque value of 0.20Nm/g (Table 4.12) which is predictive of an induction growth regime for the granules. Moreover the different operative conditions showed to lead only to modifications of the induction time and not on the Torque peak achieved (Figure 4.11).

Table 4.12: Torque peak values obtained in 'variable mix time' experiments for the formulation XG5.

L/S	Binder flow rate [ml/h]	Shafts speed [rpm]	Torque peak [Nm/g]	Predicted growth regime
0.64	1800	50	0.20 (*overload*)	Induction Growth
	1800	150	0.20 (*overload*)	
	300	50	0.20 (*overload*)	
	300	150	0.20 (*overload*)	
0.69	1800	50	0.20 (*overload*)	Induction Growth
	1800	150	0.20 (*overload*)	
	300	50	0.20 (*overload*)	
	300	150	0.20 (*overload*)	
0.74	1800	50	0.20 (*overload*)	Induction Growth
	1800	150	0.20 (*overload*)	
	300	50	0.20 (*overload*)	
	300	150	0.20 (*overload*)	

Material exchange experiments operated for this formulation are showed in Figure 4.12. As it is possible to observe, this experiment highlighted a typical distribution mechanism for the formulation XG5.

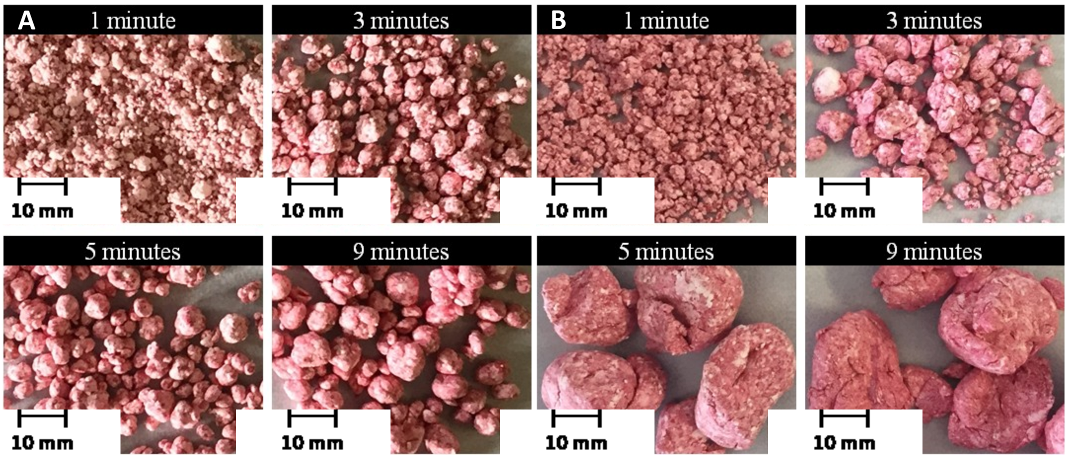


Figure 4.12: Digital microscope images of samples withdraw during exchange materials experiments for formulation XG using L/S of 0.69 and an impeller speed of 400rpm (A) and 1000rpm (B).

The blank and red granules appeared separated for a certain time, followed by a rapid and uncontrollable coalesce which led to formations of lumps in which the original red granules are recognizable. This result is a first confirmation of the successful prediction of the growth regime of granules operated by the MTR3. Extended granulation experiments conducted with XG5 at different operative conditions allowed to further confirm the results obtained with the rheometer (Figure 4.13). The granules presented an induction period where no granules growth could be appreciated. After this phase a rapid and uncontrollable growth of the granules could be observed and the growth kinetics presented the typical trend associated to the induction growth

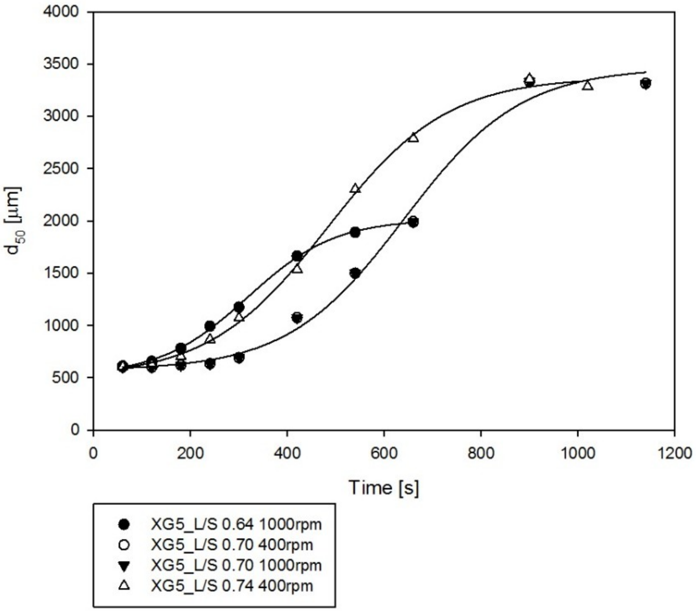


Figure 4.13: Growth kinetics evaluated by image analysis of samples withdraw during prolonged granulation experiments of formulation XG5 in different experimental conditions.

Moreover, in this case, the rheological characterization of the wet mass showed to be able to give an indication about the induction period of the granules because from the ‘variable mix time’ profiles it is possible to approximately calculate the induction time during which the granules present a stable diameter. This result is of great importance because it allows to potentially control the granulation process for those formulations which present an induction growth regime and thus are particularly difficult to handle.

4.3.2 Torque peak as a predictive tool for the CPPs of the high-shear wet granulation process

The Pareto principle was employed to operate the screening of the variables which had a significant impact on the maximum torque recorded. On this purpose, was evaluated which operative conditions considered (shafts speed, binder flow rate and amount of liquid binder), had a considerable effect on the Torque peak values (Figures 4.14 and 4.15). This analysis could be performed only for formulations MCC100 and SUCR50, because the toque peak values obtained with XG5 did not present any variation, as for all the operative conditions the overload of the instrument was achieved.

The Pareto chart of the results obtained with the formulation MCC100 is reported in Figure 4.14

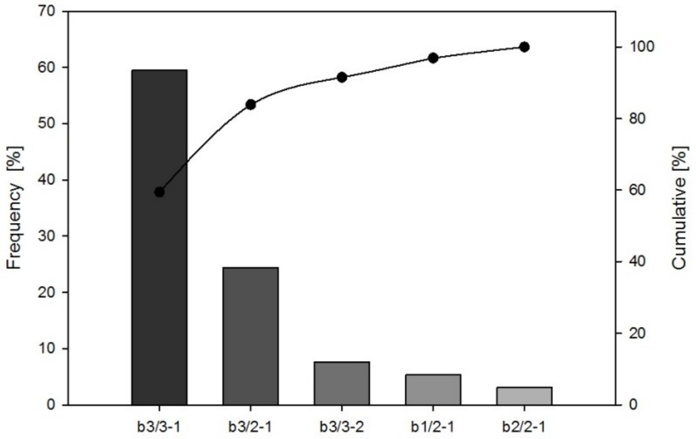


Figure 4.14: Pareto chart for the formulation MCC100. b_i are the coefficients of the mathematical model: b1 is connected to the variable X1 (binder flow rate), b2 is connected to the variable X2 (shafts speed) and b3 is connected to the variable X3 (L/S).

The analysis highlighted that for MCC100 only the amount of liquid binder (L/S) affected significantly the Torque peak values. This approach allowed to identify the parameter which had the most important impact on the Torque peak, even though it remained within a small range of values (0.039 and 0.067Nm/g).

The Pareto chart for the formulation SUCR50 is reported in Figure 4.15 and highlights that also with this formulation the main factor affecting the Torque peak values is represented by the amount of liquid binder employed.

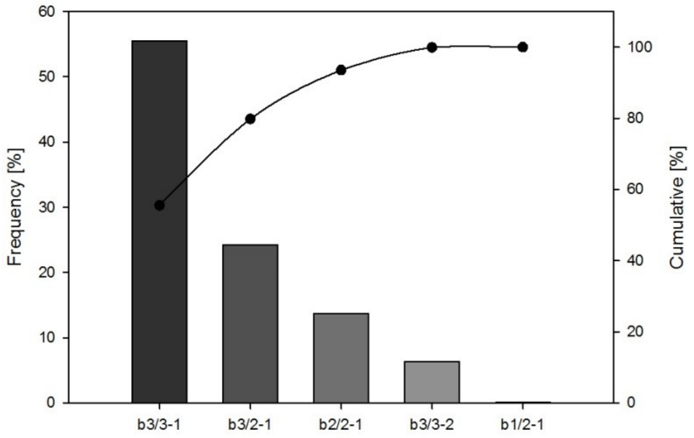


Figure 4.15: Pareto chart for the formulation SUCR50. b_i are the coefficients of the mathematical model: b1 is connected to the variable X1 (binder flow rate), b2 is connected to the variable X2 (shafts speed) and b3 is connected to the variable X3 (L/S).

In conclusion the rheological characterization has permitted to identify the material exchange mechanism and the growth regime for all the three formulations selected; in particular formulation XG5 presented always an induction growth regime while formulations MCC100 and SUCR50 presented the steady growth regime. Moreover the Torque peak values allowed to obtain information about the growth kinetic. Among the different experimental variables studied the amount of liquid seems to be the most important parameter affecting the Torque peak value and thus the degree of deformation and consolidation of the wet mass.

In order to verify if the parameters previously identified in section 4.3.2 as significant for the Torque peak value, have a considerable impact also on the granules properties, granulation experiments were conducted. These granulation experiments aimed to identify the CPPs for the high-shear wet granulation process. Following was operated a comparison between the identified CPPs and the parameters which presented a significant impact on the Torque peak. This evaluation should assess if the maximum value of torque is successful in predicting the CPPs of HSWG process.

4.3.3. Identification of the CPPs

In order to investigate if the information obtained with the rheological characterization are useful to predict also the CPPs of the high-shear wet granulation process, granulation experiments were performed using the 1.5l high-shear mixer Rotolab (IMA Zanchetta, Italy). In particular, four experimental variables were studied, named potential critical process parameters (pCPPs). These were: impeller speed (X1), binder flow rate (X2), massing time (X3) and L/S (X4).

X1 and X2 were studied at two different levels instead X3 and X4 were studied at three levels. All the experimental variables and their levels are resumed in Table 4.13

Table 4.13: pCPPs investigated, their experimental values and their codified levels.

pCPPs	Studied levels			Codified variable	Codified level
Impeller speed [rpm]	400 1000			X1	1 2
Binder flow rate [ml/h]	2200 3240			X2	1 2
Massing time [min]	1 3 5			X3	1 2 3
L/S [ml/g]	MCC100	SUCR50	XG5	X4	1 2 3
	1.04 1.16 1.28	0.16 0.20 0.24	0.64 0.69 0.74		

In order to identify which experimental variable affect significantly the granule final properties including mean diameter, hardness and roundness, a screening technique was applied and a reduced asymmetric factorial matrix $2^2*3^2//9$ was employed. The analysis of the data were performed with the software Nemrodw (Version 2015, D. Mathieu, J. Nany, R. Phan-Tan-Luu, Marseille, France). Results obtained with the different formulations are reported in the following sections.

4.3.3.1 MCC100

The experimental plan employed for the study of the MCC100 formulation is resumed in Table 4.14.

Table 4.14: Experimental plan for formulation MCC100 and proprieties of the final granules.

Exp	Impeller speed [rpm]	Binder flow rate [ml/h]	Massing time [min]	L/S [ml/g]	d_{50} [µm]	Roundness [-]	Failure load [N]
1	400	2200	1	1.04	875	0.72	12.17
2	400	3240	3	1.16	1350	0.75	39.77
3	400	2200	5	1.28	1590	0.73	37.59
4	1000	2200	3	1.28	1420	0.71	44.04
5*	1000	3240	5	1.04	805 ± 5	0.83 ± 0.01	40.29 ± 0.41
6	1000	2200	1	1.16	1300	0.71	29.56
7	400	2200	5	1.16	1290	0.72	22.53
8	400	3240	1	1.28	2200	0.70	24.87
9	400	2200	3	1.04	1210	0.77	35.34

*experiment performed in triplicate for the error estimation.

All the granulation experiments were performed and the experiment 5 was repeated three times to estimate the variance. At the end of the process, granules were dried in a ventilated oven and characterized evaluating the mean diameter, crushing strength and roundness. All the data are collected in Table 4.14.

Coefficients of the mathematical model used for the screening study were calculate and the Pareto approach was used in order to highlight the CPPs. Pareto charts for the mean diameter, crushing strength and roundness are reported in Figure 4.16.

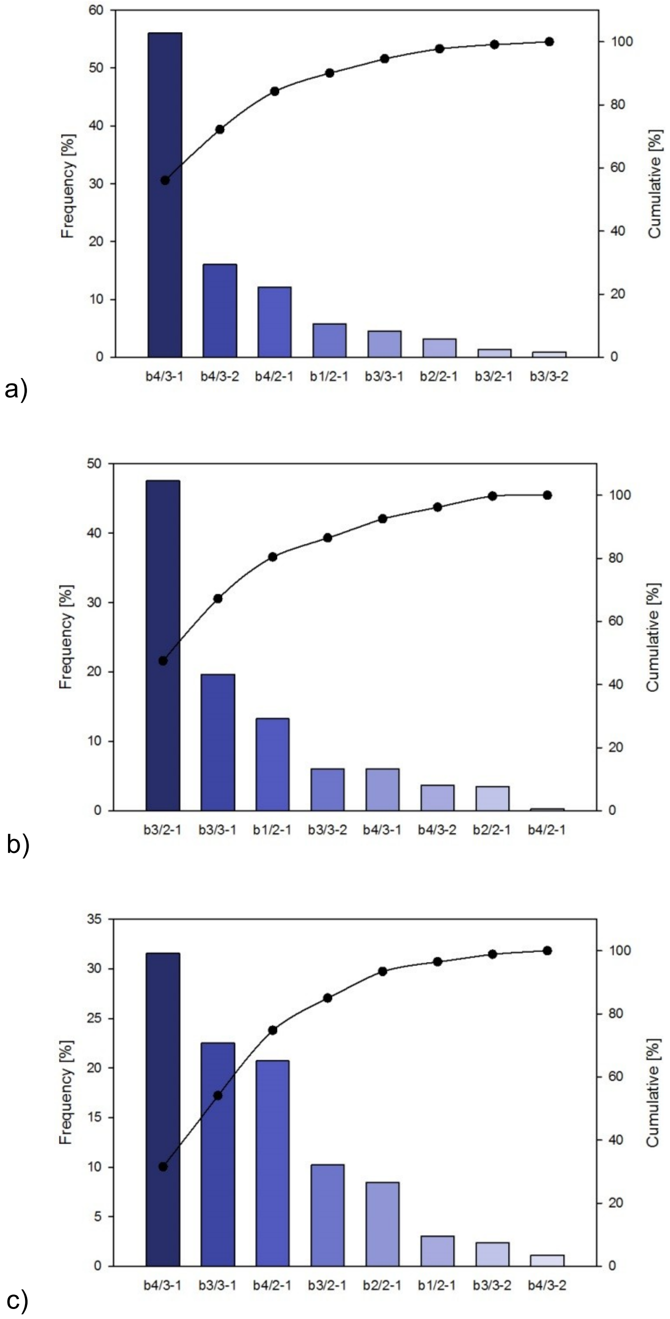


Figure 4.16: Pareto chart for a) mean diameter; b) crushing strength; c) roundness of granules having the formulation MCC100. b_i are the coefficients of the mathematical model: b1 is connected to the variable 1 (impeller speed), b2 is connected to the variable 2 (binder flow rate), b3 is connected to the variable 3 (massing time) and b4 is connected to the variable 4 (L/S).

Figure 4.16a highlights that the mean diameter of granules for the formulation MCC100 is mainly affected by the amount of liquid binder. This result is in accordance to the data present in literature which address to the amount of liquid employed the greatest effect on the particle size distribution [2]. Impeller speed, massing time and binder flow rate appear to have a negligible influence on the mean diameter of the granules. The rheological characterizations, the extended granulation experiments and the material exchange procedure highlighted a steady growth regime; consequently the granules are expected to grow linearly during the massing time and an influence of the massing time on the d_{50} was expected. However, the results obtained with the extended granulation experiments show that the growth kinetics for this formulation are very low and this can explain the outcomes found with the Pareto chart. It is possible that in the limited range of massing time investigated the granules do not present a significant enlargement of the mean diameter.

Another important propriety of the final granules is represented by crushing strength that it is a measure of the consolidation degree of the granules. Pareto chart for this experimental response is reported in Figure4.16b and shows that the hardness of the granules is mainly affected by the massing time and by the impeller speed. This result could be explained because both the granulation time and the impeller speed are parameters which generally influence granules densification [15]. Change in the densification of granules are generally associated with differences in the granules failure load [16].

The Pareto chart for the roundness of granules is shown in Figure 4.16c. Data highlight that the granule shape is mainly affected by the amount of liquid binder and massing time. This result is probably due to the increased roundness of granules given by longer massing time which allow the spheronization of the produced agglomerates [17]. Moreover a reduction of the roundness is experienced by the granules when higher L/S values are employed [18].

The CQAs of the granules produced with MCC are influenced mainly by the L/S employed for their production and the massing time applied to the wet mass. Moreover a certain influence is also showed by the impeller speed applied. The binder flow rate on the other hand do not show a significant influence on the characteristics of granules produced. The results achieved were compared to those obtained with the MTR3 in section 4.3.2. The data analysis operated on the Torque peak achieved at the different operative conditions highlighted a significant influence of the L/S employed on the maximum value of torque, while the other parameters did not show significant effect. This outcome is in accordance with the results obtained in terms of the mean diameter of the granules.

4.3.3.2 SUCR50

The experimental plan employed for the study of the formulation SUCR50 is resumed in Table 4.15. All the granulation experiments were performed and the experiment 2 was repeated three times for variance estimation. At the end of the process, granules were dried in a ventilated oven and characterized evaluating the mean diameter, crushing strength and roundness. All the data are collected in Table 4.15.

Table 4.15: Experimental plan for formulation SUCR50 and proprieties of the final granules.

Exp	Impeller speed [rpm]	Binder flow rate [ml/h]	Massing time [min]	L/S [ml/g]	d_{50} [µm]	Roundness [-]	Failure load [N]
1	400	2200	1	0.16	330	0.75	0.21
2*	400	3240	3	0.20	695±45	0.56±0.02	5.75±0.98
3	400	2200	5	0.24	4090	0.74	112.60
4	1000	2200	3	0.24	4070	0.75	121.20
5	1000	3240	5	0.16	1450	0.72	19.03
6	1000	2200	1	0.20	610	0.66	4.94
7	400	2200	5	0.20	780	0.70	19.18
8	400	3240	1	0.24	560	0.49	1.12
9	400	2200	3	0.16	320	0.66	1.48

*experiment performed in triplicate for the error estimation.

The results were elaborated using the software Nemrodw to calculate the coefficients of the mathematical model applied and to develop the Pareto chart for the identification of the most critical process parameters (Figure 4.17).

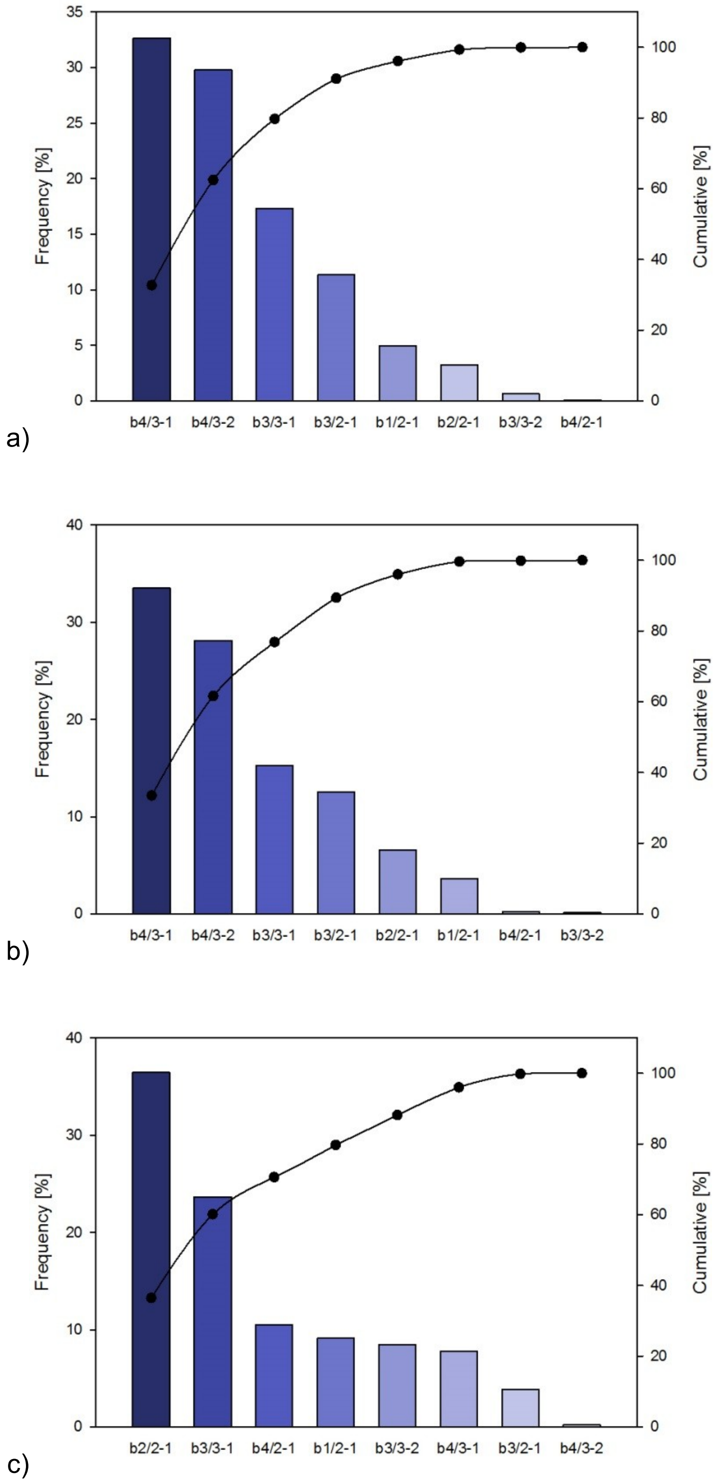


Figure 4.17: Pareto chart for a) mean diameter; b) crushing strength; c) roundness of granules having the formulation SUCR50. b_i are the coefficients of the mathematical model: b1 is connected to the variable 1 (impeller speed), b2 is connected to the variable 2 (binder flow rate), b3 is connected to the variable 3 (massing time) and b4 is connected to the variable 4 (L/S).

The Pareto chart regarding the results obtained in terms of mean diameter are showed in Figure 4.17a. The graph highlights that the mean diameter of granules is mainly affected by the amount of liquid binder and massing time. This result is in accordance to the steady growth regime, predicted by the rheological studies, and the results obtained from the evaluation of the Torque peak variation due to the different operative conditions applied. In particular this formulation present high Torque peak values which are indicative of a rapid growth of the granules. Moreover, the Torque peak showed to be strongly affected by the amount of liquid binder, as previously discussed. This mean that the rheology of the wet mass and the growth kinetic are strongly affected by the L/S. The mean diameter is strongly affected also by the massing time, this is accordance with the granules growth regime predicted since the growth kinetic could be rapid with this formulation [19].

Crushing strength of the granules showed to be influenced by the L/S employed and the massing time applied to the wet granules. This can be appreciated by the Pareto representation showed in Figure 4.17b. This result is probably due to the solubility of the sucrose on the granulating liquid. A higher L/S is related to a greater amount of water available to solubilize the sucrose present in mixture, this is associated with the presence of viscous liquid bridges involved the formation of numerous strong solid bridges which improve the strength of the final granules. As previously observed with MCC100 the massing time applied have an influence on the granules crushing strength [15]. In this case longer massing time could promote the solution of sucrose in the granulating liquid with the generation of liquid bridges with a higher viscosity or the different massing time can be associated with a different densification of the granules. Both the situation could explain the significant changes on the granules strength [16].

Finally the shape of the granules showed to be mainly influenced by the binder flow rate and the massing time applied to the wet granules. The obtained roundness is generally lower compared to that which characterize the granules produced using MCC100; this is probably due to the higher viscosity of the liquid bridges formed by the solution of sucrose, which lower the mobility of the liquid binder. The differences on the granules shape observed for the different binder flow rate are probably due to a diverse distribution of the liquid binder on the moving powder bed. A more efficient distribution is generally associated with more favorable characteristics of the final granules [20]. The massing time showed an influence on the roundness of granules. Generally longer processing time are associated with the spheronization of the produced granules, this might be the reason of the critical influence of the massing time on the agglomerates shape.

The CQAs of the agglomerates produced using SUCR50 are influenced by the L/S employed for their production, the massing time applied to the wet granules and in a minor extent also the binder flow rate. The impeller speed seems to not have critical effects on the characteristics of the final granules. Focusing on the parameters which influence the mean diameter of the granules, the L/S and the massing time appeared to have the highest impact. These results are in accordance with those observed with the MTR3. The data analysis on the maximum value of torque for this formulation highlighted a significant influence of the L/S employed on the maximum value of torque. Moreover the critical influence of the massing time is perfectly in accordance with the growth regime predicted for this formulation. In fact, for some processing conditions, this formulation can be included in the rapid growth regime defined by Iveson and Litster [19], thus the massing time employed have a great impact on the final granules size.

4.3.3.3 XG5

The experimental plan employed for the study of the formulation XG5 is resumed in Table 4.16. All the granulation experiments were performed and the experiment 2 was repeated three times to estimate the variance of the experimental responses. At the end of the process, granules were dried in a ventilated oven and characterized evaluating the mean diameter, crushing strength and roundness. All the data are collected in Table 4.16.

Table 4.16: Experimental plan for formulation XG5 and proprieties of the final granules.

Exp	**Impeller speed [rpm]**	**Binder flow rate [ml/h]**	**Massing time [min]**	**L/S [ml/g]**	**d_{50} [µm]**	**Roundness [-]**	**Failure load [N]**
1	400	2200	1	0.64	300	0.49	9.64
2*	400	3240	3	0.69	760±80	0.59±0.01	158.50±4.50
3	400	2200	5	0.74	1190	0.56	1369.00
4	1000	2200	3	0.74	4120	0.52	2000.00
5	1000	3240	5	0.64	1140	0.65	2149.00
6	1000	2200	1	0.69	650	0.51	335.80
7	400	2200	5	0.69	990	0.56	988.50
8	400	3240	1	0.74	430	0.55	75.80
9	400	2200	3	0.64	560	0.57	49.07

*experiment performed three times for error estimation of the experimental responses.

Results obtained by the experimental plan were elaborated using a software Nemrodw to determine the coefficients of the mathematical model and the Pareto representations for the assessment of the CPPs.

The Pareto chart regarding the mean diameter, crushing strength and roundness of the granules produced using the formulation XG5 are shown in Figure 4.18.

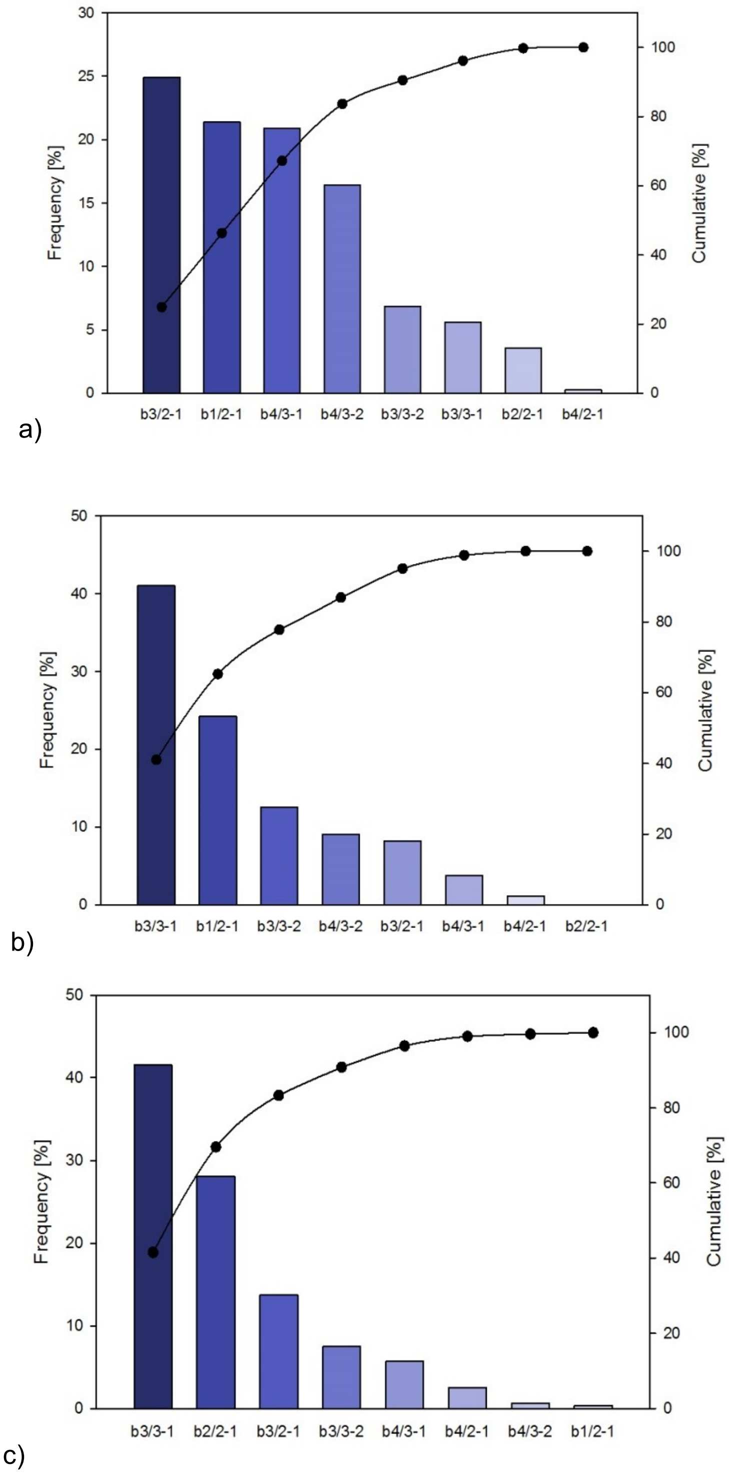


Figure 4.18: Pareto chart for a) mean diameter; b) crushing strength; c) roundness of granules having the formulation XG5. b_i are the coefficients of the mathematical model: b1 is connected to the variable 1 (impeller speed), b2 is connected to the variable 2 (binder flow rate), b3 is connected to the variable 3 (massing time) and b4 is connected to the variable 4 (L/S).

The d_{50} of the granules are influenced by the impeller speed, the massing time and the L/S used with this formulation, thus most of the studied parameters influence the PSD of the granules. This result is in accordance with those obtained by the rheological characterization of the wet mass. In fact, the formulation present an induction growth regime of the granules. From both the torque profiles and the extended granulation experiments was clear that the induction period was strongly influenced by the amount of liquid binder and the impeller speed employed. Moreover, during the induction period the diameter of the granules remain constant while it rapidly grows when a sufficient densification of the mass is achieved [19]. The granulation time is thus typically a critical parameter with this peculiar granules growth regime.

Pareto chart for the granules crushing strength is presented in Figure 4.18b. The granules strength is influenced by the impeller speed and the massing time. Both of them are parameters which are known to influence the granules densification and thus the granules strength [15,16]. Moreover a faster and prolonged agitation of the wet mass can be associated with a more efficient distribution of the granulating liquid. This can lead to a better distribution of the viscous liquid bridges formed by the hydration of the xanthan gum present in mixture with the formation of granules characterized by greater strength values. This could be potentially the reason of the significant effect of these two parameters on the strength of the granules produced with XG5.

Results obtained in terms of granules shape are presented in Figure 4.18c using the Pareto chart. The presented data show the influence of the binder flow rate and the massing time on the roundness of the granules. The difference due to the binder flow rate are probably caused by a different distribution of the liquid binder on the moving powder bed. A more efficient distribution is generally associated with more favorable characteristics of the final granules [20]. The massing time showed an influence on the roundness with all the formulation in study. Generally longer processing time are associated with the spheronization of the produced granules, this might be the reason of the critical influence of the massing time on the roundness of the granules produced with all the formulations in study.

The characteristics of the granules produced using XG5 formulation showed to be influenced by all the pCCPs in study. This result was expected as for the formulation was predicted an induction growth regime by the rheological characterization operated with the MTR3. Formulations presenting this peculiar growth regime are expected to be critical to be processed because of the uncontrollable growth which can occur at any moment during the granulation. However, the analysis of the torque profile allows to identify changes of the induction period due to different operational conditions. The results obtained with the granulation experiments are in accordance with the results obtained from the rheological characterizations. The operational conditions which leaded to significant changes in the torque profiles recorded, emerged to be confirmed as CPPs for the processing of the XG5 formulation in a high-shear equipment.

4.4 Conclusions

The results obtained with the formulations studied in the present work showed the potential of wet mass rheology to describe the granulation process. Wet mass rheology can be employed to predict optimal liquid amount for the HSWG and the granules growth regimes. This is possible by monitoring torque evolution of wet masses over the time. In particular the maximum torque value (Torque peak) measured for different formulations in different conditions is able to predict the different growth regimes of the granules produced as defined by Iveson and Litster. This was confirmed by granulation and material exchange experiments. In particular, the higher is the torque peak value and the lower is the deformability of the wet mass. Thus, for considerably high Torque peak values the consolidation and the granule growth are difficult; this situation corresponds to the induction growth mechanism. Lower Torque peak values, which range between 0.025 and 0.18 Nm/g, are indicative of the steady growth regime; in this case, the value of the Torque peak provides also useful information about the growth kinetic. Moreover a deeper rheological characterization have demonstrated how the MTR3 could represent a potential tool for the prediction of the critical process parameters (CPPs) for HSWG. Further study need to be accomplished to better evaluate the application of wet mass rheology for process understanding and for Quality-by-Design applications, thus facilitating the HSWG process development.

4.5 References

[1] P. Pandey, S. Badawy, A quality by design approach to scale-up of high-shear wet granulation process, Drug Dev. Ind. Pharm. 42 (2016) 175–189. doi:10.3109/03639045.2015.1100199.

[2] D.M. Parikh, M. Mogavero, Batch Fluid Bed Granulation, in: D.M. Parikh (Ed.), Handb. Pharm. Granulation Technol., 2nd ed., Taylor & Francis Group, 2005: pp. 247–304.

[3] S.I.F. Badawy, A.S. Narang, K. LaMarche, G. Subramanian, S.A. Varia, Mechanistic basis for the effects of process parameters on quality attributes in high shear wet granulation, Int. J. Pharm. 439 (2012) 324–333. doi:10.1016/J.IJPHARM.2012.09.011.

[4] S.I.F. Badawy, M.M. Menning, M.A. Gorko, D.L. Gilbert, Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer, Int. J. Pharm. 198 (2000) 51–61. doi:10.1016/S0378-5173(99)00445-7.

[5] I. Conference, O.N. Harmonisation, O.F. Technical, R. For, R. Of, P. For, H. Use, Requirements for Registration of Pharmaceuticals for Human Use - Guildlines for Elemental Impurities, ICH Harmon. Guidel. 8 (2014).

[6] A.C. Santomaso, R. Baggio, F. Zorzi, G. Salviulo, N. Realdon, E. Franceschinis, Sugars with different thickening power in high shear granulation, Powder Technol. 317 (2017) 391–399. doi:10.1016/j.powtec.2017.05.017.

[7] T.M. Chitu, D. Oulahna, M. Hemati, Rheology, granule growth and granule strength: Application to the wet granulation of lactose-MCC mixtures, Powder Technol. 208 (2011) 441–453. doi:10.1016/j.powtec.2010.08.041.

[8] A.M. Bouwman, M.R. Visser, G.M.H. Meesters, H.W. Frijlink, The use of Stokes deformation number as a predictive tool for material exchange behaviour of granules in the “equilibrium phase” in high shear granulation, Int. J. Pharm. 318 (2006) 78–85. doi:10.1016/j.ijpharm.2006.03.038.

[9] T. Allen, Particle Size Measurement Volume 1: Powder sampling and particle size

measurement, Fifith Edi, Springer Netherlands, 1996.

[10] A.M. Nazar, F.A. Silva, J.J. Ammann, Image processing for particle characterization, Mater. Charact. 36 (1996) 165–173. doi:10.1016/S1044-5803(96)00044-7.

[11] R.M. Dhenge, K. Washino, J.J. Cartwright, M.J. Hounslow, A.D. Salman, Twin screw granulation using conveying screws: Effects of viscosity of granulation liquids and flow of powders, Powder Technol. 238 (2013) 77–90. doi:10.1016/j.powtec.2012.05.045.

[12] M.J. Adams, M.A. Mullier, J.P.K. Seville, Agglomerate strength measurement using a uniaxial confined compression test, Powder Technol. 78 (1994) 5–13. doi:10.1016/0032-5910(93)02777-8.

[13] O.-R. Arndt, R. Baggio, A.K. Adam, J. Harting, E. Franceschinis, P. Kleinebudde, Impact of different dry and wet granulation techniques on granule and tablet properties: A comparative study, J. Pharm. Sci. (2018). doi:10.1016/J.XPHS.2018.09.006.

[14] S.M. Iveson, P.A.L. Wauters, S. Forrest, J.D. Litster, G.M.H. Meesters, B. Scarlett, Growth regime map for liquid-bound granules: Further development and experimental validation, Powder Technol. 117 (2001) 83–97. doi:10.1016/S0032-5910(01)00317-5.

[15] P. Pandey, J. Tao, A. Chaudhury, R. Ramachandran, J.Z. Gao, D.S. Bindra, A combined experimental and modeling approach to study the effects of high-shear wet granulation process parameters on granule characteristics, Pharm. Dev. Technol. 18 (2013) 210–224. doi:10.3109/10837450.2012.700933.

[16] K.A. Macias, M.T. Carvajal, The influence of granule density on granule strength and resulting compact strength, Chem. Eng. Sci. 72 (2012) 205–213. doi:10.1016/J.CES.2012.01.026.

[17] E. Franceschinis, A.C. Santomaso, L. Benda, B. Perissutti, D. Voinovich, N. Realdon, Influence of process variables on the properties of simvastatin self-emulsifying granules obtained through high shear wet granulation, Powder Technol. 274 (2015) 173–179. doi:10.1016/j.powtec.2015.01.026.

[18] A.M. Bouwman, Form, Formation and Deformation - The influence of material properties and process conditions on the shape of granules produced by high shear granulation, University of Groningen, 2005.

[19] S. Iveson, J. Litster, Growth regime map for liquid bound granules, AIChE J. 44 (1998). http://onlinelibrary.wiley.com/doi/10.1002/aic.690440705/full.

[20] K.P. Hapgood, J.D. Litster, R. Smith, Nucleation regime map for liquid bound granules, AIChE J. 49 (2003) 350–361. doi:10.1002/aic.690490207.

General Conclusions

High-shear wet granulation (HSWG) is one of the most employed technologies for particle size enlargement, however the complete control of the process is far to be reached. This is mainly due to the several variables which affect the resulting product as HSWG presents several process parameters which need to be controlled and most of them are formulation dependent. For this reason the process development is particularly difficult, with the risk for this equipment to become the last choice when a new formulation needs to be granulated. This thesis aimed to employ wet mass rheology to gain knowledge and to predict several aspects of the process. The first issue which was investigated was the possibility to use the wet mass rheology to predict the correct amount of liquid binder for a successful process. In particular, in the first part of the study a reliable method based on the use of a mixer torque rheometer (MTR) was developed using mixtures containing high amount of water soluble e sticky materials such as the sweeteners. Granulation experiments have confirmed the ability of the mixer torque rheometer to predict optimal liquid amount. Furthermore, this instrument showed the great possibilities of measuring the rheology of the wet masses to predict important parameters for the granulation process. On this purpose, in the second part of this thesis the MTR was employed to measure the wet granules strength and the wet mass cohesion in order to investigate if existed a relationship between those characteristics and the growth mechanisms of the produced agglomerates. Results highlighted a relationship between the wet granules strength (expressed in terms of wet mass consistency) and the growth mechanism followed by the granules during the process. Moreover additional rheological studies, based on the evaluation of the torque profile over the time, highlighted that the Torque peak of this profile can provide an indicative measure of the maximum cohesiveness and it is directly related to the final consistency of the granules produced with the same formulation. Consequently, the Torque peak measured for a formulation seems able to predict the growth regime of the granules.

In the last phase of the project the possibilities of the mixer torque rheometer were further investigated. In particular the aim was to evaluate the possibility to predict the critical process parameters of the HSWG through the wet mass rheology. On this purpose the effects of some process variables (shaft speed, amount of liquid binder and binder flow rate) on Torque peak values obtained with the mixer torque rheometer were studied using a DoE technique. Afterward, the effects of the same variable on final granule properties were also investigated on a high-shear mixer. Results highlighted that Torque peak values could represent a potential tool for critical process parameters assessment. In particular, Torque peak showed to be able to give important indications about the granule growth kinetic for formulations presenting the steady growth regime. Moreover it seemed to be a feasible tool for the prediction of the parameters which had the most significant impact on the mean diameter of the granule. In fact, the data acquired with the mixer torque rheometer in terms of Torque peak showed good accordance with the results obtained from granulation experiments. In conclusion, wet mass rheology showed to be an important characterization to gain preliminary information about the behavior of a certain formulation when processed in a high-shear mixer. However, further studies need to be accomplished to better evaluate the application of wet mass rheology for process understanding and for Quality-by-Design applications.

Future perspective of the present work will involve the validation of the obtained results in high-shear mixer characterized by different layout. Moreover the results obtained should be useful for the scale-up of the process; thus experiments should be carried out on equipments with different batch sizes in order to investigate how the predictive ability of wet mass rheology can aid this phase of process development.