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# Dry granulation process and compaction behavior of granulated powders

Lucia Perez-Gandarillas

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# THÈSE

**En vue de l'obtention du  
DOCTORAT DE L'UNIVERSITÉ DE TOULOUSE**

**Délivré par :** École Nationale Supérieure des Mines d'Albi-Carmaux

---

**Présentée et soutenue par :**

**Lucia PEREZ-GANDARILLAS**

Le 13 décembre 2016

**Titre :**

**DRY GRANULATION PROCESS AND COMPACTION BEHAVIOR OF  
GRANULATED POWDERS**

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***A mis padres.***

*Por abrir mis alas y dejarme volar lejos de su nido.*

*Por su incondicional compañía en los caminos que escogí.*

*“Caminante, son tus huellas,  
el camino y nada más;  
Caminante, no hay camino,  
se hace camino al andar.  
Al andar se hace el camino,  
y al volver la vista atrás  
se ve la senda que nunca  
se ha de volver a pisar.  
Caminante no hay camino  
sino estelas en la mar.”*

(Antonio Machado)



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A Spanish philosopher, named Ortega y Gasset, wrote in 1914 his famous quote “I am I and my circumstances”, expressing the relation between each person and the time and place where they are. This PhD work has been influenced by extraordinary “circumstances”. The friends I met, the colleagues I worked with, the places I had the opportunity to go, the smiles I found, the coffees I enjoyed... I hope that each person contributing to this work could find in these words my sincerest gratitude.

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Finally, I would like to thank the most important people to me: my family, my boyfriend and my Spanish friends. Wherever I live, they will always be my home. They defined who I am today. Far from science, they taught me what matters in life. Gracias!



## Abstract

Particulate solids such as pharmaceutical powders often require size enlargement processes to improve the manufacturing properties like flowability. For that reason, dry granulation by roll compaction has been widely used in the pharmaceutical industry. The process consists of compressing powders between two counter-rotating rolls to produce ribbons that will be subsequently milled into granules. The obtained granules are tableted for oral dosage. In this process there are two main limitations: the existence of different designs of the roll compactors, milling systems and the interaction between process parameters and raw material properties are still a challenge and the roll-compaction process leads to an inferior tensile strength of tablets compared with direct compression. These aspects are investigated in this work. In the first part of this thesis, an analysis on the effect of different roll-compaction conditions and milling process parameters on ribbons, granules and tablet properties was performed, highlighting the role of the sealing system and the ribbon density distribution characteristics. In the second part, die compaction of roll-compacted powders, as the last stage of the process, is further investigated in terms of experimental analysis (effect of the granule size and composition and stress transmission measurements) and modelling the compaction behavior of granules.

## Resumé

Les solides divisés telles que les poudres pharmaceutiques nécessitent souvent des processus d'agrandissement de taille par agglomération pour améliorer leur comportement mécanique, notamment la coulabilité. Pour cette raison, le procédé de "granulation en voie sèche" est utilisé dans l'industrie pharmaceutique. Le procédé consiste à comprimer la poudre en la faisant passer entre deux rouleaux séparés par un entrefer, pour produire des plaquettes qui sont ensuite broyées en granulés et comprimés en compacts. Dans ce procédé, l'existence de différents modèles de compacteurs à rouleaux et de systèmes de broyage d'une part, et l'interaction entre les paramètres des procédés et des propriétés des produits (plaquettes, granulés et comprimés) d'autre part, rendent difficile la compréhension des phénomènes et des mécanismes sous-jacents. En particulier, le procédé entraîne une perte de résistance mécanique des comprimés formés à partir de granulés (comparativement à celles des comprimés de poudres non-granulés) et ce phénomène est encore mal compris. Ces aspects sont étudiés dans ce travail de thèse en menant des caractérisations expérimentales et des modélisations numériques permettant de mieux comprendre les modifications micro et macro structurales des poudres mises en forme par granulation sèche. Le but ultime est de progresser dans la compréhension des relations "propriétés des poudres - paramètres des procédés". Enfin, la compréhension des différences de comportement en compression de poudres granulées et non-granulées est menée à l'aide d'une modélisation du comportement dans le cadre de la mécanique des milieux continus poreux.





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## LIST OF SYMBOLS

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$m$	Powder mass	(g)
$h$	Tablet height	(cm)
$D$	Tablet diameter	(cm)
$\rho_t$	True density	(g/cm <sup>3</sup> )
$\rho_r$	Relative density	-
$P$	Applied compaction pressure	(MPa)
$K$	Heckel coefficient	(MPa <sup>-1</sup> )
$A$	Heckel constant	-
$P_y$	Mean yield pressure	(MPa)
$F_d$	Force (required to break the tablet diametrically)	(N)
$F_c$	Force (required to break a tablet in axial compression)	(N)
$\sigma_d$	Diametrical tensile strength	(MPa)
$\sigma_c$	Compression failure strength	(MPa)
$\sigma_u$	Pressure upper punch	(MPa)
$\sigma_l$	Pressure lower punch	(MPa)
$\sigma_r$	Pressure in the die wall	(MPa)
$\phi_{axial}$	Axial stress transmission	-
$\phi_{radial}$	Radial stress transmission	-
$p$	Hydrostatic pressure	(MPa)
$q$	Equivalent stress	(MPa)
$F_s$	Shear failure function	-
$F_c$	Cap surface function	-
$d$	Cohesion	-
$\beta$	Angle of internal friction	(°)
$R$	Cap eccentricity	-
$\alpha$	Transition constant	-
$P_a$	Hydrostatic pressure at the intersection of the shear failure and the cap surface	
$P_b$	Hydrostatic pressure at the intersection of the cap with the p-axis	(MPa)



# Introduction

---

Dry granulation by roll-compaction consists basically of passing a mixture of powders through two rotating rolls, which converts the powder into a ribbon under the application of mechanical actions. The ribbons are subsequently milled into granules using a milling system. The produced granules with improved properties are used in subsequent processes as tableting or capsule filling. The process was firstly developed for metal and ceramic powders and it has been widely used in the pharmaceutical industry in the last decade. The major advantage of dry granulation is the continuous production without drying stage, leading to the reduction in costs.

Although the dry granulation by roll-compaction process may appear rather simple at first glance, the diversity of factors affecting the quality of materials renders the interpretation of results difficult. The structural changes to which the powder is subjected in order to be transformed into ribbons, granules and tablets remains not fully understood. The lack of process understanding makes the product development and the process design a challenging task. Currently, the trial-and-error method has been used for the optimisation of each specific production, which results in time and cost consumption, and up to date, the knowledge to scale-up the process from development equipment to commercial equipment is still limited.

In this context, the project IPROCUM (ITN-Marie Curie Actions) was created to develop robust process models that can be used to predict the properties of intermediate (ribbons/granules) and final products (tablets) based on the properties of individual particles. The overall approach is to bridge the current knowledge gap on how material properties of single particles and process conditions govern the product properties. For that, a multi-disciplinary approach was employed, including experimental studies at microscopic and macroscopic scales, multi-scale numerical models and computational intelligence modelling.

This doctoral research was integrated in the IPROCUM project and it has been developed at the RAPSODEE Centre-UMR CNRS in the School of Mines of Albi (France), in collaboration with the other project partners.



The main objective of this thesis is to obtain a deeper understanding of the dry granulation process through detailed experimental studies of roll-compaction, milling and die-compaction for different model pharmaceutical powders. More specifically, the objectives of this thesis include:

- i) To explore the effect of roll-compaction and milling conditions on the ribbons, granules and tablet properties. The experiments carried out will give key hints for the comprehension of the process and its effect on the variability of the product attributes such as ribbon density, granule size distribution and tablet tensile strength.
- ii) To investigate how roll-compaction affects the uniaxial compaction behaviour of powders. In particular, the impact of the mechanical granules properties on the properties of compacted tablets is analysed. For that, it is essential to compare feed powders with produced granules.

This doctoral thesis is organised in distinct chapters:

**Chapter 1** describes the state-of-the-art of the research and development related to the roll-compaction, milling and die-compaction processes. The dry granulation process and the theoretical background of the processes are introduced. The impact of the process on mechanical properties of the processed powders and the intermediate products (ribbons, granules and tablets) are also reviewed. The research progress on the understanding of the complex relationships between process parameters and measurable properties are discussed through the literature results.

**Chapter 2** presents the pharmaceutical excipients with distinctive properties (to evaluate the sensitivity of the process to the properties of the feed powder), the equipment (including roll-presses, milling systems and die-compaction presses), the experimental procedures (experiments under diverse operational conditions were carried out) and the techniques used for characterizations (such as ribbon density, granule size distribution or compactability of tablets). Moreover, in this Chapter, the Drucker-Prager Cap model is presented, with the goal of comparing the compaction mechanisms of feed powder and granules. The equations of the model and the calibration procedure are included.

**Chapter 3** includes the discussion of the roll-compaction and milling results. In this chapter, the effect of different roll-compaction conditions and milling process parameters on ribbons, granules and tablet properties was investigated in order to

establish the interrelation between the parameters and product properties, having a global consideration of the chain process. First, operational parameters such as the roll-compaction force, the sealing system, the mill type, the mill speed and the angle of rotation were evaluated in terms of amount of fines and tablet tensile strength. In addition, the most significant parameters were determined through the performance of a statistical analysis. Secondly, the role of the sealing system is further investigated based on the measurement of the ribbon density distribution. Moreover, the milling mass throughput and the granule size distribution are also presented as a function of the obtained results of the ribbon density distribution.

**Chapter 4** presents the results of the compaction of dry granulated material. The effect of the roll-compaction process on the compaction behaviour of granulated powders was analysed and discussed through the characterization of the Drucker-Prager Cap model, analysing the material parameters such as cohesion or angle of internal friction for both feed powder and granules. Also in this chapter, the densification mechanisms of roll-compacted binary mixtures (mixtures of plastic and brittle materials) are investigated, focusing on the role of the composition, the granule size effect and the measurements of the stress transmissions.

**General conclusions and perspectives.** In this part, the main conclusions from the discussed results in this thesis are included, together with the opened perspectives that can be further developed as a continuation of the present results.



# Chapter 1.

## State-of-the-art

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### **Abstract**

*The aim of this chapter is to present the state of the art of the research and development related to the chain of process “roll-compaction, milling and die-compaction” used in pharmaceutical industry and their impact on mechanical properties of the processed powders and the intermediate products (ribbons, granules and tablets). Firstly, dry granulation process based on roller compaction technology and the theoretical background of the process are introduced. In particular, the significant progress on the understanding of the complex relationships between process parameters (feeding systems; roll surfaces and speed; sealing systems; de-aeration systems) and measurable properties (ribbon density distributions, roll pressure distribution...) are reviewed and discussed. Secondly, the milling process, which transforms ribbons into granules by mechanical actions, is described and the main results from the literature are reviewed, especially for the effect of the process parameters on the production of fines. Finally, the basic mechanics of die compaction as the final step of the production chain is then introduced and the main phenomena of the granules behaviour and properties of tablets produced from roll-compacted granules (comparatively to tablets compacted from raw material) are reviewed and discussed. Results from the literature, which are generally focused on each process alone rather than the whole production chain, show that the full understanding of the changes in the mechanical behaviour from the raw material to tablets remains a challenge and the progress in this topic, probably needs to be based on the combination of both experimental analysis by developing new measurements for local properties and multi-scale modelling approach.*

### **Resumé**

*Le but de ce chapitre est de présenter l'état de l'art de la recherche et de développement liés à la chaîne de procédés "compactage à rouleaux, broyage et compactage" utilisée dans l'industrie pharmaceutique ainsi que leurs impacts sur les propriétés mécaniques des produits intermédiaires (plaquette, granulé et comprimé). Tout d'abord, le procédé de granulation sèche*

basé sur la technologie de compactage à rouleaux ainsi que les connaissances théoriques de base sont introduits. Les progrès significatifs concernant la compréhension des relations complexes entre les paramètres du procédé (système d'alimentation; surface des rouleaux; vitesse; système de confinement des rouleaux; système de désaération de la poudre) et des propriétés des plaquettes produites (distributions de densité de plaquette, distribution de pression appliquées par les rouleaux...) sont ensuite revus et discutés. D'autre part, le procédé de broyage, opération qui transforme les plaquettes en granulés par des actions mécaniques, est décrit ainsi que les principaux résultats de la littérature sont discutés, en particulier, l'effet des paramètres du procédé sur la production de particules fines. Enfin, les mécanismes de base de compactage en matrice sont ensuite décrits et les principaux phénomènes observés lors de la compression de poudres granulés et de poudres avant granulation, sont examinées et discutées. Les résultats de la littérature, qui généralement concentrent chaque procédé seul plutôt que considérer toute la chaîne de production, montrent que la compréhension des changements de comportement mécanique des poudres reste un défi technologique et scientifique et que les progrès dans ce domaine, nécessiteront probablement, une analyse expérimentale fine par des mesures locales des propriétés combinée à des approches de modélisation multi-échelles.

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## 1.1. DRY GRANULATION AND TABLETING

In the pharmaceutical industry, the compressed tablets are one of the most widely prescribed dosage forms in use today. Moreover, this success also covers many other industries such as fine chemicals, ceramics, metallic and food. In order to produce tablets of high quality in production scale rotary presses, it is essential that the pharmaceutical formulation filled into the press is dry and with uniform particle size. In addition, the intrinsic complex nature of the powdered materials makes their conveying and handling a challenging task in the pharmaceutical sector and sometimes the tableting operation cannot be simply achieved after the blending of the ingredients. Therefore, prior to the compression step, the formulation can go through an additional granulation process to improve their handling properties (flowability) and to assure the composition homogeneity of the product (to guarantee a uniform content of active ingredient in the mixture). The modifications of the mixture's properties (structural and mechanical properties) are essential for the die compaction process in order to avoid the demixing problem during the filling step and to reduce the variability of the tablets mass using a rotary press with a high speed. For that goal, mainly two industrial processes are often employed to gather the particles together forming larger particles or agglomerates: wet granulation and dry granulation. While wet granulation involves the production of granules by the addition of liquid binders to the powder mixtures followed by a drying operation, the dry granulation is a continuous process in absence of liquids, which results well suited for active pharmaceutical ingredients that are sensitive to water and other solvents.

Dry granulation, which uses a roll press to compact a powder mixture into a ribbon (roll-compaction) that will be subsequently milled in granules using a milling system, was firstly developed for metal and ceramic powders and after has been widely used in the pharmaceutical industry for more than 50 years. The resulting granules, with the improved properties, can then be employed for tableting process. Results from the literature show that the powder deformation history through the production chain of “roller compaction, milling and die compaction” (Fig. 1.1) leads to modifications of the intermediate product behaviours at different scales (ribbons, granules and tablets) and, up to date, these changes are not completely understood and even less predictable, although it has been investigated intensively in the last decade.

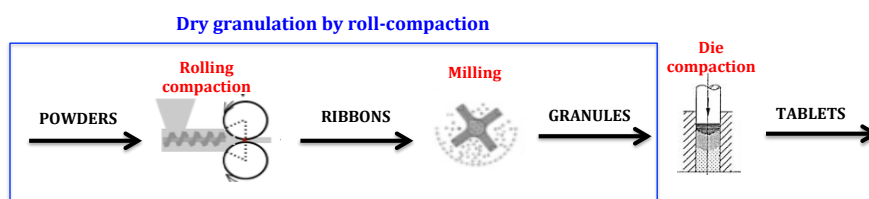


Fig. 1.1. Scheme of roll compaction, milling and tableting processes

## 1.2. ROLL-COMPACTION PROCESS AND CHALLENGES

### 1.2.1. Roll-compaction technology & theoretical background

The roll-compaction process compresses feeding powders between two counter-rotating rolls in order to form a ribbon. One of the rolls has fixed position whilst the other roll is allowed to move in one plane under the action of pressure. This pressure, applied evenly across the entering amount of material, causes the material compaction into a ribbon that subsequently is reduced in size to granules using a milling system.

The rollers can be mounted so that their axes of rotation are vertical, inclined or horizontal, as shown in Fig. 1.2. The configuration of the roll compactors differs between suppliers established in the pharmaceutical field: vertical (Alexanderwerk®, Komarek®), inclined (Gerteis®) or horizontal (Fitzpatrick®). They also offer a kind of configurations in different scales for various production capacities.

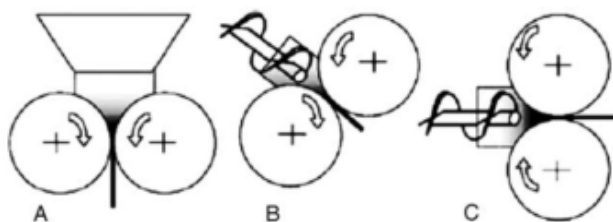


Fig. 1.2. Configuration of roll compactors (A) horizontal (B) inclined (C) vertical (Guigon and Simon, 2003).

As a general rule, the main process steps are: feeding and compaction. Each step is an important factor in the process. Depending on material properties, the feeding devices (hopper and screw feeder) are critical in the control of the material entering into the compaction zone. Indeed, the materials must flow from the hopper to be presented to the rollers in a continuous and uniform manner in order to achieve a consistent ribbon.

In the pharmaceutical industry, different roller press designs are used. Each technology has its advantages and weaknesses depending on the raw material properties. In general, the orientation of the screw will define how the powder must be fed. For non-cohesive powders, vertical feed systems, which are dependent only on the gravity, tend to maintain a uniform powder fill weight into the compaction zone with a small loss of powder. On the other hand, for light bulk density materials (fine powders), the horizontal or inclined feedings force the material to be drawn into the compaction zone by using a screw. In addition, for poorly flowing powders, a vacuum de-aeration system is often used to improve the delivery of material to the rollers. In order to limit the loss of powders from the roll sides, roller presses are generally equipped with a sealing system. Two types of side seals are mainly designed, stationary side seals (cheek plates)

that reduce powder loss on roll sides and a rimmed roll which confines the powder during its movement toward the gap.

Rolls are available in different dimensions and with different surface finishes. A specific surface gives a specific kind of product (Fig. 1.3). There are three basic types: smooth, circumferential corrugated and corrugated in the axial direction across the width of the roll. Powders that tend to stick to the roll surface must be pressed with smooth or circumferential grooved surfaces. On the other hand, products that release cleanly from the roll should be pressed with one of the pocketed design or grooving in the axial direction.

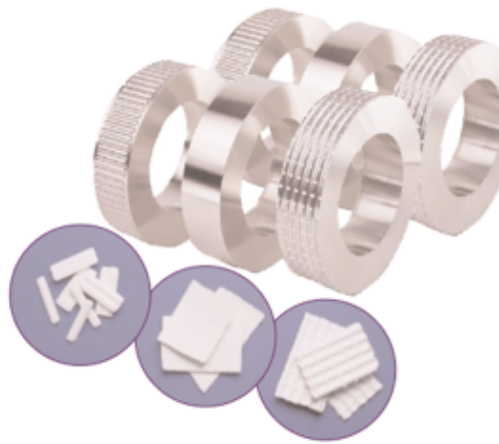


Fig. 1.3. Roll surfaces and correspondent compacts (Fitzpatrick®)

Modifying the roll-surfaces, the friction between the powder and the rolls is increased and, consequently, the maximum compaction pressure is increased. Sheskey and Hedren (1999) compared two roll surfaces: smooth and axial-corrugated. They hypothesized that the pressure exerted when increasing the concavity of the rolls was not that homogeneously applied as with the smooth roll surface but they could not find differences on the particle size distribution or tensile strength when comparing smooth and axial grooved surfaces to compact. Even though, corrugated surfaces are preferred to reduce ejection problems and breakage of compacts. Dawes et al. (2012) evaluated the effect of magnesium stearate (MgSt) on the transmission of a placebo formulation from the hopper to the rolls during screw fed roller compaction. When knurled roll surfaces were used, the addition of MgSt as a lubricant was observed to increase the throughput of material, which lead to increase the roll gap. Conversely, if two smooth rollers were used, this effect was reduced. The condition of friction at the roll/powder interface was insufficient to allow the powder to be gripped at the roll surface and hence drawn through the rolls.



- *Theoretical background*

As outlined before, in the roll-compaction process, mainly two parts are combined to work in a coordinated manner: the feeding system and the rolls. The feeding system delivers the raw material to the rollers. Then, the material is drawn towards the narrow space separating the rolls (roll gap) where a high stress is applied to form the ribbon. For horizontal and inclined roller presses, the screw feeder achieving a uniform and continuous flow should be synchronized with the speed of the rollers in order to avoid under-feeding or over-feeding problems (Guigon et al., 2003). A correlation between the screw speed and the roll velocity is needed to determine a good compaction rate: operating rate between subfeeding and overfeeding. (Simon et al., 2003; Michrafy et al., 2011; Lecompte et al., 2005).

To describe the process by which the powder is drawn and compacted between rolls, Johanson introduced the concept of the nip angle, showed in the Fig. 1.4, which defines the transition between the feeding zone and the compaction zone. Before the nip angle, the powder slips along the roll surfaces and the densification is only due to rearrangement of particles in this zone (low stresses). Once the nip angle is reached, the powder is drawn by sticking to the roll surface and is densified by deforming under the high roll pressure.

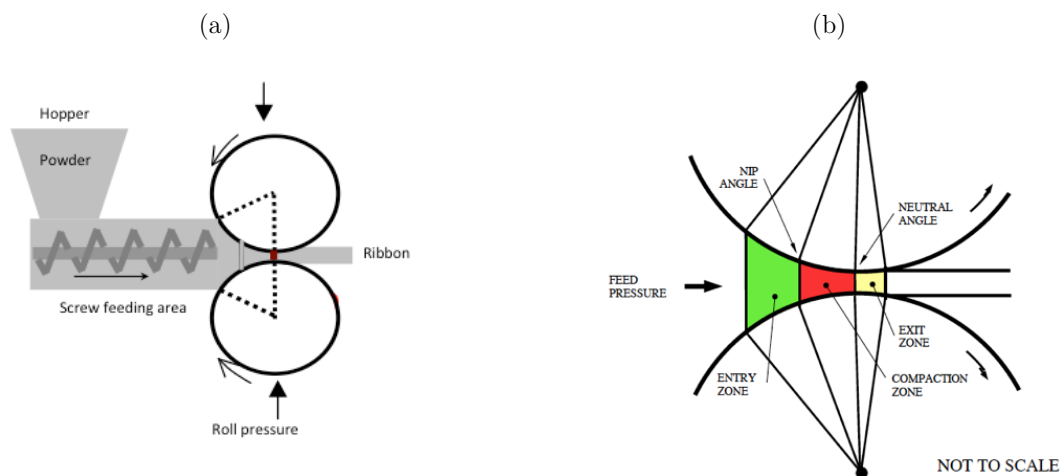


Fig. 1.4. (a) Schematic roller press with horizontal feeding and vertical axis; (b) Scheme of roller compaction regions and nip angle

To predict the powder behaviour between rolls, Johanson (Johanson, 1965) introduced a continuous model. The powder was considered compressible, cohesive and could be characterized with the Jenike-Shield yield function (Jenike, 1959). In this model, the granular material is described by the internal friction angle, the wall friction angle and the compressibility coefficient. Following these assumptions, two equations are used for the determination of the nip angle and the pressure distribution in the compaction

area. The merit of the Johanson model is to propose a semi-analytic description of the basic properties of a granular material and the rolling process variables. However, this model has limitations (Sommer and Hauser, 2003) and shows discrepancies between calculated and measured values for compressible material. The basic description of the powder behaviour and the a priori definition of two zones with two types of properties of contact (slip and stick) to determine the nip angle are the most critical hypothesis. To improve the understanding of the process and to develop a new approach to better predict the final properties of the ribbon, other models of roller compaction were developed for pharmaceutical applications. A review of some of them was published in (Dec et al., 2003).

### 1.2.2. Process design and operational parameters

At first sight the rolling compaction may look simple, but the dependence of the properties on the parameters renders the process design difficult. The following powder roll compaction parameters can be considered in developing models and can be divided into the following categories:

*System configurations:* feeding system, sealing system, deaeration system

*Operating Parameters:* roll force, roll torque, roll speed, feed pressure, gravity and inertia

*Geometric Parameters:* roll diameter, roll width, gap

*Powder Parameters:* Internal (effective) Angle of Friction, Cohesion, Admissible Stress, Compressibility, Bulk density

*Tribological Parameter:* Friction between powder and roll surface

Nevertheless, the choice of the good process parameters is essential to obtain an appropriate quality of the ribbons. In this section, the system configurations are described and, in the next section (1.2.3), the effect of the operation parameters on the properties of the ribbons are discussed based on the literature results.

#### 1.2.2.1. Feeding system

The role of the feeding system in the process is to draw the powder into the gap. It is essential that the delivery of material (feed throughput) is adapted to achieve a uniform and continuous flow in order to produce a consistent ribbon. For that, the feed throughput should be assured by increasing or decreasing the screw speeds. However, the feeding system should be in agreement with the roll speed, the desired gap and the

roll pressure. The interrelations between these parameters are detailed in the following sections (1.2.2.4-1.2.2.5)

According to the properties of the powder, the type of feeding system can vary: for powder with good flowability, gravity-feeding systems are appropriate, while for poor flowability, the use of screws is recommended. Generally, roller press with horizontal or inclined axis are equipped with one or two screw feeders to control the throughput of powders to improve the delivery of raw material to the rollers. When there are two screws, as in the case of an inclined setup of the rolls, the critical speed and the overall feeding rate will be determined by the first one (feeding auger). The second one is known as the tamping auger and it operates normally at twice the speed of the feeding auger.

### **1.2.2.2. Vacuum de-aeration system**

Due to the relative low bulk weight of fine powders (talc, bentonite,...), the amount of air can have significant effects of handling powders by screw feeder (limitation of the throughput) and in the compaction zone (air pressure can overcome the cohesion and damage the ribbon when it is liberated from the stress exerted by the press. For that needs, roller press must be equipped with a vacuum de-aeration to extract the excess of air from the powder and to ensure a good production. It should be noted that the optimization of the rate of roller press throughput will depend on the powder properties and their ability to release air. This means that even though a vacuum de-aeration is used, speeds of screw and rolls need to be adapted to the material properties. A progress in understanding the role of air in roller compaction will be reviewed and discussed on the light of the available knowledge (Section 1.2.3.3).

### **1.2.2.3. Sealing systems**

After being fed, in the compaction zone the loss of powder should be minimised. For that reason, rolls are normally sealed in order to prevent the escape of powder during the compaction. The sealing systems reduce the amount of non-compacted fines that can pass directly to the milling step. Two types of side seals are mainly designed (Fig. 1.5):

- Cheek plates: It consists on two stationary side plates. The use of cheeks avoids the loss of powder on the sides of the rolls but it acts as a resistance to the powder flow, thus reducing the amount of powder that enters into the gripping zone.
- Rimmed roll: One of the two rolls is attached to two rims on the sides that rotate together with the roll. Therefore, there is no relative movement between the powder and the roll, allowing a homogenous conveying of the powder.

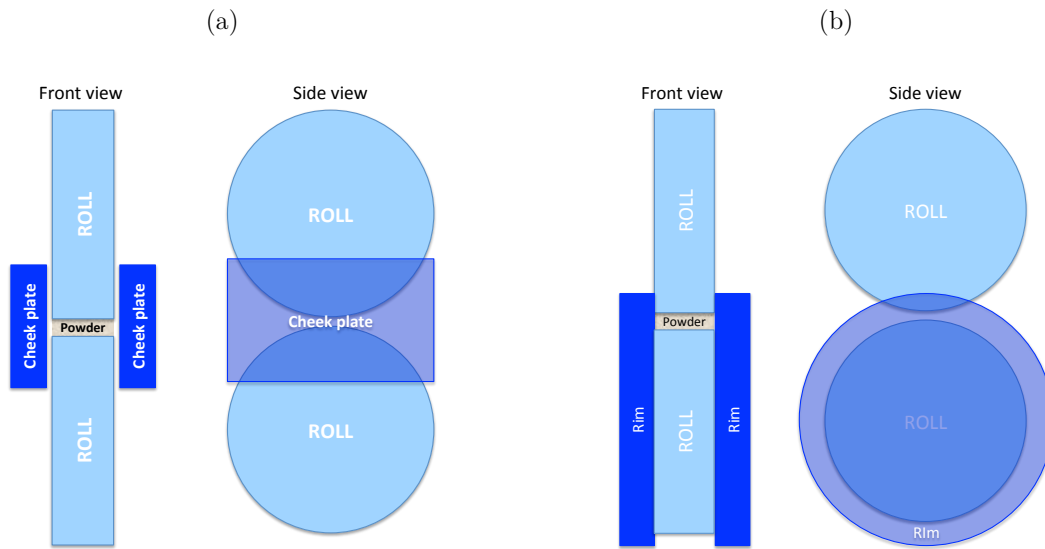


Fig. 1.5. Sealing system designs (a) Cheek plates (b) Rimmed-roll

In the section 1.2.3.1, the impact of these designs on the compacted ribbons and the progress in understanding the mechanisms that the powder undergoes during the process will be reviewed and discussed.

#### 1.2.2.4. Screw and rolls speeds

Generally, the roll-compactors allow setting a wide range of speeds of rolls and screws. It is important that they are synchronized (good operating rate) in order to warrant the formation of a compacted ribbon. These parameters have a direct relation between them but also their modification affects other parameters as the nip angle or the maximum compaction pressure, that decrease when increasing the roll speed causes a decrease in the nip angle and in the maximum compaction pressure.

The roll speed controls the residence time of the powder between the rolls, and therefore, the throughput of the roll press. The selection of roll speed depends on the material properties such as flowability, plasticity and elasticity.

For plastic materials, the residence time has an effect on the ribbon due to physical property of the material. On the other hand, for brittle materials, the residence time is independent of the compact quality; the fragmentation of particles is achieved rapidly and increasing the residence time has a limited effect on the ribbon strength (Teng et al., 2009).

In general, the roll speed is fixed before the screw speed. Consequently, the powder flow, the de-aeration conditions and the rolls speed will determine the operating range of the screw speed.

If the screw speed is too low, insufficient material will be fed to the compaction zone and the powder will not be compacted or the ribbon will be lowly densified. On the other hand, a high screw speed will cause an increase in the roll gap and even melting of particles on the flight, which may interrupt powder flow (Teng et al., 2009).

When there are two screws, as in the case of an inclined setup of the rolls, the critical speed and the overall feeding rate will be determined by the first one (feeding auger). The second one is known as the tamping auger and it operates at twice the speed of the feeding auger (Herting and Kleinebudde, 2007; Sakwanichol et al., 2012).

Fig. 1.6 represents the interdependence between both parameters, roll speed and screw speed, and three different zones can be distinguished (Simon and Guigon, 2000).

- *Sub-feeding*: The screw speed is too small in relation to the roll speed. The quantity of material that arrives to the compaction zone is insufficient and it can not be compacted.
- *Over-feeding*: The rolls turn slowly in relation to the screw speed. If the gap is fixed, it cannot absorb the amount of material and the system will be blocked. If the gap is movable, it will increase to be able to accept the powder into the compaction zone. In this case, lamination can occur because the compact is too thick and it is not compacted in the middle of the ribbon height.
- *Good compaction rate*: It is represented by the grey area in the figure. In this region, the ribbon is compacted, exhibiting cohesion and strength.

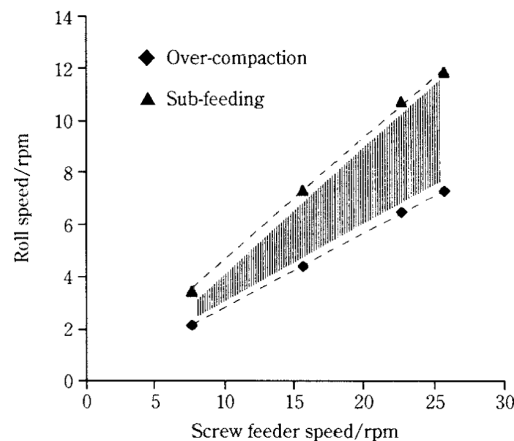


Fig. 1.6. Roll speed as a function of the screw speed (Simon and Guigon, 2000)

For MCC, Michrafy et al. (2011a) also analysed the relation between the roll speed and the screw speed for a Komarek press. They determined the good compaction ratio, highlighting that both speeds (rolls,  $V_r$ , and screw,  $V_s$ ) can be modified as long as the rate ( $V_s/V_r$ ) between them is conserved.

Trial-and-error experiments should be done to find the “good-compaction” region. It will differ depending on the model of the compactor and on the powder. When a good compaction rate is not reached, defects can be observed in the ribbon, such as compacted material of poor quality or breakage after ejection.

### 1.2.2.5. Gap and compaction pressure

The gap (space between the rolls) should be defined at the beginning of the operation in combination with the pressure exerted by the rolls. The roll gap and the compression force are proportional (Guigon and Simon, 2003). If the two rolls are fixed, the gap will be constant during the process and, thus, the compaction pressure will vary depending on the quantity of material entering in the compaction zone. On the other hand, if one roll is movable, the compaction pressure can be kept constant and the gap will vary to assure this pressure (Kleinebudde, 2004). This way of operating is known as gap-control mode, which is more effective to reach ribbon homogeneity.

To maintain a certain densification of the powder, the gap and the roll-compaction force should be adjusted in accordance. This is, if the gap increases, the roll-compaction force should be also increased in order to keep the same density (assuming that the powder is fed in a constant manner).

Guigon and Simon (2003) reviewed the main features of roll compactors. They plotted the relation between the maximal normal stress (measured with piezoelectric transducers) and the gap for different materials. For all the materials, the resulting curves were more or less straight, which means that the iso-gap curves can be assimilated to iso-maximum normal stress curves (Fig. 1.7). This is, the thickness of the ribbon (assuming that is the same as the gap) can be defined and this relation will determine the maximum stress to be applied in order to obtain a desired density for a certain material.

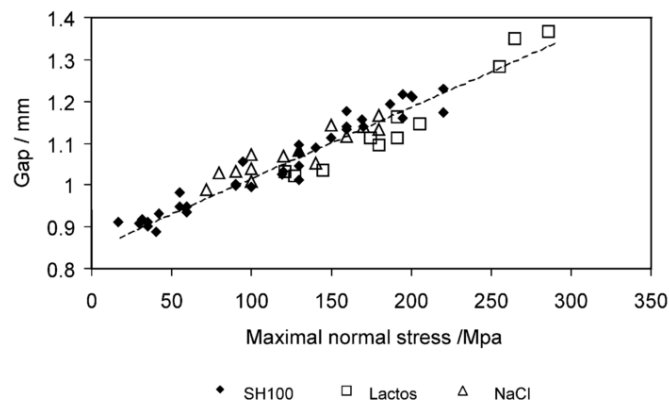


Fig. 1.7. Maximum normal stress measured with the piezoelectric transducers versus roll gap in order to achieve a certain densification. Solids hydrargilite (SH100), salt and lactose. (Guigon and Simon, 2003).

In theory, the same rate stress/gap will lead to the same quality of compact, but in practice, this does not always happen due to difficulties to control the material throughput.

### 1.2.3. Common problems and progress

Despite the simplicity of the roller compaction process, a quantitative understanding of the process has proved difficult to develop because of the complexity of the powder behaviour and the large number of operating parameters. Indeed, in roller compaction process, the powder undergoes a large change of its properties from feeding stage to ribbon formation. In the feeding part, which is known as the critical factor in the control of the material entering into the compaction zone, particulate solids flow within the feeder at a relatively low density and a low pressure up to the rolls entry. The delivered throughput material and the deformation state reached are depending on different parameters such as screw design, screw speed and also material properties (particle size distribution, friction and permeability). After that, the solid undergoes a high pressure applied by the rolls that decrease the porosity of the material under complex mechanisms (rearrangement, fragmentation, densification). The resulted ribbon properties are direct consequence of the deformation history of the raw material.

Over the past two decades, significant progress has been made in the instrumentation of the process to acquire observations and measurements to better understand the roller compaction process. In the following sections, we focus our review on several known common problems that receive (and continue to receive) more attention from researchers. These include heterogeneity of ribbon's properties that controls the heterogeneity of granule's quality, the air entrapped in fine powders that may cause instabilities in the feeding system and poor quality of ribbon, and scalability of the process which currently limits the widespread use of the process in the pharmaceutical industry.

#### 1.2.3.1. Heterogeneity of ribbon density

- *Across the ribbon width*

The heterogeneity of properties over the compacted ribbon width is one of the complex features that have been demonstrated in several experimental investigations. Tundermann and Singer (1969) performed roll compaction experiments of iron, copper, nickel, and stainless-steel powders and investigated density variation across the ribbon using a Metals Research Limited Quantitative Television Microscopy (QTM). This apparatus transmits a picture of the region on two television monitoring screens and indicates, via a logic circuit, the percentage of the area under consideration that is dark

or light. They obtained symmetrical variation of density distributions about the centre-line (Fig. 1.8) with relatively constant density in the central portion of the ribbon and low density on the edges due to the side flow effect. More, roller compaction of sponge-iron powders MH300 and MH100 (same material but different PSD) showed non-uniform density over the ribbon width with a distribution that depended on the particle size of the powder (Fig. 1.9): density profile of the finest powder (MH300 – PSD=40  $\mu\text{m}$ ) showed lowest density at the central portion than the edges. In this case, the air effect has been retained as responsible of this density distribution: the air escapes more easily at the strip edges and consequently, the powder flow at the edges is less affected and the density is then high.

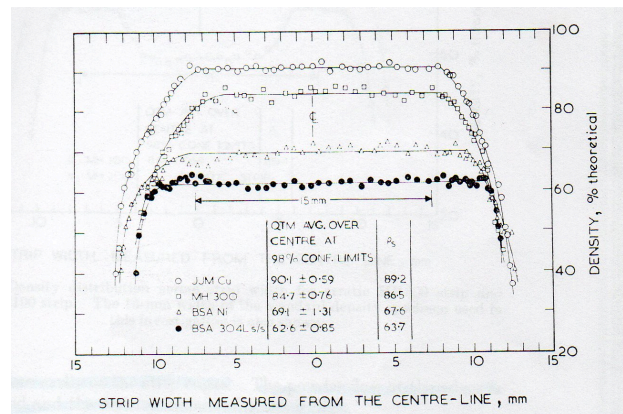


Fig. 1.8. Density distribution across ribbon width for different metallic powders (Tundermann and Singer, 1969)

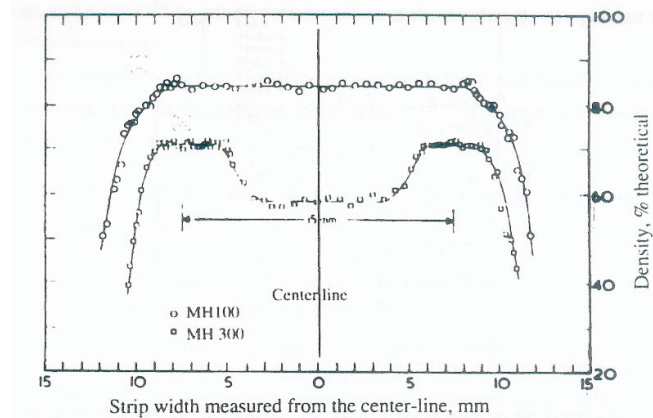


Fig. 1.9. Density distribution along the ribbon width for iron powders of different particle sizes: MH100: 150 $\mu\text{m}$  and MH300: 40 $\mu\text{m}$ . (Tundermann and Singer, 1969)

The density along the ribbon width can be also affected by the effect of the sealing system. The sealing systems reduce the amount of non-compacted fines that can pass directly to the milling step. Due to the friction of the powder with the plates, the use of cheek plates results in a non-uniform flow of powder into the compaction zone and,



as consequence, a higher compression pressure is applied toward the middle of the ribbon than toward the edges. Therefore, the density distribution of the ribbon width is not homogeneous.

To avoid this heterogeneity, Funakoshi et al. (1977) designed a concavo-convex roll pair, to improve the homogeneity of the compact. This design minimized the loss of powder. The flanges of the concave roll were subjected to several experimental variations of the wall slope angles ( $45^\circ$ ,  $65^\circ$ ,  $75^\circ$ , and  $90^\circ$ ). The efficiency of the sealing system was evaluated through a uniformity index of maximum and minimum pressures across the roll width ( $P_{\max}/P_{\min}$ ) obtaining the best results at a rim angle of  $65^\circ$ . Previous to this improvement, the powder leakage was 15%.

Later, Parrot (1981) demonstrated later that by using a concavo-convex roller compactor, an improvement in the density distribution could be achieved for several pharmaceutical powders. The presence of the inner walls of the rims increases the area in contact between the powder and the roll, reducing the resistance against the powder flow. Moreover, the rimmed roll improves the delivery of powder into the gripping and compression zones to form a compacted strip because more powder can be conveyed into the gap.

Previous experimental studies evaluated the heterogeneity along the ribbon width. These density distribution profiles were determined using different techniques. Miguélez-Morán et al. (2009) analysed the density distribution in roller-compacted ribbons of microcrystalline cellulose (Avicel PH102) using three different techniques: (1) sectioning; (2) micro-indentation and (3) X-ray micro-computed tomography. They found an heterogeneity when using cheek plates, which is shown in Fig. 1.10, obtaining lower densities at the edges of the ribbon width and higher at the center.

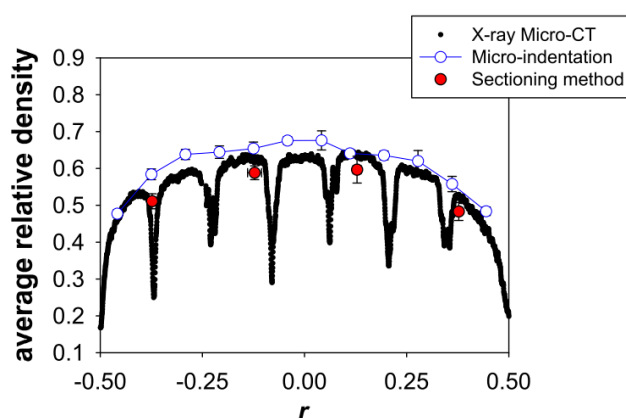


Fig. 1.10. Density profiles along the ribbon width when using cheek plates (from Miguélez-Moran, 2009).

Other authors also reported results using different techniques: X-ray tomography and ultrasonic (Akseli et al., 2011), near infrared chemical imaging (Lim et al., 2011;

Khorasani et al.,2015; Souihi et al., 2015a), sectioning (Miguélez-Morán et al., 2008; Zhang et al., 2016), , pressure gauges (Cunningham et al.,2010; Souihi et al., 2015b), GeoPyc-1360 (Muliadi et al., 2013) and terahertz pulsed imaging (Zhang et al., 2016).

Above all, these studies highlighted the relatively complex interrelationship between the sealing system designs and the resulting compacted material properties. The ribbon properties will altered directly the properties of the granules. Because of this, the investigation of the ribbon heterogeneity is of high importance in order to better understand its effect on the properties of granules and tablets. In this thesis, an experimental study comparing both sealing systems through the characterization of the ribbon density distribution is included in Chapter 3.

- *Across the ribbon length*

The design of the feeding system may also have a direct effect on the ribbon density. Simon and Guigon (2003) carried out roll compaction of lactose, alumina and sodium chloride in order to determine the influence of powder properties and roll press feeding on the compaction. A single screw feeder was used to drive the powders into the compaction zone and two piezoelectric transducers fitted on the upper roll measured the distribution of the applied stress in the roll gap. The results showed that the measured pressure fluctuated and was not homogeneous along the roll width during the process (Fig. 1.11a). They concluded that heterogeneity of the feeding pressure caused heterogeneity of the compact properties characterized by measuring the transmission of light through the ribbons. The same measurement was done with the powder moving like a piston. In that case, stress distribution resulted symmetrical from the centre being constant with time (Fig. 1.11b). In this case, a maximum stress was applied at the centre and a minimum stress on the edges.

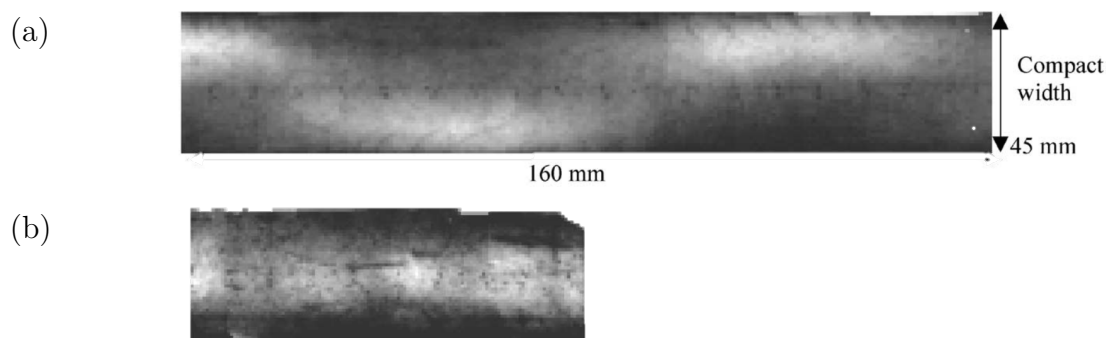


Fig. 1.11. Results from light transmitted through the compact for (a) screw feeding; (b) piston feeding (Simon and Guigon, 2003).

Michrafy et al. (2011a) found similar ribbon heterogeneity for a screw feeding. They performed roll compaction experiments on MCC (Avicel PH 102) using a vertical-

layout roll compactor combined with a horizontal feeding screw. They analysed the density homogeneity of the ribbons also using light transmission (Fig. 1.12) and mercury porosimetry measurements. Both approaches resulted in heterogeneity of the density across ribbon width: the light transmission revealed periodic heterogeneity shown by darker and lighter zones of the compacted strip as in the work of Simon and Guigon. On the other hand, the mercury porosimetry showed higher densities at the central part of the compact and lower densities at the sides.

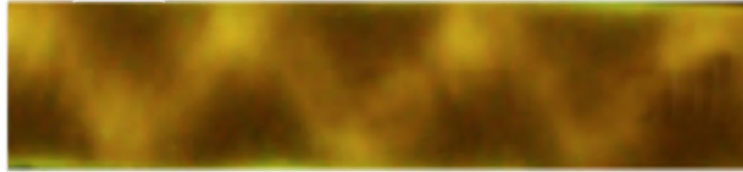


Fig. 1.12. Results from light transmitted through the compact (Michrafy et al., 2011a).

- *Across the ribbon thickness*

There are few results reported in the literature about the density distribution across the ribbon thickness. As pressure distribution exists between the roll surfaces during compaction, it may induce a density distribution in the thickness for low density ribbons (larger gaps), with lower density in the middle of the thickness and higher at the points close to the rolls surfaces.

To investigate this point, Tundermann and Singer (1969) obtained density data along transverse and longitudinal directions using QTM technique for roll-compacted metallic ribbons (Fig. 1.13) produced at different gaps (from 1.6 to 2.66 mm of thickness). For the ribbon produced at large gap (specimen A), the central density was similar to that of the surface. On the other hand, for high-densified ribbons (above 70% of relative density), the density was higher in the centre of the thickness than in the surface of the strip. The authors explained this through the progressive deformation of this specific material (Plasticine) as a whole. The particles on the surface are anchored to the roll surfaces and the densification is only due to deformation. On the contrary, the particles in the centre of the strip are under the effect of the deformation due to the roll pressure but also under the effect of the restacking of particles.

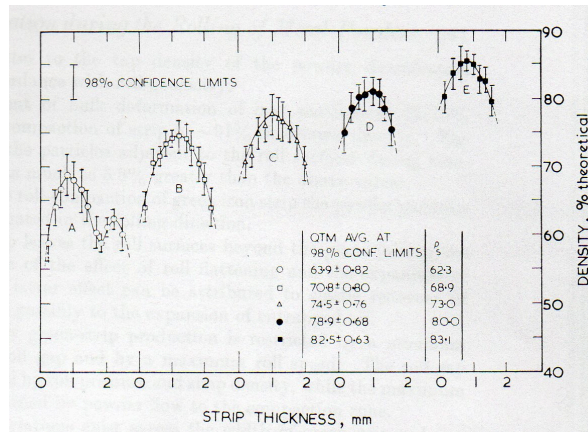


Fig. 1.13. The density distribution through the ribbon thickness for 304 L s/s (Tundermann and Singer, 1969)

Concerning pharmaceutical powders, Michrafy et al., (2011b) investigated the variation of density across the ribbon depth for MCC ribbons using a numerical microscope (Keyence® France). For low ribbon density, a view of the microstructure through the thickness is plotted in Fig. 1.14, demonstrates also the heterogeneity of microstructure across the depth and shows relatively low density in the middle than the surface.

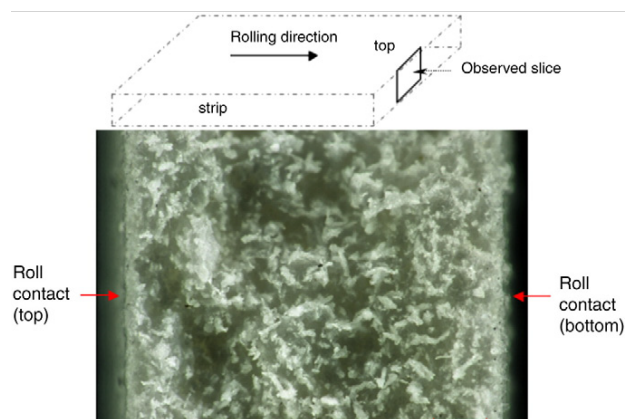


Fig. 1.14. Micrograph of MCC ribbon surface (plane surface area cut through the thickness). View obtained using a numerical microscope (Keyence® France) (Michrafy et al., 2011b)

These results outlined the complexity of the process and the effect of powder properties on final properties of roller compacted ribbon and highlighted the importance of controlling the density distribution on the three dimensions of the ribbon (width, length and thickness).

### 1.2.3.2. Heterogeneity of roller pressure

The roller force is applied by the rolls to densify the material. Depending on the powder properties and the design of the roll press, the powder will deform under a

distributed pressure on the ribbon surface. The knowledge of how the roller pressure is distributed is one important factor for understanding the resulting density distribution discussed before.

The heterogeneity of roll pressure was demonstrated in the work of Cunningham et al. (2010) during the roller compaction of MCC powder. Using an instrumented textured roll (100 mm of diameter and 35 mm of width) with five sensors across the width, it was showed that the location of overall maximum roll pressure varied from across the roll width on both sides of the center. The movement of the position of the overall maximum roll pressure across the width was related to the rotating nature of the screw feeder. Results of this study are plotted in Fig. 1.15.

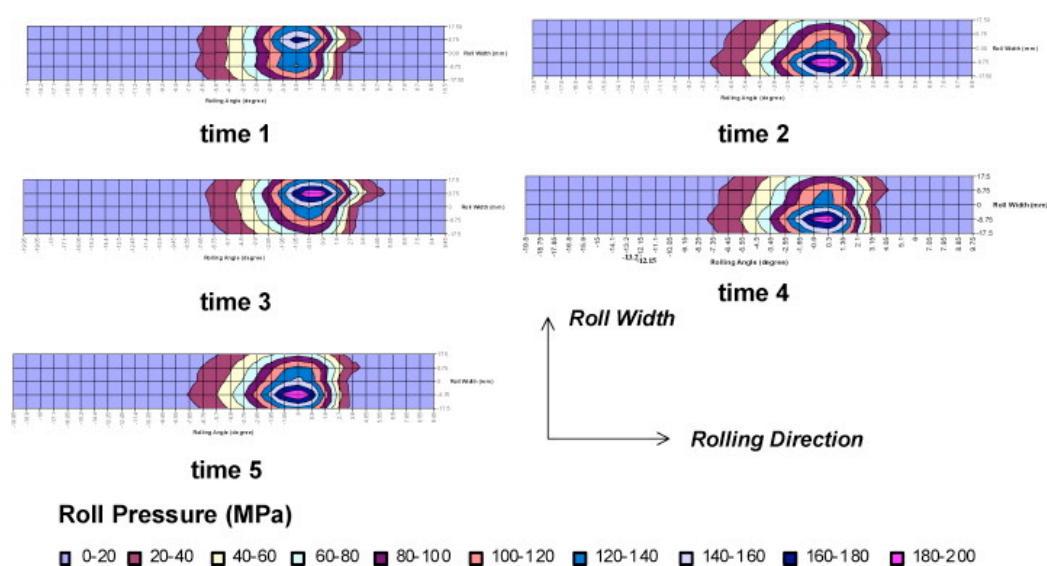


Fig. 1.15. Contours of roll pressure with respect to rolling directions and roll width. The middle of the roll along its width is designation of 0mm. Time 1–5 represent five successive revolutions.

The heterogeneity of pressure over the roll width was also observed in the work (Nesarikar et al., 2012) during the compaction of a placebo (blend of microcrystalline cellulose and anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate) using an instrumented knurled roll installed on a roll press. It was noted that normal stress values on roll side were lower than the normal stress in the middle and showed greater variability than the measured stress in the middle. This is attributed to heterogeneity of feeding pressure in the last flight of the feed screw. However, in the investigations of Lecompte et al., 2005, on the roll compaction of organic powder using a roll press equipped with large-sized smooth rolls (240 mm diameter and 50 mm width) and horizontal helical feed screw, the measured maximum pressures for several consecutive rotations did not show variation over the roll width. Moreover, with an increase of feeding rates, the pressure distribution gets more

homogeneous. This result was explained by the fact that the screw was positioned further from the rolls.

### **1.2.3.3. Trapped air into powders**

The air entrapped in the powders is another challenging problem for the process. Particularly for fine powders, the amount of air can have significant effects in the production. This problem is often emphasized in the literature but few works have been addressed. Indeed, compaction creates an air transport away from the compacted zone through the feed zone (Vinogradov and Fedorchenko, 1961). This in turn generates a pressure gradient that can disturb the incoming flow. In the case of gravitational feeding, where particles are only subjected to their own weight, it can even result in the fluidization of the particles, which totally disorganizes the press feeding. The gap starts to increase or decrease as cycles of fluidization/consolidation of the feed arise (Schwechten and Milburn, 1990). Screw feeding allows for greater tolerance to airflow but it is eventually disrupted by the pressure gradient (Johanson and Cox., 1989). Such instabilities are detected by significant fluctuations in gap, roll pressure and torque, and in some cases by vibrations and a popping noise generating rattling in the whole drive system (Dec, 1995).

### **1.2.3.4. Scalability of the process**

The scalability of the process is considered as the major obstacle to massive employment of the process in pharmaceutical industry. Indeed, as the cost of the active ingredients is expensive, it is necessary to develop the product at laboratory scale and then move to the pilot or production scales by ensuring the same quality of the product. However, this operation is often done by trial and error.

A common method to scale-up the compaction process is to use a parametric strategy, obtained from previous experiments, using equivalency factors to pass from a roll-press to another (Sprockel, 2010). Inherently, roller compaction is challenging to scale up, due to the availability of multiple configurations.

The scale-up can be understood in two senses: from one press with certain characteristics to another of the same scale but with other configuration or from one press to another with larger scale.

The strategy of scaling-up roll compaction differs between the suppliers. Gerteis, for example, offers roll-presses with the same diameter but varying the roll width. On the other hand, other suppliers (Alexanderwerk, Freund-Vector) increase the diameter of the rolls. However, the increase of the roll diameter results in a greater densification area as the nip angle is independent from the roll diameter (Fig. 1.16).

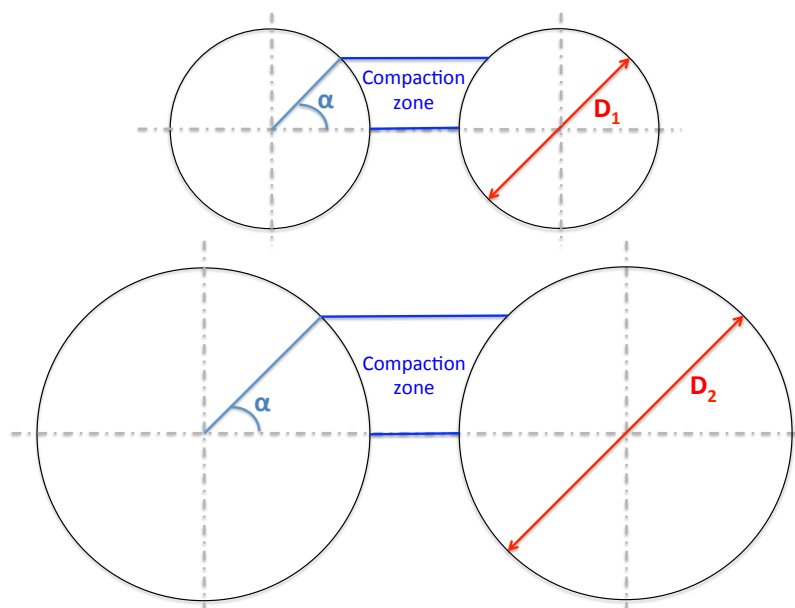


Fig. 1.16. Comparison between the compaction zone of two roll-compactors with different diameter

Most of the scale-up models are based on Johanson's model (Reynolds et al., 2010a, Nesarikar et al., 2012). Johanson (1965) proposed that the compaction force could be determined from the pressure distribution profiles on the rolls, which are dependent of nip angle. Therefore, a simple power-law relationship established a relation between the ribbon density and the compaction force. Nevertheless, the calculation of the roll force from the pressure on the nip angle may not be precise. Later, Reynolds et al. (2010a) presented a practical approach for roller compaction process modelling and scale-up, which improved Johanson's approach. In this case, the peak pressure was used to calculate the roll force. Also based on Johanson model, Nesarikar et al. (2012) developed an approach, using the roll force equation from Johanson, in which the requirement of pressure value at nip angle was eliminated. The roll force equation was validated using normal stress, gap, and nip angle data of the placebo runs. The model was capable of predicting the ribbon density as a function of gap and the roll force.

From the experimental point of view, very little attention has been given to using the data previously obtained to propose scale-up models. Sheskey et al. (2000) performed experimental scale-up study of a model drug formulation. They used three compactors from laboratory scale to full-scale production equipment (from Freund-Vector company). The samples were prepared using similar range of linear compaction force but different roll speeds. Results showed that the roll force and speed scaled directly and the tablet crushing strength increased from laboratory through pilot-plant to production trials. All tablets, regardless of equipment scale, exhibited acceptable physical properties.

Lui et al. (2011) used the historical data from a laboratory-scale roller compactor and a full-scale roller compactor to build a Joint-Y Partial Least Squares (JYPLS) model to estimate the required conditions of the process to yield a desired set of properties in the final product, in this case, the ribbon density. This model was then used for scaling up several grades of ribbon. The results confirmed that the methodology can provide very good scale-up of drug formulations and machine settings between two roller compactors from Fitzpatrick company. An iterative approach to scale-up was also proposed for extrapolations to new formulations. Also Souihi et al., (2015b) developed a latent variable model for both the horizontal and vertical fed roll compactors to express ribbon porosity as a function of geometric and process parameters. The model validation, performed with new data, resulted in overall good predictions.

Recently, Boersen et al. (2015) proposed a dimensionless variable for the scale-up and transfer the operating parameters of a formulation between two different pieces of equipment. They hypothesized that ribbons of the same porosity made with different equipment have similar properties and that it is possible to establish an objective relationship between ribbon porosity and a combination of operating parameters and raw material attributes. They found a dimensionless variable to correlate the ribbon porosity and the operating parameters for the formulations and equipment used in their experiments. However, this variable should be further investigated in other equipment of different manufacturers, larger scale processes or different formulations.

The development of methodologies to scale the process is a challenge of high importance for pharmaceutical applications. This could be studied through multi-disciplinary skills. There are some propositions of models based on empirical approach for a specific material and roller press. Up to date, there are no predictive models able to scale up roller compaction process.

#### **1.2.4. Conclusions**

The works cited above demonstrate a significant progress on the study of the system designs and the operational parameters of roll-compaction. Notable improvements have been done in instrumentations and measurements to better understand the process.

From the literature, the resulting properties of ribbons were described through the experimental results. It was highlighted that the properties of the ribbons (mainly the density distributions) depend on both raw material properties and process parameters. The relation between feed powder, roll-compaction and ribbon is complex and some challenges were reported and summarized. Particularly, results highlighted the role of the powder particle size, the effect of the feeding conditions, sealing system layout, processing parameters (i.e. roll pressure, roll gap and roll speed).



The heterogeneity can be obtained along the ribbon length (caused mainly by the feeding system), along the ribbon width (caused by the sealing system) and the ribbon thickness (caused at large gaps). This characterization can help in the understanding of the results in the subsequent stages of the process.

In addition, mathematical models, like Johanson model, have been developed to improve the process design. The scale-up of the process is still not fully understood due to the multiple possibilities of operation. Nevertheless, experimental and numerical progresses have been done in this aspect.

## 1.3. MILLING PROCESS AND CHARACTERIZATION APPROACHES

### 1.3.1. Milling process technology

Milling is the mechanical process of reducing the size of particles or aggregates. During milling, the material is strained, crushed and reduced in size through the application of mechanical stresses. In general, the step of milling after roll-compaction consists of an impeller in proximity to a screen (Sprockel, 2010), where the material is subjected to different fracture mechanisms:

- *Impact*: The force is applied normal to the surface of the agglomerate. It receives collisions that cause its breakage into smaller particles/agglomerates.
- *Shear*: Also known as attrition force, where the force is applied parallel to the surface of the ribbon.
- *Compression*: The pressure applied on the ribbon against the screen or other agglomerates causes the breakage.

As a porous material, depending on the dimensions of the body and the level of force applied, various mechanisms of milling can take place at the same time during the milling step. Firstly, the ribbon fractures by impact and, then, the smaller pieces are submitted to shear-compression forces. When the stress is high, the breakage of the aggregate into smaller fragments takes places. If the force is lower, compression is the main cause of breakage (Seibert, 2010).

With the continuous manufacturing in mind, it is necessary to integrate the mills in the process in an effective and optimal way, developing predictive understanding of the milling mechanisms and their product properties, like particle size distribution. The considerations to choose the type of milling system should be based on the desired characteristics of the product (granules), but also on the properties of the precedent ribbons. The ribbons should be strong enough to be fractured in the form of granules and not into fines. In an ideal pharmaceutical milling process, the residence time in the chamber should be short and the capacity large and the integrity of granules should be kept after passing the mill screen (Vendola and Hancock, 2008). Hard materials need a longer residence time and produce coarser particles in combination with fine particles.

The milling process is decisive in dry granulation in order to control the particle size distribution. Until now, the process of milling is still poorly understood due to the complexity to relate the physical phenomenon with the obtained product properties.

### 1.3.2. Process parameters and granules properties

The most important resultant property of the milling step is the granule size distribution (GSD). In order to improve the efficiency of dry granulation by roll compaction, it is required to control the granule size through the selection of an appropriate milling system and optimal milling conditions. In general, a specific granule size must be achieved and the amount of fines, which is the most important parameter influencing flowability, should be limited especially when active ingredients are involved in the formulation. The amount of fines should be minimized not only during roll-compaction (produced due to powder leakage) but also during the milling step. Therefore, measuring the amount of fines appears to be a good characterization method to evaluate the effectiveness of a combination of parameters.

- *Selection of the mill type based on the GSD*

In most of the pharmaceutical applications, low-energy mills are used for size reduction. Normally, during roll compaction, the size reduction of ribbon takes place in a conical mill or an oscillating granulator, which can be also integrated in the roll compactor to mill the ribbons in a continuous way, right after being compacted. Some authors evaluated different milling technologies and tried to understand their effect on the properties of granules, mainly focused on the particle size distribution.

Vendola and Hancock (2008) evaluated the effect of various mill types on granules properties such as particle size distribution, flowability, tableability and compactability. Four mill types were selected: oscillating (integrated with the Gerteis roller compactor), conical (Comil), hammer mill (Fitzmill) and a no-attrition size-reduction mill (Gran-U-Lizer) which controls the particle size reduction through the roll compaction variables (surface, roll speed, gap...). Two formulations were used: MCC-Lactose and MCC- dibasic calcium phosphate (DCP). The major difference between the conventional mill types and the Gran-U-Lizer was the requirement of several passes for the last one (under different conditions) to achieve the desired particle size distribution. The results showed up that Gran-U-Lizer produced the largest particles and that the mill type does not have a great influence on the tableability. Overall, not the mill type but the formulation composition had the most significant effect on the obtained properties.

In their patent, Woldu and Cunningham (2008) developed a method for dry granulation to improve the flow characteristics and to reduce the amount of fine particles. They reported that using an oscillating granulator (from Stokes or other manufacturers), coarser granules are produced comparing to Comil or Fitzmill.

Sakwanichol et al. (2012) evaluated the granules properties obtained from an oscillating granulator and a roll mill. They varied four oscillating-granulator parameters i.e. rotor

speed, oscillating angle, aperture of mesh screen and rotor type, and six roll-mill parameters, *i.e.* throughput, speed ratio in both first and second stages, gap between roll pair in both stages and roll-surface texture. They compared the granules with similar median particle size from both mills. For an oscillating mill, they concluded that all the examined parameters affected significantly the granule size distribution. However, the rotor types of the oscillating granulator did not affect the amount of fine particles.

- *Milling settings and GSD*

The main operational parameters affecting the milling process are the screen size and thickness, the impeller shape, the rotation speed, the angle of rotation and the mill-chamber capacity.

The milling paradox has been observed in several studies (Verheezzen et al. 2004; Schenck and Plank (2008); Reynolds, 2010b). Basically, under the same milling conditions, smaller pieces of ribbons give coarser milled product. They suggested that this is due to the mechanisms of impact breakage, which produces a large amount of fines. For a given screen aperture size, a coarser input requires more impact breakage before the fragments become small enough to be able to pass through the mill screen.

Regarding the evaluation of the different parameters during the milling operation, several authors analysed their effect mainly based on the results of the granule size distribution and they are detailed below.

Motzi and Anderson (1984) investigated some processing variables associated with the comminution of pharmaceutical granulations (aspirin). A conical mill (Comil®) was used and the influence of the screen size, the mill speed and impeller shape were evaluated. The authors performed an analysis of variance of the experimental results and it indicated that there is a statistically significant effect of all the variables and they interact to determine the milled granule size distribution.

Verheezzen et al. (2004) investigated the effects of the formulation and the influence of the mill settings in an impact mill. The granulates were prepared in a high shear granulator with different types of lactose, corn starch and different amounts of hydroxypropylcellulose as a binder. The mill settings that were varied were: impeller speed, screen size and screen type. In order to quantify the degree of milling, a size reduction ratio of the mean size (SRR), relating the proportion between the granules before and after milling, was calculated. Regarding the formulation, the results showed that a decrease in the particle size of the feeding powder or an increase in the amount of binder had an effect in the breakage behaviour; which was translated into a decrease in the SRR. Attending to the particle size of the milled, the most influent parameter was the mesh size. The results exhibited the size reduction paradox that coarser

particles are obtained when the mill is fed with smaller agglomerates. The milling settings had not a big influence in the production of fine particles independently, but to reduce this formation, multiple milling steps with separation of in-size particles was necessary.

Schenck and Plank (2008) investigated the milling of agglomerates in wet and dry state in a conical screen mill. They reported that the fundamental mechanism governing dry granule breakage was impact attrition. The results showed up that, for both wet and dry milling, the mill screen did not play a dominant role in determining the mode of agglomerate breakage.

Samanta et al. (2012) evaluated the effects of various process parameters (impeller shape, impeller speed and screen surface) for roll compacted flakes of a blend of MCC, lactose and MgSt in a conical mill. The mill was operated at five different speeds. For the comparison, two types of screen surface profile, grater and smooth (Fig. 1.17), and five different impeller shapes (Fig. 1.18) were evaluated.

Regarding the screen surface, Samanta et al., found that the grater screen consistently produced granules with significantly larger median diameter ( $d_{50}$ ) than the smooth screen at different impeller speeds for the same type of impeller. This was in agreement with the results of Schenck and Plank (2008) where screens with grater surface texture produced fines.

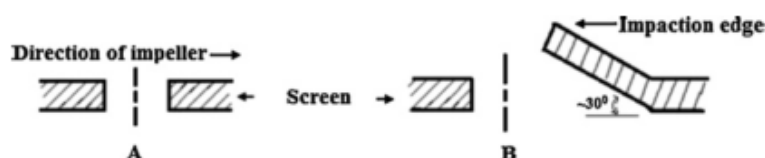


Fig. 1.17. Surface profile of screens (A) smooth and (B) grater (Samanta et al., 2012)

Fig. 1.18 shows the size reduction mechanism related to the each shape of impeller. Round impeller traps the flakes in between the impeller and the screen, allowing compressive forces on the screen surface to eject smaller flakes. If teeth are added to the round impeller, a pre-breaking step takes place. The size reduction mechanism of triangular impellers was the high shear force due to the presence of a sharp edge. Although the pyramidal impeller has edges as well, the presence of a flat face produces low shear action and, therefore, smaller granules than the triangular impeller. If a leading edge is added to the pyramidal shape, compressive forces are acting but reducing the ability to efficiently break the flakes.

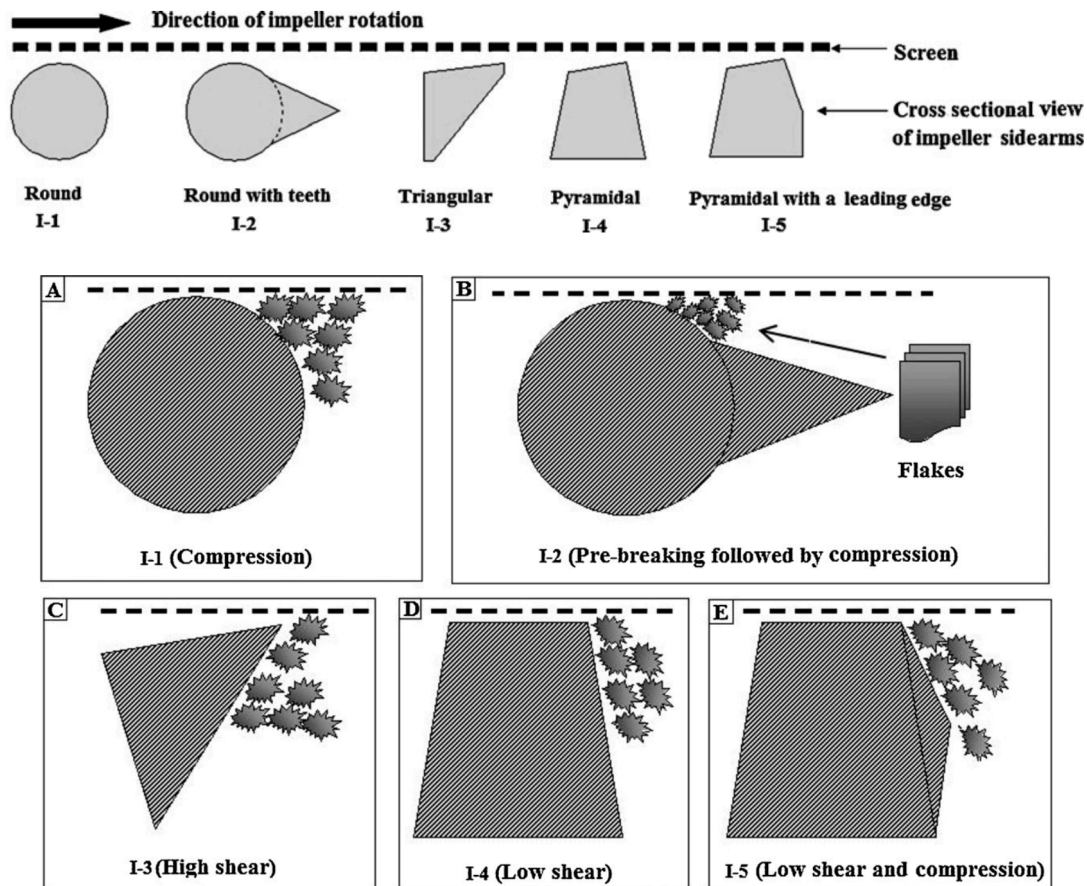


Fig. 1.18. Shape of impeller and size reduction mechanisms depending on the shape (Samanta et al., 2012)

Both screen type and impeller shape play important roles on the characteristics of milled granules. The particle size and the production of fines were evaluated. The differences in the granules sizes produced by different impellers were relatively small when grater screen was used but the granules sizes become large when the smooth surface was used. The smooth surface had an influence when rounded impeller were used, but not for triangular and pyramidal ones. The effect of impeller sidearm shapes, screen types and impeller speeds on the amount of fines (%) results in a higher production for smooth screen than for grater. However, the smooth screen performance was comparable with the grater screen when the round impeller with teeth was employed. This type of impeller produced the lowest amount of fines. It was found that the combination of round impeller with teeth and grater surface is the best option for the production of granules.

In order to model the milling performance, some authors have used population balance models to simulate the change in the granule size distribution as the result of granule breakage. Reynolds (2010b) developed a model for particle size reduction in a conical mill. The model for granule breakage required identifying a suitable break- age rate

constant and a breakage function (or fragment distribution). A fragment distribution that captured both the localised disintegration and multiple fragmentation modes of agglomerate impact breakage were proposed. The model accurately describes the milled granule size distribution. Moreover, the results are consistent with the literature observations as the reduction paradox, where by coarser input material results in increased generation of fines.

### 1.3.3. Ribbon properties and granules properties

The granules properties depend directly on the properties of the ribbons and they are highly influenced by the roll-compaction force. In this context, various researchers studied the dry granulation of excipients at different roll-compaction forces and showed clearly a decrease of the amount of fines by increasing the roll pressure (Freitag and Kleinebudde, 2003; Herting and Kleinebudde, 2008; Wagner et al. 2013). As it is shown in Fig. 1.19 (from the work of Herting and Kleinebudde, 2008), the median granule size increased with the specific compaction force, whereas the amount of fines was decreased (28.2–7.5%). This was mainly due to stronger ribbons with lower porosity.

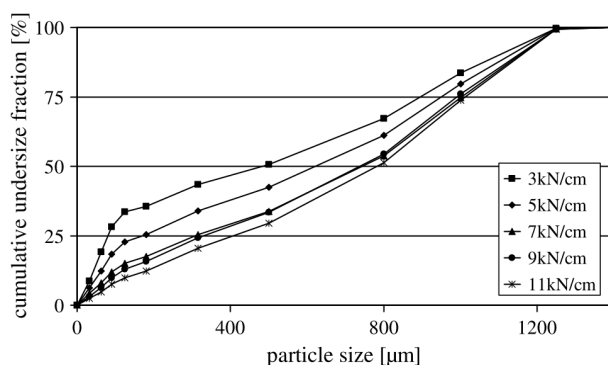


Fig. 1.19. Particle size distribution roll-compacted MCC 101 at different specific roll-compaction forces (Herting and Kleinebudde, 2008)

### 1.3.4. Conclusions

In this section, the main mechanical process of reducing the size of agglomerates was reviewed together with the effect of the milling process parameters on the granules properties.

Nevertheless, the results are sensitive to changes in the properties of feed material, the formulation and parameters. Although size reduction has been lately investigated, there is still a need of deeper understanding of the following points:

- Which kind of stress is applied to the ribbon to converted into granules? It will depend on operational parameters such as the impeller shape, the speed, the gap between the impeller and the screen,...
- How to measure the stress? The characterization of the breakage of the ribbon under different kind of stresses is still a challenge.

Results from the literature highlighted that the granules size distribution (GSD) is the most important property of the milling step. Diverse studies analysed the effect of different milling systems and operational parameters in order to control the GSD. The ultimate goal of these studies was to minimize the production of fines and hence to improve the flowability of the produced granules. In these studies, the proportion of fines was linked to the bulk density of the ribbon and/or the applied forces. However, the origin of the fines and their link with the ribbon properties and the roll-compaction parameters is still poorly understood.



## 1.4. MECHANICS OF DIE-COMPACTION AND MODELING

Successful compaction and tableting of pharmaceutical powders requires an understanding of the fundamental properties of powders and how they behave during tablet processing. After the powder filling, powders go through different stages during the compression cycle: initial packing and rearrangement of particles, formation of temporary structures, elastic deformation, plastic deformation and breakage of particles, bond formation, and consolidation, followed by elastic recovery during the decompression process (Train, 1956; Huffine and Bonilla, 1962) These mechanisms can happen sequentially or in parallel.

The Fig. 1.20 shows the different steps of the compaction process. Basically, after filling the powder into the die, a force is applied on the powder bed in order to reduce the volume and to form bonds between particles (loading step). After that, the load is released and the compact is ejected out of the die. With an instrumented press, the resulting compaction cycle as shown in the Fig. 1.21, shows a signature of the powder behaviour. The purpose of this section is to review the recent works on the compaction behaviour of dry granulated powders including experimental characterizations and modelling approaches.

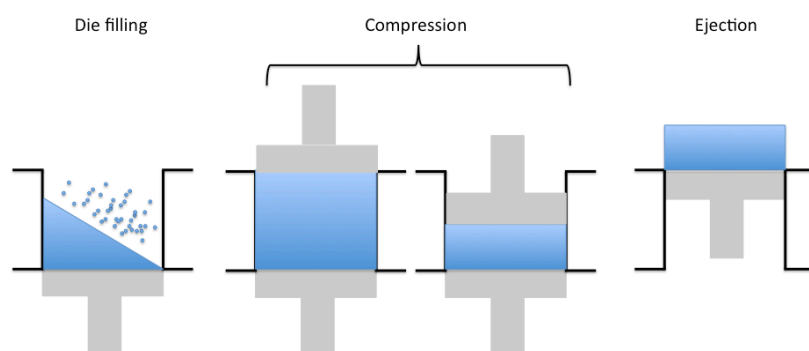


Fig. 1.20. Die compaction process

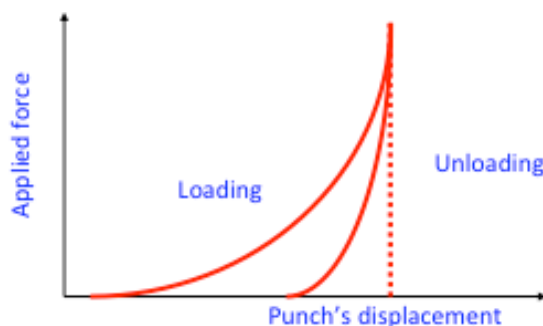


Fig. 1.21. Compaction cycle

The material property that predominantly affects the tableting of powders is the deformation behaviour of powder under stress. The stress-deformation state developed in the tablet depends on the magnitude of applied pressure, the contact time (dwell time), the speed, and physical properties of the material. To better understand the mechanical properties of materials, information about particle deformation behaviour in terms of compressibility (ability of material to undergo volume reduction under pressure) and compactability (ability of material to yield and compact with adequate strength) of the material are provided. In this context, the difference in compaction behaviour of raw material and the corresponding dry granulated powders are not completely understood, particularly the effect of the granulation on the rearrangement, the plastic deformation and properties such as tensile strength. Probably, the progress in this way has to go through the analysis of the compaction mechanisms of granulated powders by experiment and modelling.

#### **1.4.1. Compaction behaviour of granulated powders**

The deformation behaviour of powder under stress is one key factor that determines the densification process and the tablet properties. Indeed, properties such as particle size distributions, microstructure, specific surface, shape and strength are essential in the understanding of the compaction behaviour of granulated powders, in particular, compressibility, compactability, strength, friability or disintegration properties.

Significant progress has been recently made in the characterization and modelling in order to better understand the compaction behaviour of granulated powders, mainly for pharmaceutical and ceramic applications. The compaction mechanisms of dry granulated powders and the loss of compactability are reviewed and discussed. The focus here is not only for granules from roll-compacted pharmaceutical powders, but also for granules from other materials and processes.

##### **1.4.1.1. Granules compaction effects on rearrangement and plastic deformation**

Understanding how granulated powders behave during die compaction and why they exhibit different behaviours from those showed by the raw material is still a challenge. Tablet formation depends on particle rearrangement and on the densification of the particulate material. As described by Cooper and Eaton (1962), the rearrangement consists of filling the holes of the same order of size as the original particles. This occurs primarily by particles sliding past one another. After, the remaining voids (substantially smaller than the original particles) can be only filled by plastic flow or by fragmentation. Plastic flow is more efficient than fragmentation because material is

always forced into the voids. Considering this, Cooper and Eaton developed an equation (Eq. 1.1) to describe the compaction process by two largely independent probabilistic processes in terms of the reduction of volume ( $V$ ) as a function of the applied pressure ( $P$ ). The first term corresponds to the compaction behaviour due to the filling of holes by the movement and rearrangement of powder particles in the early stage. The second term indicates the compaction behaviour by the plastic deformation of the particles.

$$V^* = \frac{V_0 - V_p}{V_0 - V} = a_1 \cdot \exp\left(\frac{-k_1}{P}\right) + a_2 \cdot \exp\left(\frac{-k_2}{P}\right) \quad (\text{Eq. 1.1})$$

where  $V_0$  means the initial total volume at zero compaction pressure (no holes filled), and can be calculated by using the apparent density of each particle.  $V_p$  means the volume of the green compact when all large holes, but no other holes, are filled.

The dimensionless coefficients,  $a_1$  and  $a_2$ , indicate the fraction of theoretical compaction that would be achieved at infinite pressure by each particular process. Their total ( $a_1 + a_2$ ) equals unity when compaction can be completely described in terms of two separate processes. The coefficient “ $k$ ” corresponds to the magnitude of the pressure at the start of each compaction behaviour (rearrangement or plastic deformation).

Kondoh et al. (2000) used this equation to analyse the compaction behaviour during the consolidation of granulated powder and raw of an aluminium alloy powder. The granulated aluminium alloy powder was produced in a fluidised bed wet type granulator, using polyvinylalcohol (PVA) aqua as a bonding binder. Even if this process is different from the dry granulation, in terms of deformation, the densification process of granulated powders obeys to similar rules. All the coefficients were calculated by a non-linear optimizing method with the compacting test data of the relationship between the applied pressure and the compaction volume. This analysis enables the evaluation of the effects of the above two compaction mechanisms on the fractional compaction volume quantitatively. The authors showed that, the  $a_1$  value of the granulated powder is larger than that of the raw powder and decreases in proportion to the increasing apparent density (Fig. 1.22). This is because in feeding the powder with a small apparent density (granules) into the die, the pores between the powder particles increase. When pressing the powder in the die, it easily moves owing to the filling of such pores. Accordingly, Kondoh and al. demonstrated that the particle rearrangement effectively contributes to the compaction behaviour in that the apparent density decreases.

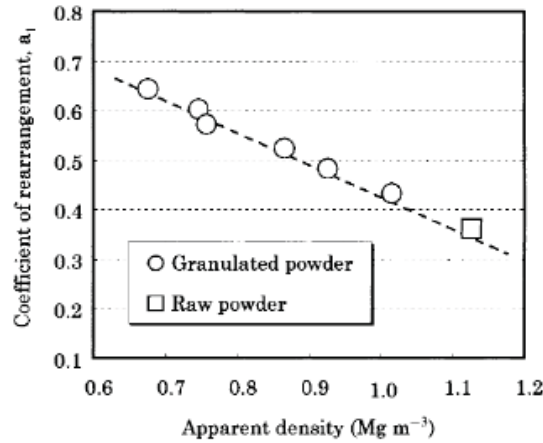


Fig. 1.22. Dependence of coefficient of rearrangement calculated by conventional Cooper–Eaton equation on apparent density of powder [Kondoh et al., 2000]

They also showed that the traveling of the granulated powder during the compaction is large at a comparatively low compacting pressure range up to 100 MPa (Fig. 1.23).

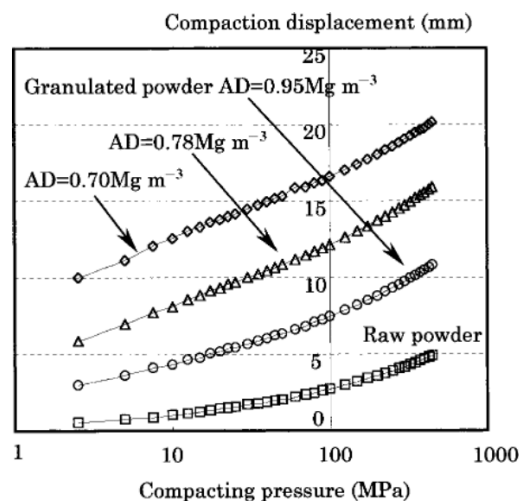


Fig. 1.23. Compaction displacement vs pressure for raw and different granulated powders (Kondoh et al., 2000).

The compaction behaviour of the granulated powder at a low compacting pressure is relative to the filling of both intrapores (the large pores between the granules) and interpores (small pores between particles of raw material into the granule). Accordingly, a new model for the compaction behaviour of the granulated powder was proposed as the schematic shown in Fig. 1.24. First, macroparticle rearrangement and microparticle rearrangement are dominant when applying a low compacting pressure. The former indicates the movement of powder by filling up intrapores between granulated powders. The latter occurs by filling up interpores in the granulated

powder. Second plastic deformation or fragmentation of the primary raw particles in the granulated powder occurs at high compacting pressure.

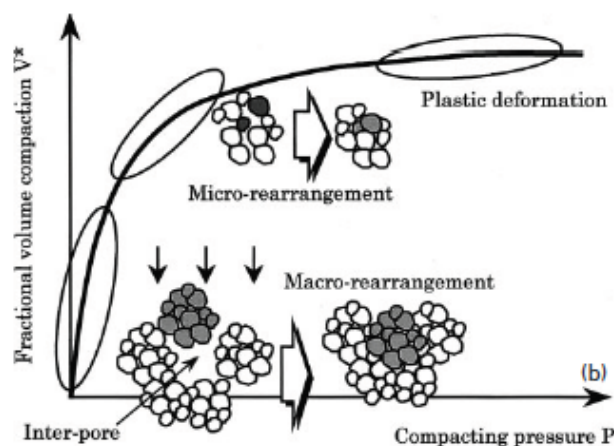


Fig. 1.24. Densification process for granulated powders (Kondoh et al.,2000).

#### 1.4.1.2. Granules compactability

After die-compaction, tablet characteristics such as tensile strength are generally measured. Roll compaction process has been reported to reduce the tensile strength of granulated tablets. This phenomenon of reduced tensile strength after roll-compaction is known in the literature as “loss of reworkability” or “loss of compactability”. This was first described and attributed to work-hardening by Malkowska and Khan (1983), concluding that the first compression step limits the binding potential of granules. Many researchers have worked on understanding the influence of the raw materials on the phenomenon of “loss of reworkability”. Although no mechanism for the compaction granules has been universally accepted, two critical material attributes are highlighted to be critical for this effect: the mechanical behaviour of the powder and the particle size.

Regarding the mechanical behaviour of the material under compaction, it has been demonstrated that the loss of compactability is more significant for plastic materials (Falzone, 1992, Sun & Himmelpach, 2006). Plastic materials are more sensitive to roll compaction process due to the consumption of binding potential in the first compression step by modifying properties such as specific surface area, that plays an important role in the bonding propensity. On the other hand, brittle materials show, in general, lower tensile strength than plastic materials, and they are less sensitive to granule size enlargement by roll compaction due to the fact that the extensive fracture of brittle granules (fragmentation behaviour) during compaction minimises the differences in granule size (Wu & Sun, 2007).

Nevertheless, Malkowska and Khan compared feed powders with granules of the same sieved fraction, assuming for both cases the same particle size distribution. Therefore, the theory of “loss of reworkability” or work-hardening excluded the impact of a possible different particle size distribution without a direct evidence of hardening of powders and granules due to the difficulties of measuring the hardness of individual particles.

Sun and Himmelpach (2006) further investigated this fact. They used different grades of MCC and compared non-compacted and compacted material. The larger particles always resulted in lower tabletability. The compactability of granules was similar to the feed powder with the same size distribution. Moreover, granules of smaller size showed greater compactability than a feed powder with larger size. Thus, they hypothesized that the granule size enlargement is the primary mechanism to the reduction of tensile strength. Herting and Kleinebudde (2007) continued in this direction of investigation. They roll-compacted binary mixtures of MCC and theophylline. Results showed that a decrease in particle size of MCC or theophylline resulted in an increase of tensile strength, even after roll compaction. The tensile strengths of tablets made from bigger feed powder were comparable to the ones made from granules with small sized MCC. One year later, they reconsidered the statement by Sun and Himmelpach in their work: Herting and Kleinebudde (2008). The authors roll-compacted MCC of different particle sizes at different roll-compaction forces (Sun and Himmelpach performed their experiments at a constant compaction force). In contrast with Sun and Himmelpach, they proved that after a mechanical process (dry granulation) the resistance of the material towards plastic deformation was increased. Thus, they claimed that the particle size of the feed powder is important but the work-hardening effect also causes the partial loss in compactability. The use of feed powders with small particle sizes or producing smaller granules can counterbalance the reduction in tensile strength.

Contrary to these statements, Kuntz et al. (2011) reported that the roll compaction induced an increase in compactability for acetames. This increase in tensile strength was associated with an increase in the specific surface area after roll-compacting these materials. For this reason, they proposed to take into account the surface activation by roll compaction as an additional impact factor on the compaction performance of acetames.

The tablet properties are also affected by the roll-compaction parameters such as the roll-compaction pressure applied. The higher the roll-compaction force, the denser the ribbons and, consequently, the granules. Harder granules show more resistance to be compacted. The previously mentioned effect of “loss of reworkability” is then highly influenced by the roll-compaction force exerted. As it was reported by Herting and

Kleinebudde (2008), an increase in the compaction force is translated in a reduction of tensile strength (Fig. 1.25). This observation supported the theory of “work-hardening”, proving that after mechanical treatment, the material increases the resistance towards plastic deformation.

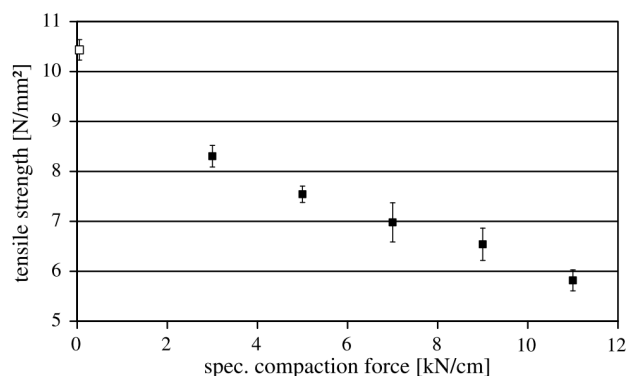


Fig. 1.25. Tensile strength of roll-compacted MCC 101 at different specific roll-compaction forces (Herting and Kleinebudde, 2008).

The compaction behaviour of granulated powders was also studied by Kenedy et al. (1997). Using model granules produced from pharmaceutical powders, a mechanism for their compaction was established and then applied to ceramic granules obtained by different granulation technics such as spray drying, slugging and agitating to produce granules with different properties. Basic properties such as granule size and size distributions, granule shape, specific surface area and apparent specific volume were measured and considered in the analysis of the compact’s strength. They concluded that, in general, granules with higher specific volume lead to higher compact’s strength. Granules with a low specific area and large pores leads also to higher strength while granules with high specific surface area and small pores result in low strength compacts. Finally, in this study, the authors showed that the number and size of pores present in the granules influenced the mechanism of compaction. Larger pores led to a greater degree of compaction. They demonstrated also that the compaction behaviour of selected ceramic granules was similar to that of the pharmaceutical materials studied.

Recently, Mitra et al. (2016a) analysed how the granule solid fraction impacts on the compaction behaviour of plastically deformable granules of microcrystalline cellulose (MCC). The analysis was based on the calibration of the model parameters of Drucker-Prager Cap. For that, first, small cylindrical compacts (minitables of 1.5 mm diameter and 1.5 mm thickness) with solid fractions in the range of 0.40 to 0.70 were used as model dry granules, which were monodisperse in both size and solid fraction. Then, raw material and granules were compressed into tablets with relative density in the range of

0.70 to 0.90. Results showed that both virgin MCC and monodisperse granules required the same in-die compaction stress state to achieve a certain tablet density. It was also found a decrease of the cohesion of tablets formed from the granules in comparison with the feed powder. They stated that the reduced strength of tablets formed from granules is due to the less uniform microstructure formed than as the result of strain hardening. However, in this study, the granules were small cylindrical compacts, monodisperse, probably have compaction behaviour different from that of roller granules where the shape and the microstructure are certainly different.

Mitra et al. (2016b) also investigated the impact of the granule composition on the compaction properties based also on DPC analysis. Dry granules of the same solid fraction were prepared in the same manner as before but using binary mixtures (MCC and mannitol) as formulation. Results showed that, properties such as cohesion and diametrical tensile strength go through a maximum as the mannitol level increases in the binary mixture. It was proved that these properties do not follow a simple linear mixing rule. At high tablet density, the granules with a high percentage of mannitol exhibited the highest cohesion, and produced the strongest tablet. Nevertheless, these suggestions are valid when granules of the same characteristics are produced. In both studies, Mitral et al., produced monodisperse granules to avoid the difference caused by the variation of solid fraction and size. However, the process differs from the real production of roll-compacted granules.

### **1.4.2. Conclusions**

The works cited above demonstrate a significant progress in understanding the mechanisms of the compaction behaviour of granules. Properties such as granule size and size distributions, granule shape and specific surface area have the main effects on the densification of the granules under pressure. These effects occur during the rearrangement stage and plastic deformation. Significant differences have been found when comparing properties of tablets produced from raw material and granules. In most of the cases, it was clearly identified a reduction of tensile strength of tablets compacted from granulated powders, even though some specific studies showed the inverse for certain powders (Kuntz et al., 2011). Up to date no really general theory is prone to predict the compaction behaviour of granules. A jump in the technical characterization by, for example, the simultaneous combination of compaction and X-Ray Tomography analysis of the densification process, will certainly allow us to advance in the understanding of these multi-scale phenomena.



## 1.5. CONCLUSIONS

In this chapter, the fundamentals of the dry granulation by roll-compaction process have been presented. Roll compaction is generally combined with milling and tableting processes. The understanding of the roll-compaction process is essential but also the understanding of the other two downstream processes, in order to control the quality of all intermediate and final products. Although many interesting research efforts have been made (experimental and numerical), the understanding of the process is still limited due to the complex interrelation of feed powder-process-products.

A review on the system designs of the equipment and the operational parameters has been presented. The resulting properties of ribbons, granules and tablets were described through the experimental results. The relation between feed powder-process-product is complex and some challenges were reported and summarized, together with perspectives to be investigated. Two material attributes resulted critical: particle size and mechanical characteristics of the powder (elasto-plastic, brittle,..). The election of the materials that composed a formulation should be based on its properties and quality by design should be incorporated in order to be able to make prediction when new raw materials are used.

Multiple configurations of roll-compactors are available. Many researchers worked on the analysis of the effect of the feeding conditions, sealing system layout, processing parameters (i.e. roll pressure, roll gap and roll speed). Mathematical models, like Johanson model, have been developed to improve the process design. The scale-up of the process is still not fully understood due to the multiple possibilities of operation. Nevertheless, experimental and numerical progresses have been done in this aspect.

Through the literature results concerning roll-compaction, it was highlighted that the control of the ribbon density distribution have attracted considerable attention. The heterogeneity can be obtained along the ribbon length (caused mainly by the feeding system) and along the ribbon width (caused by the sealing system). This characterization can help in the understanding of the results in the subsequent stages of the process.

During the milling step, the most important resultant property is the granule size distribution. Different fracture mechanisms were presented. In general the amount of fines should be limited especially when active ingredients are involved in the formulation. The control of the percentage of fines looks a good method to control the quality of the milling. Further investigation on the understanding how to relate the milling mechanisms with the granules properties needs to be done.

Regarding the die compaction, it was highlighted that the most challenging limitation of using the roll-compaction process is the “loss of reworkability”, which is traduced in an inferior tensile strength of tablets. The mechanism of work hardening was proposed to explain the loss in compactability. The understanding on how the stresses are distributed within the die can help the understanding of this effect. It was highlighted the importance of investigating this phenomenon in order to better understand the modification of behaviour, in terms of compressibility and compactability, of the pharmaceutical powders after roll-compaction under diverse conditions.



## Chapter 2.

# Materials and experimental procedures

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### Abstract

*In this chapter, the materials and devices to produce samples (ribbons, granules and tablets) are presented. This concerns roll-presses, milling systems and presses for die-compaction. Then, the characterization techniques are described to measure properties such as ribbon density, particle size distributions and tensile strength, among others. With the perspective of better understanding the compaction behaviour of granulated powders under complex stress, Drucker-Prager Cap model was selected and the procedure for its calibration based on experimental data is included. Both, feed powder and granules, were compared using this procedure.*

### Resumé

*Dans ce chapitre, les matériaux et les dispositifs pour produire des échantillons (plaquette, granulé et comprimé) sont présentés. Ensuite, les techniques de caractérisation employées dans ce travail sont décrites. Dans la perspective de mieux comprendre le comportement de compactage de poudres granulées sous contraintes complexes et leurs différences de comportement par rapport à celui des poudres non-granulés, le modèle Drucker Prager-Cap, qui prend en compte plusieurs propriétés caractéristiques des solides divisés, a été considéré et la procédure pour sa calibration à partir de données expérimentales a été décrite.*

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## 2.1. PHARMACEUTICAL POWDERS

This work is a part of the collaborative European project IPROCUM (Marie-Curie ITN). Based on the need of the project topics, it was decided to investigate common pharmaceutical excipients. Among these, microcrystalline cellulose (MCC) and mannitol, but also mixtures of MCC and lactose are used as sample materials in this work.

Microcrystalline cellulose (MCC) is a white crystalline powder with needle-shaped particles. It is the most used excipient in the pharmaceutical industry for direct compression due to its excellent compactability. In this work, two grades of MCC were used: MCC 101 and MCC 102 (Avicel PH-101 and Avicel PH-102, FMC BioPolymer). Both are considered as plastic materials and the main difference between them is the particle size.

Lactose (Granulac® 140, Meggle GmbH) is a cohesive powder with sharp-edged particles. It is an excipient with low hygroscopicity and high storage stability. Regarding its mechanical behaviour, it is commonly considered as a brittle material.

Mannitol 200SD (Pearlitol® 200SD, Roquette), a spray-dried grade of mannitol, which has a larger surface and better compactability compared with the unprocessed mannitol.

Most of the pharmaceutical formulations consist of a mixture of powders in order to confer a variety of properties to the final product. In this thesis, we investigated single materials but also binary mixtures to understand the role of each material and the effect of the proportions on the compaction process. For that, binary mixtures were prepared in a Turbula mixer (Turbula® System Schatz, Switzerland) for 15 min at 32 rpm. Various mass fractions of MCC were studied: 25%, 50% and 75%.

The basic characteristics of all the excipients and the binary mixtures are presented in Table 2.1 and scanning electron microscopy images of the excipients are shown in Fig. 2.1. The bulk densities were obtained from the manufacturer and the true densities were determined by using a helium pycnometer (AccuPyc 1330, Micromeritics Instrument Corp., USA)

Table 2.1. Basic characteristics of excipients

Material		Mean particle size ( $\mu\text{m}$ )	Bulk density ( $\text{g}/\text{cm}^3$ )	True density ( $\text{g}/\text{cm}^3$ )
MCC 101		50	0.30	$1.5659 \pm 0.0005$
MCC 102		130	0.35	$1.5717 \pm 0.0006$
Lactose		60	0.63	$1.5391 \pm 0.0003$
Mannitol		170	0.48	$1.4686 \pm 0.0003$
Binary mixtures	0.75MCC/0.25Lactose	105	0.39	$1.5614 \pm 0.0022$
	0.50MCC/0.50Lactose	92	0.48	$1.5563 \pm 0.0019$
	0.25MCC/0.75Lactose	76	0.55	$1.5537 \pm 0.0002$

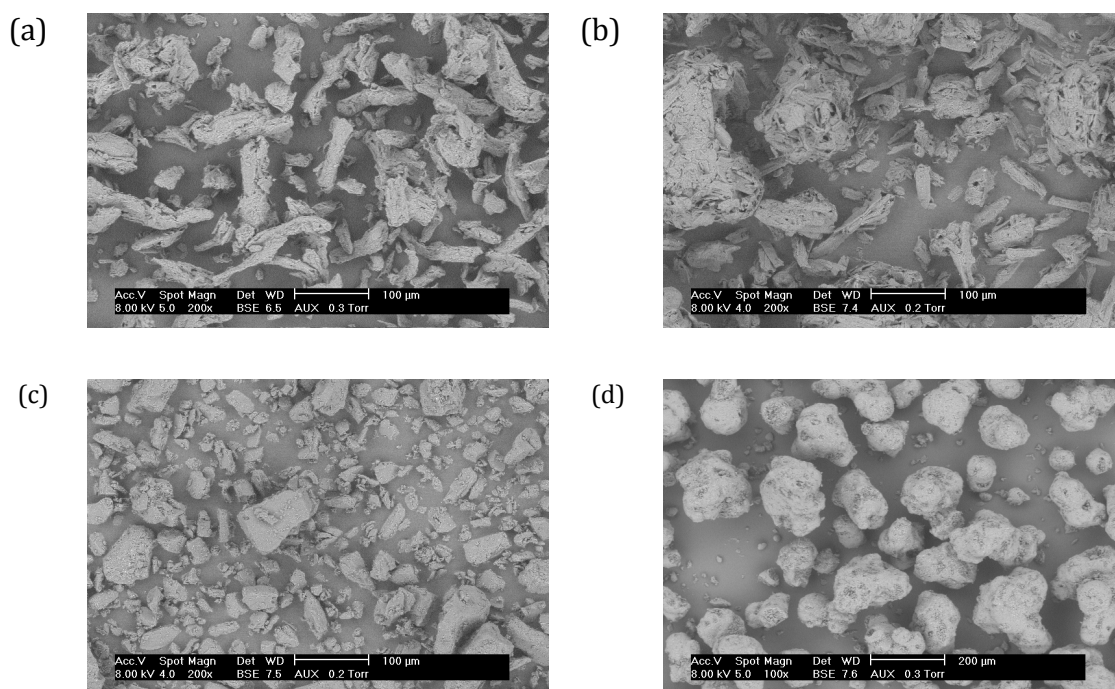


Fig. 2.1. Scanning Electron Microscopy images of powders (a) MCC 101, (b) MCC102, (c) Lactose and (d) Mannitol.

## 2.2. PROCESS EQUIPMENT

The chain of equipment used is composed of roll press, milling system and uniaxial die compaction press. There is a wide range of roll compactors and milling systems available in the market. Several devices with different configurations were used to

develop this work. They are listed in the table below and more detailed information can be found in the following sections.

Table 2.2. List of dry granulation equipment used in the experiments

	Model (Supplier)	Specification	Experiments (Section)
ROLL- COMPACTORS	Komarek® B050PH (Komarek)	Vertical rolls (100mm diameter/38 mm width)	4.2/4.3/4.4
	MiniPactor® (Gerteis)	Inclined rolls (250 mm diameter/ 25 mm width)	3.2/3.3
MILLING SYSTEMS	Erweka AR 402 (Erweka)	Oscillating mill	3.3/4.2/4.3/4.4
	Gerteis Rotors	Open-star Pocket mould- grooved	Oscillating mill (Integrated in the Mini-Pactor)
DIE COMPACTION PRESS	Instron® press (Instron)	Uniaxial	3.2/4.2/4.3
	Eccentric press (Frogerais)	Instrumented uniaxial	4.2/4.4

### 2.2.1. Roll-compactors

- *Komarek® B050PH laboratory press*

The Komarek® B050PH laboratory press (Fig. 2.2) is equipped with a single horizontal feed screw, fixed cheek plates and rolls of 100 mm of diameter and 38 mm of width, which are vertically arranged. The surface of the rolls can be smooth or knurled. The gap can be adjusted from 1.5 to 6 mm and the speeds can vary up to 7.5 rpm for the rolls and 137 rpm for the screw.

The gap must be fixed and the screw speed must be manually adjusted in order to feed homogeneously the powder. During this work, this roll-compactor was used under different conditions.



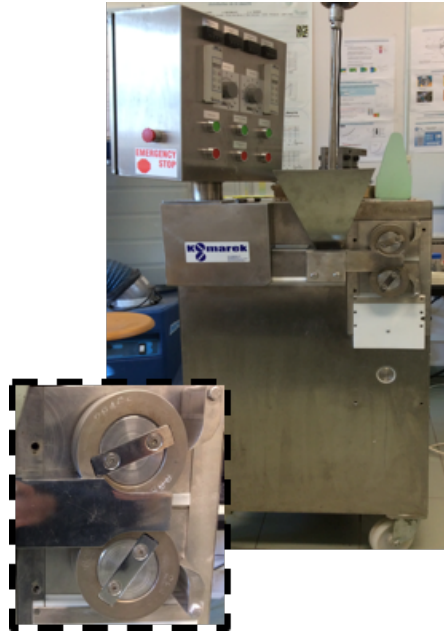


Fig. 2.2. Komarek® B050PH laboratory press.

Firstly, to produce ribbons of binary mixtures of MCC and Lactose (Sections 4.1 and 4.2), the gap was kept constant at 1.5 mm. The roll speed was 3.75 rpm and the screw speed was varied in order to produce ribbons with the same relative density ( $0.600 \pm 0.007$ ). The results concerning these experiments are included in Chapter 4. (Sections 4.3 and 4.4).

For the calibration of the DPC model, ribbons were produced fixing a gap of 1.8 mm, the roll speed ( $V_r$ ) was 2 rpm and the screw speed ( $V_s$ ) 13.5 rpm, resulting in a ratio  $V_s/V_r$  of 6. The resulting ribbon relative density was measured with the Geopyc envelope analyzer and it was 0.57. These results obtained from these experiments can be found in Chapter 4 (Section 4.2).

- *Gerteis MiniPactor®*

The smallest Gerteis roll compactor is the Mini-Pactor® 250/25 (Gerteis Maschinen + Processengineering AG, Jona, Switzerland). The configuration of this compactor consists in an inclined setup of the rolls (Fig. 2.3). The advantage of this compactor is mainly that a specific compaction force can be fixed, which is calculated from the geometry (roll width). Also the gap can be controlled by an automatic feedback system (changing the screw speed). The gap control system allows varying the distance between the rolls during compaction. In other words, if insufficient material is fed, the gap will decrease in order to maintain the required level of pressure.

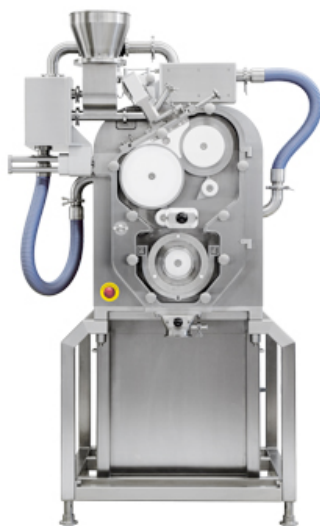


Fig. 2.3. Mini-Pactor<sup>®</sup> (Gerteis)

The Mini-Pactor<sup>®</sup> can be equipped with two side-sealing systems: cheek plates and rimmed-roll. In Chapter 3, these two sealing systems will be compared and its effect on the density distribution and the granule size distributions will be analysed.

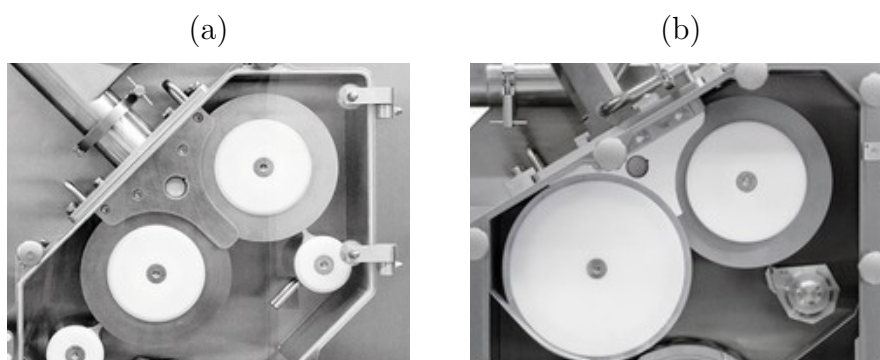


Fig. 2.4. Front view of the sealing systems (a) cheek plates and (b) rimmed-roll

Different batches of ribbons were produced with the Mini-Pactor<sup>®</sup> under different conditions (Table 2.3). The roll-compactor was placed in a climate room where also the powders were stored prior to compaction (21°C and 45% RH). The two types of sealing systems, presented above, and two specific compaction forces (4 and 8 kN/cm) were used. Therefore, 4 batches of ribbons were produced for each excipient (MCC and mannitol).

For the experiments, knurled rolls were used, the roll speed was 2 rpm and the gap was controlled by the automatic feedback system and kept constant at 1.5 mm. The ribbons were collected once the steady state was achieved for each set of conditions.

Table 2.3. Design of the experiments for the ribbon batches

Material	Sealing system	Roll-compact Force (kN/cm)
MCC	Cheek-plates	4
		8
	Rimmed-Roll	4
		8
Mannitol	Cheek-plates	4
		8
	Rimmed-Roll	4
		8

### 2.2.2. Milling systems

- *Erweka AR 402*

This mill is an oscillating system (Fig. 2.5), generally used for wet granulation but it can be used for dry granulation in absence of liquid. The impellers have a flat shape and the maximum impeller speed that can be reached is 400 rpm. The granules can be produced in varying sizes depending on the sieve mesh employed. The mesh sizes available are: 0.315, 0.63, 0.8, 1.0, 1.25, 1.6, 2.0, 2.5 and 3.15 mm.



Fig. 2.5. Erweka AR 402 milling device

The ribbons produced with binary mixtures were milled at 60 rpm using a 1.25mm sieve (section 4.2). However, the ribbons produced with the Minipactor<sup>®</sup> to analyze the milling performance (section 3.3) and the ribbons produced for the DPC analysis (section 4.4) were milled at 100 rpm with a 2 mm sieve.

- *Gerteis rotors*

In order to accelerate the dry granulation process, some roll-compactor suppliers have integrated the milling step in the system. This is the case of the roll compactors from Gerteis. The Mini-Pactor® has integrated oscillating granulators and the ribbons can be milled right after being compacted. An oscillating granulator consists, basically, on a moving rotor and a fixed sieve of a chosen size. Milling parameters such as rotor speed and angle of rotation can be adjusted.

Two types of rotors are available for the Mini-Pactor®: open star rotor and closed pocket mould-grooved type (Fig. 2.6). The rotor speed can vary between 0 - 160 rpm and the rotation angle can be adjusted from 0 to 720° in either clockwise direction, counter-clockwise or a combination of both.

In Section 3.2, different settings were compared for the two types of rotors integrated in the Mini-Pactor®. The ribbons were milled using a fixed sieve of 1 mm at 30 and 120 rpm of speed. The rotating angles were 360° clockwise and 150°/150° clockwise/counter-clockwise, in order to analyse two different modes of rotation: continuous and oscillating. In order to avoid the presence of non-compacted powder in the milling chamber, the ribbons were collected after compaction and introduced into the milling chamber separately from the non-compacted powder.

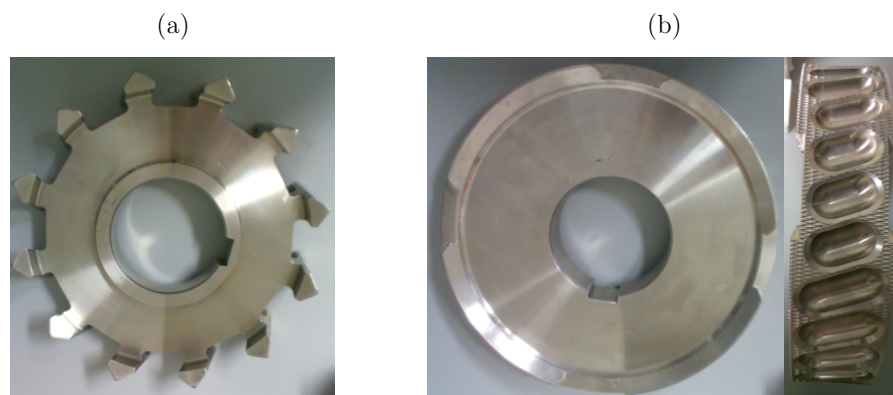


Fig. 2.6. Rotor types (a) Open star and (b) Pocket mould-grooved

### 2.2.3. Uniaxial presses

- *Instron® press*

This is a press that can be used for compression and tension tests (Fig. 2.7). Depending on the material, different load cells can be used; in this work, it has been used a load cell of 30 kN.



Fig. 2.7. Instron press ®

Also different sizes of dies and punches can be used. In this case, the size used to produce tablets was a cylindrical die of 11.28 mm of diameter (1 cm<sup>2</sup> die section) and 10 mm of height was used. The powder has to be manually poured and the speed of compaction can be adjusted.

- *Instrumented die press*

An instrumented eccentric press (Frogerais OA) has been also used. This press is equipped with a fixed cylindrical die of 11.28 mm of diameter and 10 mm of height. The pressure is applied with the upper punch and the ejection is executed with the lower one. The press is instrumented with five sensors: three strain gauges measuring pressures on the top and bottom punches and on the die wall and two LVDT sensors for the relative displacement between punches during the loading and unloading steps. During the compaction process, the displacements of the upper and lower punches, the applied axial pressure ( $\sigma_u$ ), the transmitted axial pressure to the lower punch ( $\sigma_l$ ) and the radial stress on the die wall ( $\sigma_r$ ) can be recorded. Fig. 2.8 shows a schematic representation of the measurements.

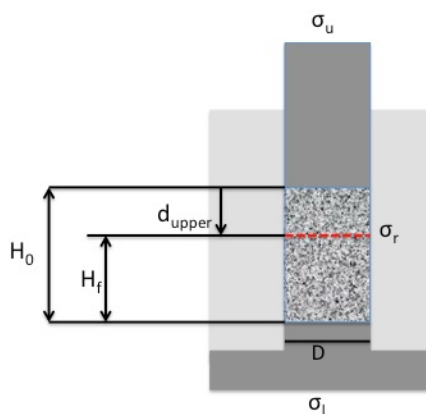


Fig. 2.8. Scheme of the instrumented die ( $D$ = die diameter,  $H_0$ = initial height of powder bed,  $H_f$ = final height,  $d_{upper}$ =displacement of upper punch,  $\sigma_u$ =upper pressure,  $\sigma_l$ =lower pressure,  $\sigma_r$ =radial pressure)

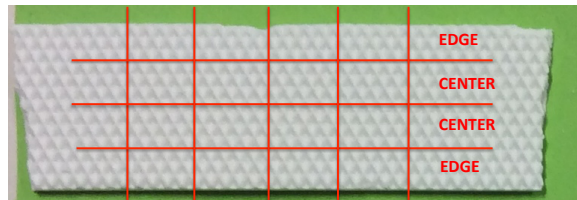
The radial strain gauge on the die wall was calibrated as a pressure using a rubbery material with isotropic behaviour, following the procedure described by Michrafy et al., (2009). As the signal of the radial gauge is dependent on the sample's height, curves of pressure (MPa) versus the signal (mV) were generated according to different heights of the rubber. The displacement of the upper punch was calibrated at zero at the top of the die (10 mm).

This press has been used to generate results discussed in Chapter 4 (sections 4.3 and 4.4), particularly for the stress transmission characterisations and the DPC model calibration.

## 2.3. CHARACTERIZATION TECHNIQUES

### 2.3.1. Ribbon properties

In order to be able to determine the existence of heterogeneity of ribbon properties along the width, the ribbons of 25 mm of width were sectioned into rectangular pieces of approximately 0.6 x 1cm (Fig. 2.9). The ribbons were cut out meticulously with a scalpel. These pieces were further analysed in terms of density distribution and milling performance.



*Fig. 2.9. Method to section the ribbon*

#### 2.3.1.1. Density distribution

The ribbon density distributions were determined using three different techniques: dimension measurement, Geopyc density analyser and mercury porosimetry. As the ribbons were sectioned into rectangular pieces, the density was measured for each piece and density profiles were created representing the variation of the density depending on the width position.

- *Dimensions:*

The width, length and thickness of each ribbon section were measured using a digital micrometre (Mitutoyo, Japan) and the mass was determined with a precision balance (CP 224S, Sartorius, Germany). Hence, the apparent density for each piece could be

calculated as the ratio of the mass to the volume. For each batch, the bulk densities of 20 sections were determined.

- *Geopyc*<sup>®</sup>:

The GeoPyc<sup>®</sup> 1360 Envelope Density Analyzer can measure the envelope density of porous samples of irregular size and shape based on a displacement measurement technique. A cylindrical chamber is filled with a certain quantity of a fine flowable powder called Dry Flo. A punch presses the powder until a certain pressure obtaining a certain displacement of the punch (The pressure should be fixed at the beginning and it depends on the size of the chamber). The ribbon sample is placed in the bed of Dry Flo, and the Dry Flo together with the sample are agitated and compressed until the same pressure as before is reached, obtaining a new displacement of the punch. Under this pressure, it is assured that the powder DryFlo covers the contours of the irregular volumes. The difference of displacement is measured and converted to volume of the sample. In this case, the chamber used for the analysis had a diameter of 12.7 mm and the consolidation force was 28 N.

- *Mercury porosimetry*:

The mercury porosimetry measurements were performed with the porosimeter AutoPore IV 9500 (Micromeritics, Norcross, USA) by applying various levels of pressure to the ribbon samples immersed in mercury. The method applied here implied a pressure cycle from 2.96 kPa (mercury filling pressure) to 207 MPa in predefined steps of 60 seconds of equilibration time. Porosimeter tests were carried out in duplicate. The bulk density at 2.96 kPa and the skeletal density were recorded and then the porosity was calculated for each section.

### **2.3.1.2. Milling performance of ribbon pieces**

In the literature results, the ribbon density distributions were not homogeneous, with a difference between the central part and the edges. To study the impact of this heterogeneity on the granules properties, the milling performance was analysed. For that, the ribbons were also sectioned as in Fig. 2.9 and the sections were divided in two groups: center pieces and edges. Each group of ribbon pieces was milled in an oscillating milling device (Erweka, AR402) at 100 rpm using a 2 mm sieve. A balance was placed (CP 224S, Sartorius, Germany) under the milling system and the evolution of the mass throughput was recorded as a function of time for each type of sections.

## 2.3.2. Granules properties

### 2.3.2.1. Morphology

Granule shape may play an important role in the densification process, affecting the inter-particulate interaction. The observation of these characteristics can help in the understanding of the particulate material behaviour. For this reason, granules were imaged with a scanning electron microscope (Phillips XL30).

### 2.3.2.2. Size distribution

For granules, the particle size distribution was determined by sieve analysis (AS 200 digit, Retsch, Germany) at amplitude of 40 for 20 min. The applied sieves were 125, 200, 315, 500, 630, 800, 1000, 1250, 1600 and 2000  $\mu\text{m}$ . Sieving is a good technique to determine the size distribution when coarse particles are involved. It should be also used to separate different size classes of granules, for further investigation of the particle size effect on tablet properties.

In order to obtain more precision on the size distribution results and to be able to determine accurately the percentage of the fines in some of the samples, also a dynamic image analysis was performed (Camsizer<sup>®</sup> XT, Retsch Technology GmbH). Representative samples of the granules (approximately 10 g) were analysed using the X-Jet module and a pressure of 30 kPa. The diameter chosen was  $X_{c,\text{min}}$ , which gives particle diameters close to the ones obtained by screening/sieving (shortest chord of the measured set of maximum chords of a particle projection). It is defined as the diameter of a circle that has the same area than the particle being characterized, calculated as the shortest of all the chords projected by the particle. For reproducibility, the measurement was done three times for each batch of granules.

The amount of fines was estimated by  $d_{10}$  (diameter at which 10% of the sample's volume lies below). Based on the definition of  $d_{10}$ , higher values of  $d_{10}$  mean bigger size and, hence, less fines are produced under a specific set of parameters. Therefore, the smallest  $d_{10}$  value indicates the biggest amount of fines.

## 2.3.3. Tablets properties

Cylindrical flat tablets were prepared by pouring a mass (from 0.3 to 0.4 grams of material depending on the experiment) into a die of 1  $\text{cm}^3$  of volume and compacting the powder at different pressures (from 20 MPa to 140 MPa). After ejection, the tablet dimensions (diameter and thickness) were measured with a digital micrometer (Mitutoyo) and tablet mass was weighted with an electronic balance (CP 224S,



Sartorius, Germany ). The relative density ( $\rho_r$ ) of each tablet was calculated following (Eq. 2.1) where  $m$  is the tablet mass,  $h$  and  $D$  the thickness and the diameter of the tablet respectively, measured after the ejection with a digital calliper, and  $\rho_t$  is the true density measured with an helium pycnometer (Table 2.1).

$$\rho_r = \frac{4m}{\pi h D^2 \rho_t} \quad (\text{Eq. 2.1})$$

### 2.3.3.1. Compressibility

The compressibility of a powder bed is the ability to be reduced in volume under pressure. The compressibility can be described by measuring the porosity changes as a function of the compression pressure (different pressure levels are required).

Numerical mathematical models are able to describe the relation between relative density and pressure. The most well known are Heckel, Kawakita and Walker equations. The compressibility of the binary mixtures and their granules (section 4.2) was determined applying the Heckel equation (Heckel, 1961). The Heckel equation (Eq. 2.2) transforms the force and displacement signals from the compaction cycle to a linear relationship assuming that the process of pore reduction during compression follows first-order kinetics:

$$\ln\left(\frac{1}{1 - \rho_r}\right) = K \cdot P + A \quad (\text{Eq. 2.2})$$

$$P_y = \frac{1}{K} \quad (\text{Eq. 2.3})$$

where  $\rho_r$  is the relative density of the compact,  $P$  is the applied pressure,  $K$  is a material-dependent constant known as the Heckel coefficient (related to the plasticity of a compressed powder bed),  $A$  is a constant that expresses the volume reduction before deformation (die filling and powder rearrangement) and  $P_y$  is the mean yield pressure (Eq. 2.3).

The Heckel model was applied to the results obtained for binary mixtures (Chapter 4) in the range of pressures from 20 MPa to 140 MPa.

### 2.3.3.2. Compactability

The compactability is defined as the ability of a powder bed to be densified into a compact of a determined strength. A diametric strength tester (Erweka TBH30, Erweka® Gmbh) was used to measure the diametrical crushing load of tablets (n=3).

The tensile strength of the compacts ( $\sigma_t$ ) was calculated according to Fell and Newton (1970):

$$\sigma_t = \frac{2F_d}{\pi DH} \quad (\text{Eq. 2.4})$$

where  $F$  is the load required to break the tablet diametrically,  $D$  and  $H$  are the diameter and the final height of the tablet, respectively.

### 2.3.3.3. Stress transmission

During the compaction process, the pressures and displacements of the upper and lower punches as well as the radial stress on the die were recorded.

The press requires defining the maximum displacement of the upper punch. This maximum displacement corresponds to a certain maximum pressure depending on the material inside the die. For this study, the maximum displacement of the upper punch varied from 6 to 7 mm in order to get tablets of approximately 3-4 mm of height at the end of the compaction.

The ratios of axial and radial stress transmissions ( $\Phi_{axial}$  and  $\Phi_{radial}$ , respectively), according to the relative density of the tablet, were used as tools to analyse mechanisms of the densification. They allow the quantification of the capacity of the binary mixtures and their granules to convert the applied pressure to the axial and radial directions during the compaction cycle (Michrafy et al., 2009). They were calculated as:

$$\phi_{axial} = \frac{\sigma_l}{\sigma_u} \quad (\text{Eq. 2.5})$$

$$\phi_{radial} = \frac{\sigma_r}{\sigma_u} \quad (\text{Eq. 2.6})$$

where  $\sigma_u$  is the upper pressure,  $\sigma_l$  is the lower pressure and  $\sigma_r$  is the radial pressure.

## 2.4. CONTINUUM MODEL AND CALIBRATION

To understand the difference of the compaction of raw and granulated material, different behaviours can be compared for similar density's state. These can include, the tablet strength (compactability), the compressibility (volume reduction under pressure) or the stress transmission during the compaction. Instead of characterizing the behaviour for a simple compressive or extensive stress, another manner is to

characterize the elastic and plastic behaviour of the material based on the determination of a yield surface and how this yield surface can expand or contract according to the loading state. The domain defined under the surface characterizes any stress state under which the material can behave elastically for a given relative density. However, for any stress that can expand the current domain, the deformation of the material is then irreversible (plastic behaviour). Comparing yield function for raw and granulated material can explain how either behaves regarding shear stress or hydrostatic pressure. One commonly used model for elastic-plastic behaviour of powders is Drucker-Prager Cap (DPC), assuming the material as continuum and porous.

The DPC model describes the material's yield surface in the space “hydrostatic pressure,  $p$  – equivalent stress,  $q$ ”, and is mainly composed of two surfaces: the shear failure surface ( $F_s$ ) and the cap surface ( $F_c$ ), as plotted in Fig. 2.10.

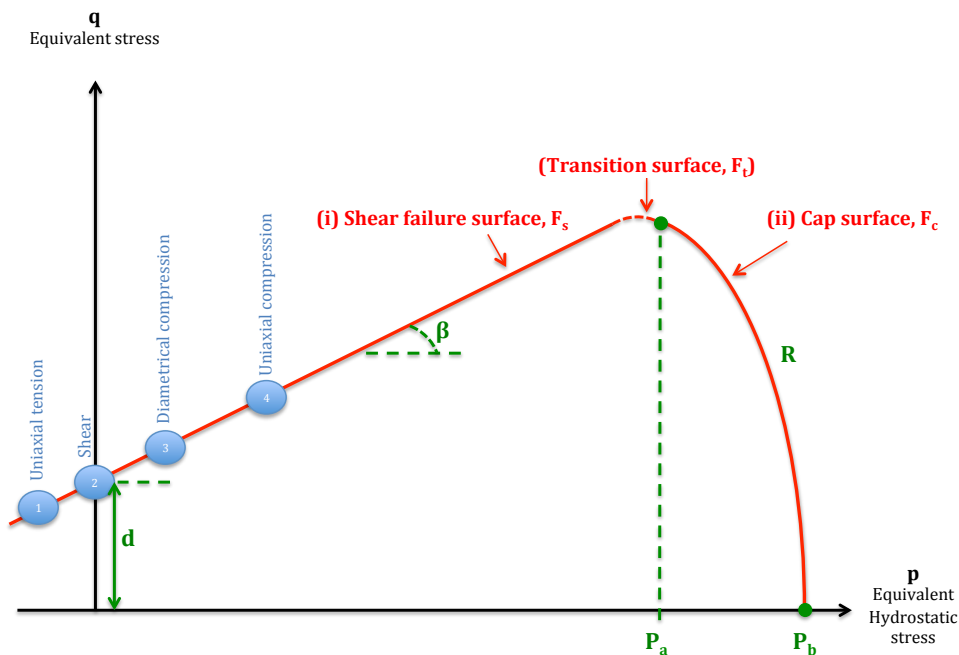


Fig. 2.10. DPC yield surface and identification of parameters

The shear failure surface ( $F_s$ ) represents the shear stress required to cause the fracture is characterized in this line, which is extremely important during the decompression and the ejection phases

$$F_s(p, q) = q - p \tan\beta - d = 0 \quad (\text{Eq. 2.7})$$

The cap surface ( $F_c$ ) governs the densification of the material and can expand as the inelastic volumetric strain increases.

$$F_c(p, q) = \sqrt{(p - P_a)^2 + \left(\frac{Rq}{1 + \alpha - \frac{\alpha}{\cos\beta}}\right)^2} - R(d + P_a \tan\beta) = 0 \quad (\text{Eq. 2.8})$$

The third surface ( $F_t$ ) does not have a physical meaning, being only a smooth transition surface to avoid numerical problems near the corner for plasticity computation.

In these equations:

- $\beta$  is the angle of internal friction
- $d$  is the cohesion
- $R$  is the cap eccentricity (shape of the cap) and it is a material constant
- $\alpha$  is the transition constant that ensures the smooth transition between  $F_s$  and  $F_c$  (Cunningham, 2004). It typically varies from 0.01 to 0.05 (Krok et al., 2014; Mazor et al., 2016)
- $P_a$  represents the hardening or softening driven by the volumetric plastic strain
- $P_b$  is the hydrostatic pressure

### 2.4.1. DPC Calibration

The material parameters that need to be identified based on standards experiments such as instrumented die compaction, simple compression and diametrical compression (Bonney and Doremus, 2004)], are powder cohesion  $d$ , internal friction  $\beta$ , eccentricity of the cap  $R$  and  $P_b$  the evolution of the cap surface according to the volumetric inelastic strain. These parameters are depending on the relative density, which is used as the state variable.

For the calibration of the DPC model, the preparation of tablets in different manners is required. The calibration procedure for each test and the calculation of the required parameters are detailed below.

#### 2.4.1.1. Determination of the shear failure surface parameters

The shear failure line can be fitted with the results of two of the tests: tension; shear, diametrical compression and uniaxial compression (Fig. 2.10). The unconfined axial compression test and the diametrical test are the simplest and most common tests to measure the tablet strengths. These experiments can be performed in a simple compression press (Mazor et al., 2016). Nevertheless, certain tablet aspects must be

kept for both tests (relation height/diameter, H/D). These tablet aspects were described by Doremus (2008).

For the diametrical compression test, the failure must be originated at the centre of the tablet. Therefore, the tablet aspect ratio H/D must be around 0.25. In this work, the procedure to obtain these results was similar to the one described in section 2.3.3.2. The feed powder and the granules were fed ( $0.350\pm 0.005$  grams) in a die of  $1\text{ cm}^3$  of volume. The applied pressure was varied in a range from 20 to 120 MPa and, therefore, a variation of the thickness was obtained (from 2.5 to 4 mm). Then, the aspect ratio varied from 0.22 to 0.35. After, the diametrical strength was measured with a diametric strength tester (Erweka TBH30). The tensile strength and the stress state in the plane p-q are defined as follows:

$$\sigma_d = \frac{2F_d}{\pi DH} \quad (\text{Eq. 2.9})$$

$$p_d = \frac{2}{3}\sigma_d \quad q_c = \sqrt{13}\sigma_d \quad (\text{Eq. 2.10})$$

where  $F_d$  is the diametrical strength and D and H are the diameter and the height of the tablets, respectively. [It should be remarked that this test is the same as the one defined before to measure the compactability of a tablet (Section 2.3.3.2) and therefore, (Eq. 2.4) and (Eq. 2.9) are the same equation].

For the axial compression test, it is important to take into account a specimen aspect ratio H/D equal or larger than 2. It is also extremely important to assure a good density distribution along the tablet height and, for this reason, the punches and the die were lubricated with MgSt.

According to this, we produced tablets with the Instron® press, using a cylindrical die of 11.28 mm of diameter and 90 mm of height. The displacement of the punch was fixed in order to obtain a final tablet height of 22 mm. The powder or the granules were filled obtaining different relative densities by varying the mass (in the range of 0.4-0.9). Once the tablets were obtained, they were submitted to the compression test using the same press and the stress at which the specimen breaks was recorded ( $F_{ac}$ ) (Fig. 2.11). For repeatability, the mean value of three measurements was used for each desired relative density for each type of granular material.

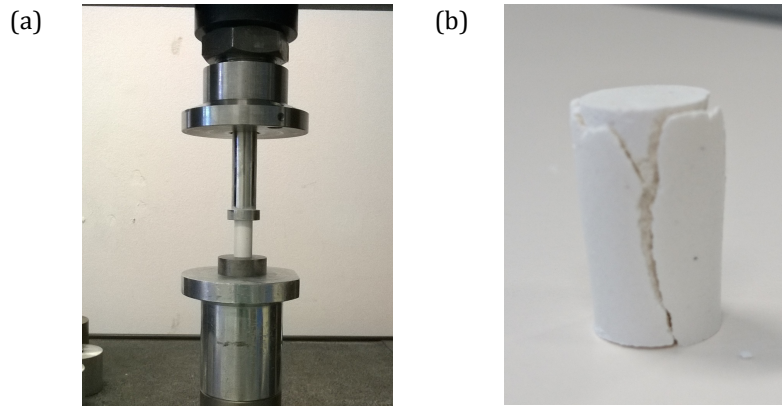


Fig. 2.11. (a) Compression test (b) Failure of a tablet

Then, the failure strength,  $\sigma_c$ , and the stress state in the plane p-q are defined as follows:

$$\sigma_c = \frac{4F_{ac}}{\pi D^2} \quad (\text{Eq. 2.11})$$

$$p_c = -\frac{1}{3}\sigma_c \quad q_c = -\sigma_c \quad (\text{Eq. 2.12})$$

where  $F_{ac}$  is the axial compression force at the yield point force and  $D$  is the tablet diameter.

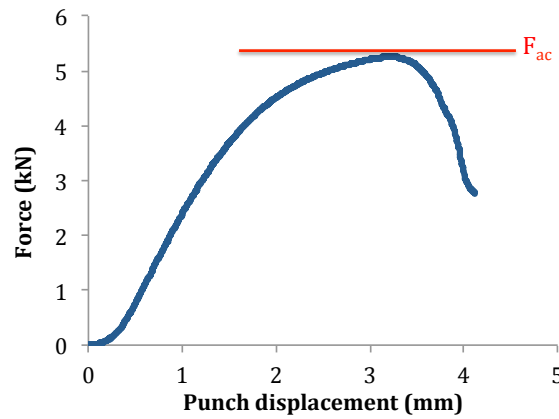


Fig. 2.12. Axial compression force (maximum of the compression cycle of the unconfined test)

Once the data  $[p_d, q_d]$  and  $[p_c, q_c]$  are plotted for different relative densities, the shear failure lines can be fitted. The slope of the line gives the internal angle of friction,  $\beta$ , and the intersection with the Y-axis represents the cohesion,  $d$ . These values can be obtained analytically (Cunningham, 2004) using the following equations:

$$d = \frac{\sigma_c \sigma_d (\sqrt{13} - 2)}{\sigma_c + 2\sigma_d} \quad (\text{Eq. 2.13})$$

$$\beta = \tan^{-1} \left[ \frac{3(\sigma_c + d)}{\sigma_c} \right] \quad (\text{Eq. 2.14})$$

#### 2.4.1.2. Determination of the cap surface parameters

The cap properties should be characterized with a fully instrumented press. For this, the instrumented press (Frogerais) detailed in section 2.2.3 was used. The tablets were prepared by automatically filling. As the granules had higher bulk densities than the feed powder, the mass varied from one experiment to another (0.30 g/cm<sup>3</sup> for feed powder and 0.35 g/cm<sup>3</sup> for granules). A range of relative densities was obtained and the axial ( $\sigma_u$ ) and radial ( $\sigma_r$ ) pressures were recorded. The obtained values were transformed in the plane  $p$ - $q$ :

$$p = \frac{\sigma_u + 2\sigma_r}{3} \quad q = |\sigma_u - \sigma_r| \quad (\text{Eq. 2.15})$$

Then, the parameters of the cap are calculated based on the following equations:

$$R = \sqrt{\frac{2}{3q} (p - P_a)} \quad (\text{Eq. 2.16})$$

$$P_b = P_a + R(d + P_a \tan\beta) \quad (\text{Eq. 2.17})$$

$$P_a = \frac{-3q - 4d \tan\beta + \sqrt{9q^2 + 24dq \tan\beta + 24pq \tan\beta^2 + 16q^2 \tan\beta^2}}{4 \tan\beta^2} \quad (\text{Eq. 2.18})$$

Once all these parameters are obtained, the functions of the model ( $F_s$  and  $F_c$ ) can be calculated and the yield surface for each density can be represented. These results can be found in Section 4.4.

## 2.5. CONCLUSIONS

In this chapter the materials used in this thesis were presented. During the development of this work, multiple systems have been used and different operational

parameters were compared. The devices and the conditions for the experimental procedures were described.

The comparison of the compaction behaviour of feed powders and granules under compaction will be done based on Drucker-Prager Cap model, and for that, the procedure of calibration of this model based on experimental data was described in this section. This methodology was applied to calculate the DPC parameters of feed powder (MCC) and granules. The idea behind is to see what is the effect of roll-compaction on the compaction behaviour of granules in order to further investigate the “loss of reworkability”. The effect of the granule size on the results was also compared.





## Chapter 3.

# Roll-compaction and milling results

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### **Abstract**

*The existence of different designs of the roll compactors, milling systems and the interaction between process parameters and raw material properties are still a challenge in the pharmaceutical industry. In this chapter, the effect of different roll-compaction conditions and milling process parameters on ribbons, granules and tablet properties was investigated. The main interest is to establish the relationship parameters-product properties, having a global consideration of the chain process.*

*In a first part, the effect of the operational parameters (roll compaction force, sealing system and milling conditions) is evaluated in terms of ribbon density, granules morphology, granule size distribution (through the amount of fines) and tablet tensile strength. The final goal is to find the balance between a good flowability by reducing the amount of fines and an appropriate tablet strength. A statistical analysis is also performed in order to reveal the most significant parameters.*

*In the second part, based on the previous results, the role of the sealing is further investigated. Two types of sealing systems are analysed in terms of ribbon density distribution and milling performance (mass throughput and granule size distribution).*

### **Resumé**

*L'existence de différents modèles de presse à rouleaux, de systèmes de broyage et l'interaction entre les paramètres de ces procédés et des propriétés des poudres rendent difficile l'interprétation des résultats et la compréhension des mécanismes physiques à chaque étape de la chaîne. Pour progresser dans ce sens, on étudie, dans ce chapitre, l'effet de deux modèles de presse à rouleaux et de paramètres procédé de broyage sur les propriétés des granulés et des compacts qui en résultent. L'intérêt principal est d'établir des relations entre les propriétés des poudres et des paramètres procédé, avec une prise en compte globale de la chaîne de production.*

Dans une première partie, l'effet des paramètres de fonctionnement tels que la pression de compactage, le système de confinement et les conditions de broyage, est évaluée en termes d'impact sur la distribution de densité dans la plaquette, la morphologie des granulés, la distribution de taille des particules et la résistance mécanique des comprimés. L'objectif final est de trouver l'équilibre entre une bonne fluidité en réduisant le taux de poudres fines, générées par le système de broyage, et une résistance mécanique appropriée des compacts. Une analyse statistique est menée pour déterminer les paramètres les plus significatifs. Dans la deuxième partie, et à la lumière des mesures obtenues précédemment, l'impact du type de système de confinement sur les propriétés des plaquettes et des granulés est étudié. Deux types de systèmes de confinement présents dans les presses industrielles, sont analysés et leurs effets sur la distribution de densité des plaquettes sont caractérisés. Par ailleurs, le système de broyage a été étudié en termes de ces performances basées sur la mesure du débit massique et distribution granulométrique des granulés.

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### 3.1. INTRODUCTION

The focus of this chapter is to determine and discuss the results of varying different operating conditions of roll-compaction and milling, that can improve the quality of the products, including ribbons, granules and tablets. This chapter is composed of two parts (Sections 3.2 and 3.3). In the first part, the effect of the operational parameters (the roll-compaction force and the sealing system for the roll-compaction step and the mill type, speed and angle of rotation for the milling step) is evaluated in terms of ribbon density, granules morphology, particle size distribution, and tablet tensile strength. The analysis of granule size distribution (through the measurement of  $d_{10}$ ) together with the characterization of the compactability (tensile strength) of granules are used to determine the optimal conditions for these systems and in the design of granules with a good quality for tableting. It is necessary to find a balance between a good flowability (reducing the amount of fines produced during the milling step) and a good tablet tensile strength (minimizing the effect of the loss of reworkability during die compaction caused by roll compaction). In addition, the results are evaluated through a statistical analysis, in order to improve the process control by identifying the critical parameters influencing the quality of the intermediates and end-products.

In the second part, the effect of the sealing on the ribbon density distribution is further investigated. Therefore, in this section, the two types of sealing systems are analysed in terms of ribbon density distribution. In addition, the milling performance of the obtained ribbons was evaluated in terms of mass throughput and particle size distribution depending on the position of the milled material along the ribbon width.

The results of this chapter concern two common materials: MCC 101 and mannitol. It is the different mechanical characteristics of each material and the response of these materials under compression and milling that are of our interest in this research.

### 3.2. IMPACT OF OPERATIONAL PARAMETERS ON THE MATERIAL PROPERTIES \*

The design of experiments created to evaluate the operation parameters is summarized in (Table 3.1). It consists of five factors in two levels and two responses:  $d_{10}$  and tensile strength. The type of material used was also included as a qualitative factor.

Table 3.1. Description of the design of experiments with different factors and responses.

<i>Sealing system</i>	Cheek plates	Rimmed-roll
<i>Roll-compaction force (kN/cm)</i>	4/8	4/8
<i>Mill type</i>	Star granulator/ Pocket mould-grooved	Star granulator/ Pocket mould-grooved
<i>Milling speed (rpm)</i>	30/120	30/120
<i>Angle (°)</i>	150/360	150/360
<b>Material</b>		
<i>MCC</i>		
<i>Mannitol</i>		
<b>Responses</b>		
<i><math>d_{10}</math> (<math>\mu\text{m}</math>)</i>		
<i>Tensile strength (MPa)</i>		

The results will allow:

1. To evaluate how pharmaceutical materials with different properties respond to the action of the certain operational conditions and to analyse how their behaviors differ.
2. To recognise the influence of parameters on the performance of materials in the process through the analysis of the products properties.
3. To reveal the most significant parameters through statistical analysis of the obtained results. This will serve to evaluate the sensitivity of the system to changes.

\* This section has been published under the reference: *Perez-Gandarillas, Lucia, Ana Perez-Gago, Alon Mazor, Peter Kleinebudde, Olivier Lecoq, and Abderrahim Michrafy. 2016. "Effect of Roll-Compaction and Milling Conditions on Granules and Tablet Properties." European Journal of Pharmaceutics and Biopharmaceutics 106. Elsevier B.V.: 38-49. doi:10.1016/j.ejpb.2016.05.020.*

### 3.2.1. Ribbons properties: appearance and bulk density

The appearance of the ribbons for both excipients is shown in Fig. 3.1 and Fig. 3.2. The quality of produced ribbons showed dependency on the material, on the sealing system and on the roll-compaction force.

MCC resulted easier to compact and less uncompacted powder was produced. On the other hand, due to its brittle characteristics, the compaction of mannitol resulted in a high amount of uncompacted material. Nevertheless, the uncompacted powder was separated from the ribbons prior to milling.

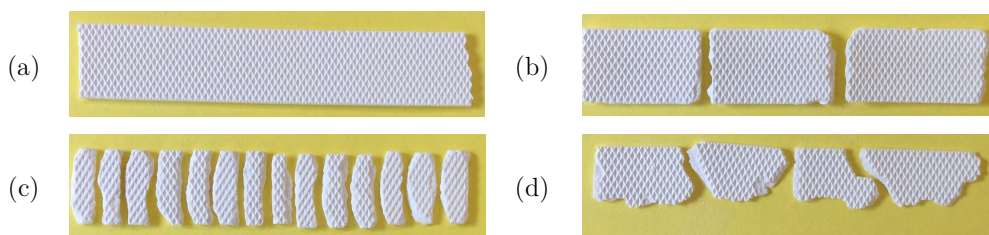


Fig. 3.1. MCC ribbons (a) CP, 4kN/cm; (b) CP, 8kN/cm; (c) RR, 4kN/cm; (d) RR, 8kN/cm [CP= Cheek Plates, RR= Rimmed-roll; Roll compaction forces: 4 and 8kN/cm]

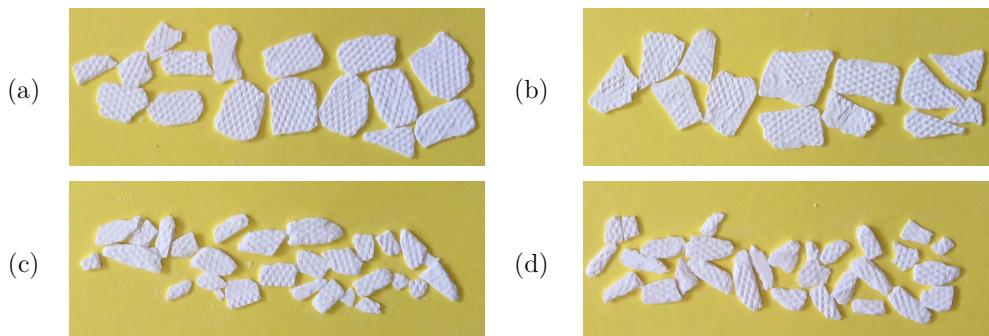


Fig. 3.2. Mannitol ribbons (a) CP, 4kN/cm; (b) CP, 8kN/cm; (c) RR, 4kN/cm; (d) RR, 8kN/cm [CP= Cheek Plates, RR= Rimmed-roll; Roll compaction forces: 4 and 8kN/cm].

The MCC ribbons (Fig. 3.1) produced using cheek plates as the sealing system showed regular shape and width approximately the same as the roll width. However, when using rimmed-roll (c and d), the produced ribbons are shorter. The drawback of using the rimmed rolls system is that the ribbons tend to stick to the rolls surface (normally to the one that is rimmed). Therefore, the ribbons are confined between the rims and the roll during ejection, as it can be seen in Fig. 3.3 (no scraper). For this reason, a scraper is included in the roll press design, allowing the separation of the ribbons from the roll and resulting in the reduction of ribbon's length.

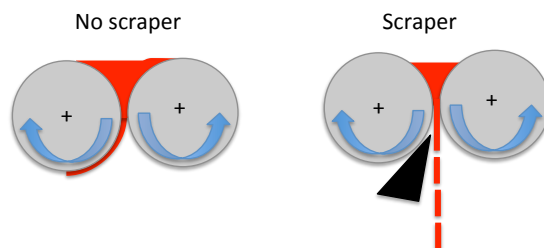


Fig. 3.3. Use of scraper

Regarding the compaction-force for MCC ribbons, in both cases (cheek plates and rimmed-roll), at higher force (8 kN/cm), the ribbons tended to laminate (separation of the ribbon into two or more layers after the ejection step due to the friction between the material and the rolls, which causes, in some cases, the stickiness of the ribbon to the rolls). Moreover, when a high compaction force and rimmed-roll were combined, not only lamination but also breakage (fracture of the ribbons into smaller pieces) in the middle of the width took place.

For the mannitol, the lamination tendency occurred under all the tested conditions due to its brittle behaviour (Fig. 3.2), meaning that it is only possible to obtain small fragments with irregular shapes. Most of the ribbons were sticking to the roll and the use of the scraper was essential for all the conditions. Furthermore, the ribbon fragments became smaller when using rimmed-roll as sealing system.

To evidence the differences of the ribbon quality according to the production conditions, the overall ribbon relative density was measured. Fig. 3.4 shows the obtained values of relative density for each type of ribbon produced.

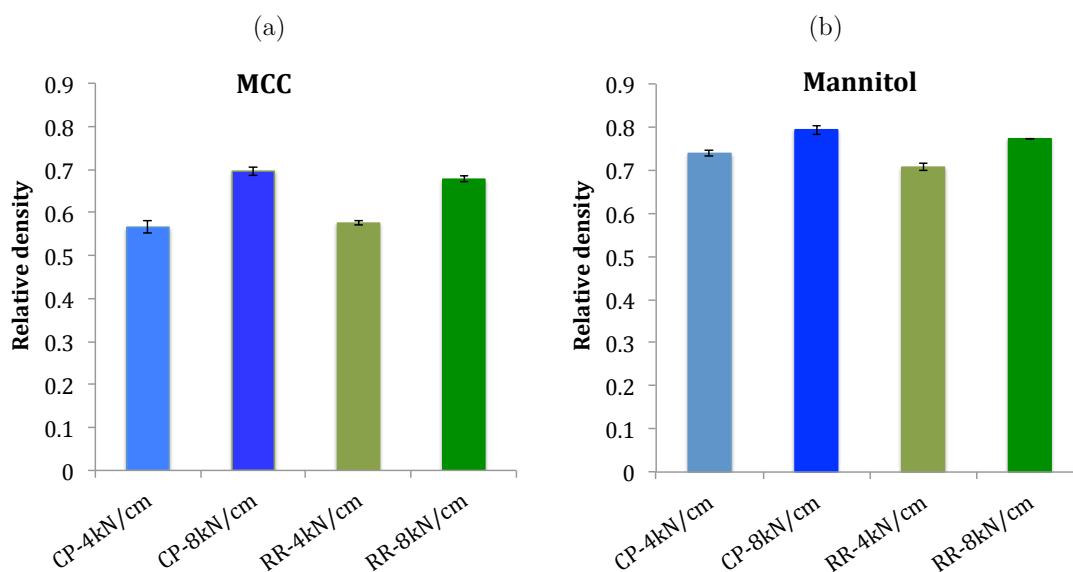


Fig. 3.4. Average relative density of ribbons (a) MCC, (b) Mannitol (CP= Cheek Plates, RR= Rimmed-roll; Roll compaction forces: 4 and 8kN/cm).

The measured solid fraction showed different wide ranges for MCC (from 0.57 to 0.70) and mannitol (from 0.71 to 0.79). Comparing the materials under the same roll-compaction conditions, it can be observed that ribbons produced with mannitol are denser than the ones of MCC.

It can be also observed that the higher densities are obtained at higher roll-force. Comparing the two sealing systems, similar values of density were obtained, slightly lower for the rimmed-roll system.

### 3.2.2. Granules morphology

In general, shape and surface roughness of granules have an impact during the filling and the rearrangement of particles in die compaction. The observation of these characteristics can help in the understanding of the powder behaviour during die compaction. In this study, granules produced after milling the ribbons were imaged with a scanning electron microscope and they are shown in Fig. 3.5 and Fig. 3.6.

For granules from MCC (Fig. 3.5), it can be observed that they represent an agglomeration of fibre-like single particles. At higher roll force, the density of granules is increased. It can be also observed that the higher the roll-compaction force, the smoother the surface becomes. In general, rough surfaces and irregular shapes of granules improve the compactability due to a better mechanical inter-locking and inter-granular bonding (Karehill et al., 1990; Mitra et al., 2015), especially for plastically deforming materials (Abdel-Hamid et al., 2011)

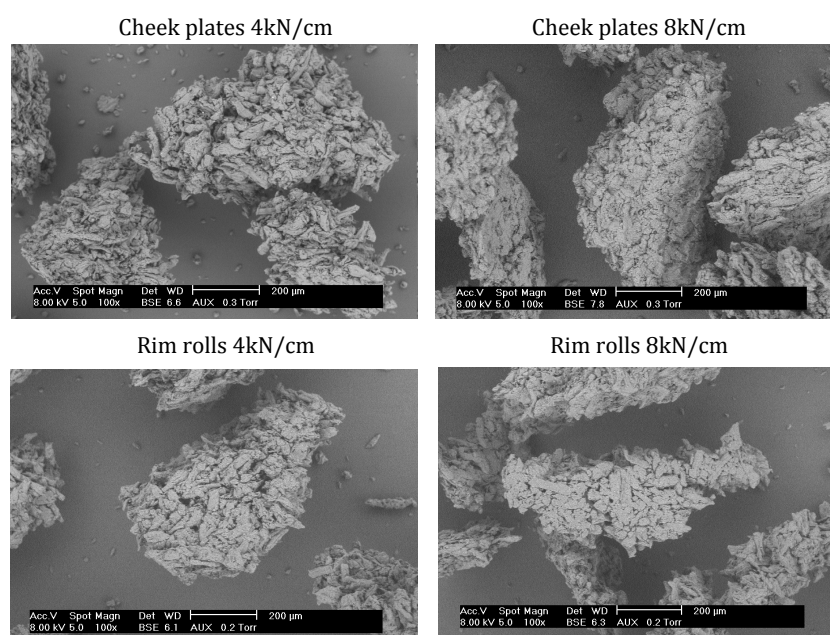


Fig. 3.5. Granules produced from MCC under different roll compaction conditions.



For mannitol (Fig. 3.6), the granules produced under different roll-compaction conditions do not show noticeable differences. Nevertheless, the granules are completely different from the original feed powder, which had a spherical shape (Fig. 2.1.d).

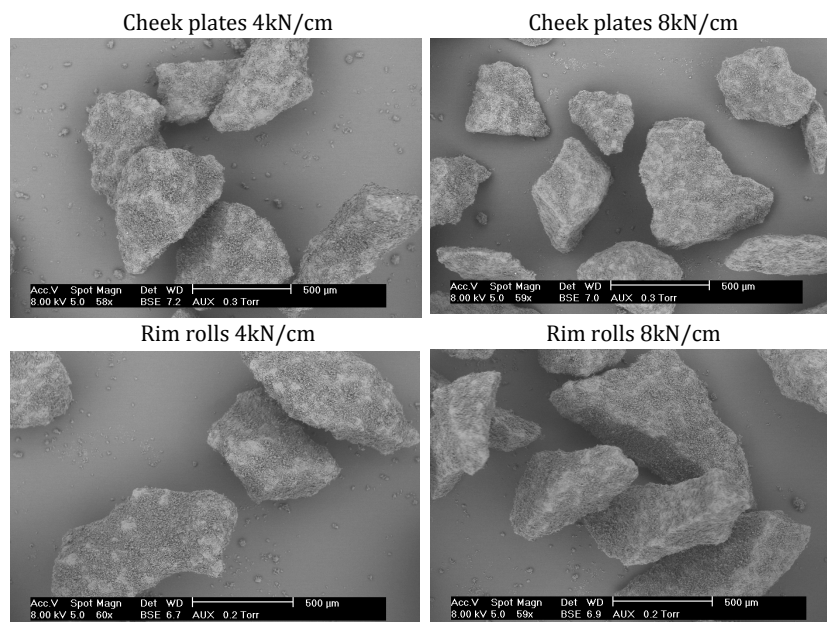


Fig. 3.6. Granules produced from mannitol under different roll compaction conditions.

### 3.2.3. Amount of fines

The granule size distribution (GSD) is the most important property resulting from the milling step. To control the GSD is of high interest in order to assure the resulting tablet's properties, in particular in die filling where demixing or segregation is one source of non-homogeneity of tablet properties.

First, the ribbons were milled under multiple conditions and, then, the GSD was measured with a digital imaging analysis (Camsizer). The results showed that, for both materials, bimodal distributions were obtained in all the cases, where the first peak represented the fines and the other the coarser particles. These distributions can be found in Annex I. It can be observed that in general, MCC batches have a higher peak in the fines and lower amount of coarser granules. On the other hand, mannitol batches have more homogeneous distributions, with a bigger amount of bigger particles. This can be directly related to the ribbon density obtained before (Fig. 3.4). Mannitol had higher relative density than MCC and, therefore, is harder to be milled, producing coarser particles than MCC. These kinds of bimodal profiles, which are characteristic for roll-compacted granules, were also obtained by Perez Gago and Kleinebudde (2016) for these two excipients and their binary mixtures.

To investigate the effect of the milling process, the analysis of results in this section has been done based on the amount of fines produced. The reason is because reducing the amount of fines, the flow properties of the final granulation and the weight variation during tableting are improved (Vendola and Hancock, 2008). Hence, the amount of fines looks a good indicator of the milling performance. As introduced in Section 2.3.2, as the feed powders (MCC and mannitol) have a different mean particle size, the amount of fines was evidenced by  $d_{10}$  (diameter at which 10% of the sample's volume lies below).

Fig. 3.7 and Fig. 3.8 show the effect of different roll-compaction/milling conditions (X axis) on the value of  $d_{10}$ . Based on the definition of  $d_{10}$ , higher values of  $d_{10}$  mean larger size and, hence, less fines are produced under a specific set of parameters. Therefore, the smallest  $d_{10}$  value indicates the biggest amount of fines. In these figures, it was also pointed out the mean particle size of the original feed powder (50  $\mu\text{m}$  for MCC and 170 $\mu\text{m}$  for mannitol). Thus, if the  $d_{10}$  value is below the horizontal line, it means that 10% of the volume of the sample has a size below the particle size of original feed powder, due to the compression action or to the breakage of single particles.

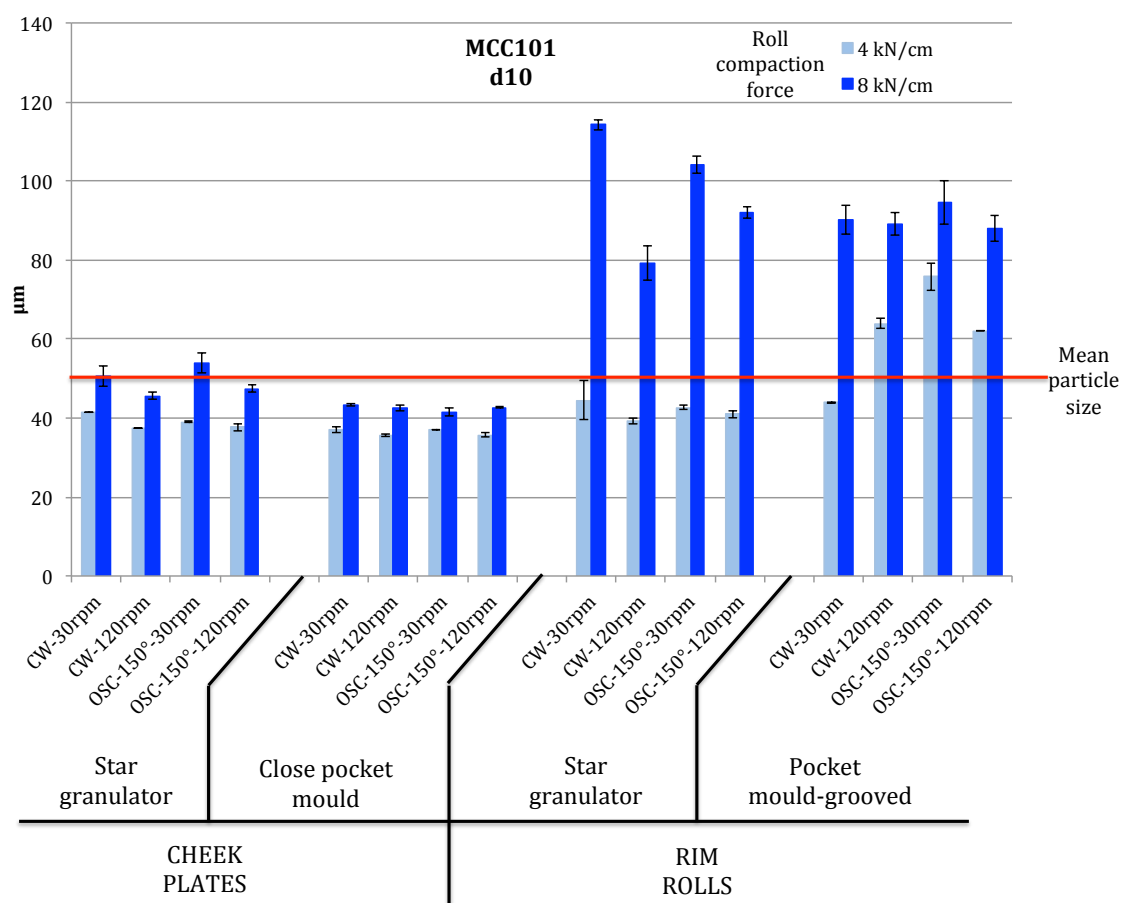


Fig. 3.7.  $d_{10}$  of MCC granules batches (CW= Clockwise; OSC= Oscillating). Mean particle size of MCC powder is 50  $\mu\text{m}$ .

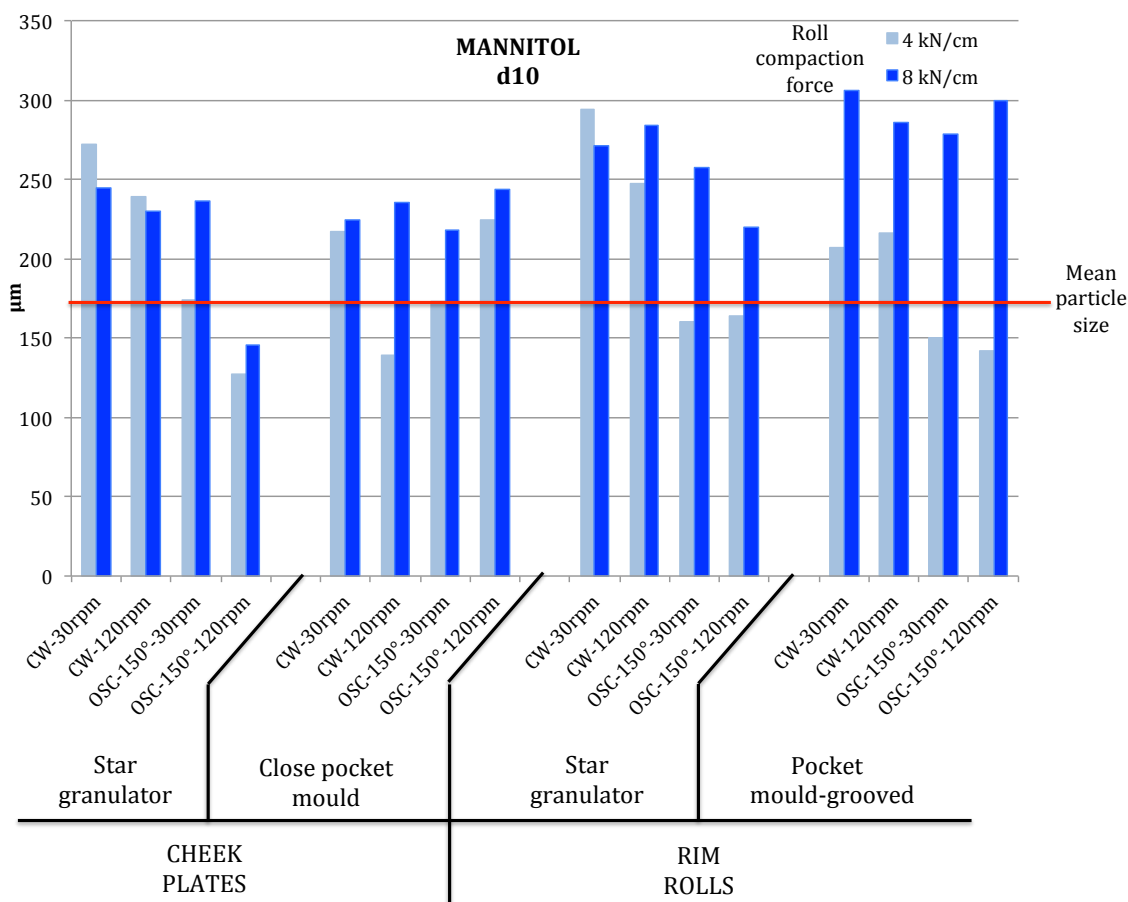


Fig. 3.8.  $d_{10}$  of mannitol granules batches (CW= Clockwise; OSC= Oscillating). Mean particle size of mannitol powder is 170 µm.

Results showed that, for MCC (Fig. 3.7), the produced granules from ribbons compacted with higher roll compaction force (8 kN/cm) generate less percentage of fines and coarser granules, having a longer residence time in the milling chamber (observation). Conversely, low densified ribbons lead to a large amount of fine particles. These results are in agreement with others studies in the literature (Inghelbrecht & Remon, 1998; Herting & Kleinebudde, 2008), where the granule size increases with the compaction force. In general, for plastic material like MCC, high-densified ribbons produce bigger granules and less fines, while weaker ribbons generate a big amount of fine particles. In addition, at high compaction-force, the use of rimmed-roll showed a reduction of the amount of fines compared to the cheek plates. The use of cheek-plates in the production of MCC ribbons induced an increase of the amount of fines, being the value of  $d_{10}$  below the particle size of as-received MCC powder.

For mannitol (Fig. 3.8), also a higher roll-compaction force (8 kN/cm) creates less amount of fines. This fact is even more evident when using the rimmed-roll system. Therefore, adopting the minimal fines approach (the objective is to produce as less

fines as possible), it can be concluded that to produce less fines, it is not only recommended to work at high roll-compaction force as proposed in the literature (Wagner, 2013-2015); but also to use rimmed-roll as sealing system.

Evaluating the effect of rotor type, it was observed during production that the milling step was faster for the star granulator, for both excipients. The star granulator is a good option for its high throughput capacity, being the residence time within the milling chamber shorter than for the pocket mould-grooved. On the other hand, the pocket mould-grooved granulator offers a different mechanism of milling, including pre-breaking as a primary step before the shearing action. Also, oscillating mode (clockwise/counter-clockwise) produces higher throughput than rotation (clockwise). Regarding the milling speed, it was reported in the literature (Samanta et al., 2012) that, in general, when the milling speed is increased, the percentage of fines is increased as well. Nevertheless, the determination of the optimal milling parameters for both excipients is difficult, because there is not a clear tendency in the results and the performance depends not only on the milling conditions but also on the roll-compaction conditions and the intrinsic material properties.

According to this, for MCC ribbons compacted using cheek plates (Fig. 3.7), the values of  $d_{10}$  are below the original particle size, regardless the rotor type, the speed or the angle of rotation. However, at 4kN/cm, the pocket-moulded granulator produced less fines (higher  $d_{10}$ ) than star granulator when rimmed-roll is used as sealing system. At 8 kN/cm, rimmed-roll is also preferred but the difference in the amount of granules produced if the two milling systems are compared is less pronounced; although fewer fines are produced with star granulator. In summary, for MCC, the pocket mould-grooved is preferred to mill low-densified ribbons and star granulator for high-densified ribbons. For MCC, the minimum percentage of fines is produced when ribbons are produced at 8 kN/cm using rimmed-roll and milled at 30 rpm clockwise using star granulator as milling system. On the contrary, for mannitol, the higher value of  $d_{10}$  is obtained for ribbons produced at 8 kN/cm with rimmed-roll milled at 30 rpm clockwise with the pocket mould-grooved granulator.

A statistical evaluation was done in order to evaluate the effect of the operation conditions on the value of  $d_{10}$ . It was performed using MODDE Pro 11.0.1 (Umetrics, Malmö, Sweden) based on multiple linear regression (MLR). The relative significance of the different factors on the responses was evaluated through the coefficient plots, which display the regression coefficients with confidence intervals. The size of the model terms reflects the magnitude of the change in the response when a factor varies. If a response increases when a factor increases, the factor sign will be positive. Therefore, the sign represents the relation of the influence (direct or inverse relation) of

that parameter on the response. A coefficient should be considered significant if the confidence interval does not cross the X-axis.

The coefficient plot for  $d_{10}$  is presented in Fig. 3.9. It can be seen that the type of material is the first and most important factor to take into account. The coefficient value for mannitol is positive, which means that larger values of  $d_{10}$  are obtained with this material. This implies that more fines are produced with MCC than with mannitol. The specific roll-compaction force and the rimmed-roll as the sealing system have a proportional influence on  $d_{10}$ , i.e. the higher the compaction force, the higher the  $d_{10}$ . As it was mentioned before, it is preferable to work at high roll-compaction force and using the rimmed-roll in order to reduce the amount of fines. The type of mill and the speed are considered non-significant factors (the confidence interval cross the X-axis), but the angle of oscillation has a direct influence, hence, the clockwise mode is preferred.

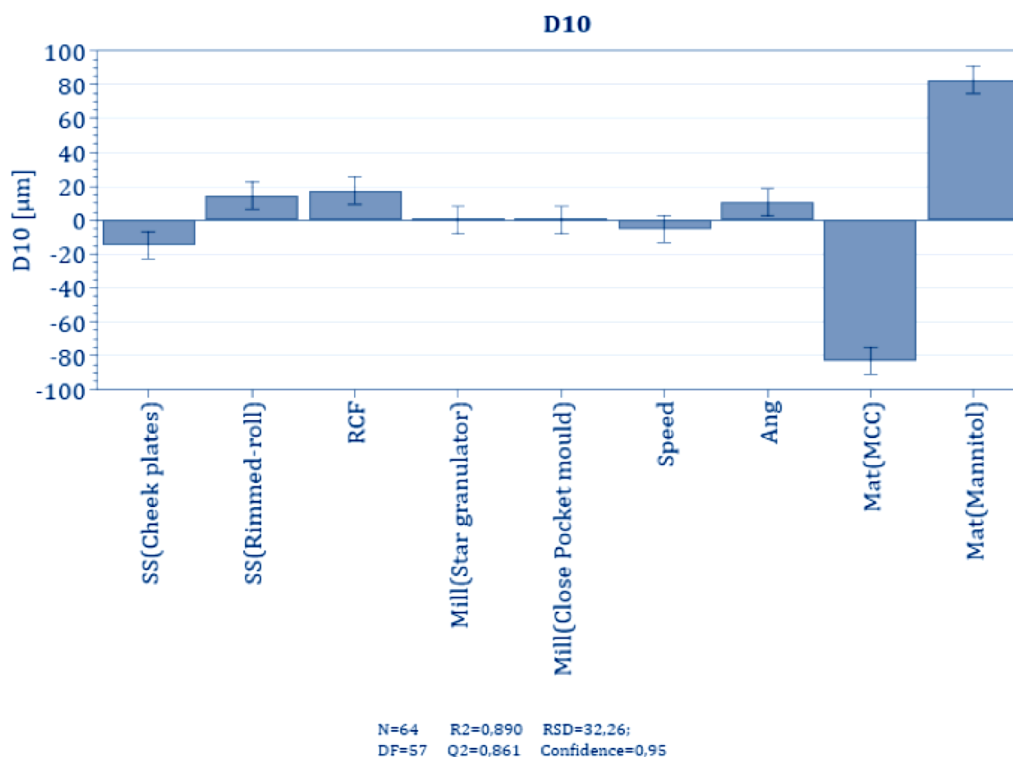


Fig. 3.9. Coefficient plot for  $d_{10}$  (SS= sealing system, RCF= Roll-compaction force; Ang= angle of rotation; Mat=material).

### 3.2.4. Tableability of roll-compacted granules

As it was seen, each batch of ribbons produced a different granule size distribution. During die filling, granule size distribution has a direct effect on the segregation of particles inside the die (different rearrangement of particles) and this can induce

afterwards a gradient of tablet density and heterogeneity of the API content. In order to avoid the impact of fine population on tablet properties, the size range was reduced. Granules were divided using sieve. This division allows evaluating and comparing the behaviour of granules under die compaction. The granule size range used for the die compaction study was 200-500  $\mu\text{m}$ . The tablets were prepared with the Instron press and their tensile strength was measured, as detailed in Chapter 2.

- *How do roll-compaction conditions affect the compactability of tablets?*

In order to be able to analyze the effect of the roll-compaction conditions on the tablets properties, the differences due to the milling step should be minimized. Therefore, only granules obtained under the same milling conditions were compared (but different roll-compaction conditions). Therefore, the granules obtained with the star granulator at 30 rpm clockwise were used. In Fig. 3.10 and Fig. 3.11, the tensile strengths are shown for feed powders and granules as a function of the tablet relative density.

Regarding the excipients, as it was expected, the tablets produced with MCC had higher tensile strength. On the other hand, the compaction of mannitol takes place predominantly by brittle fracture and, therefore, the tensile strength is lower than for MCC.

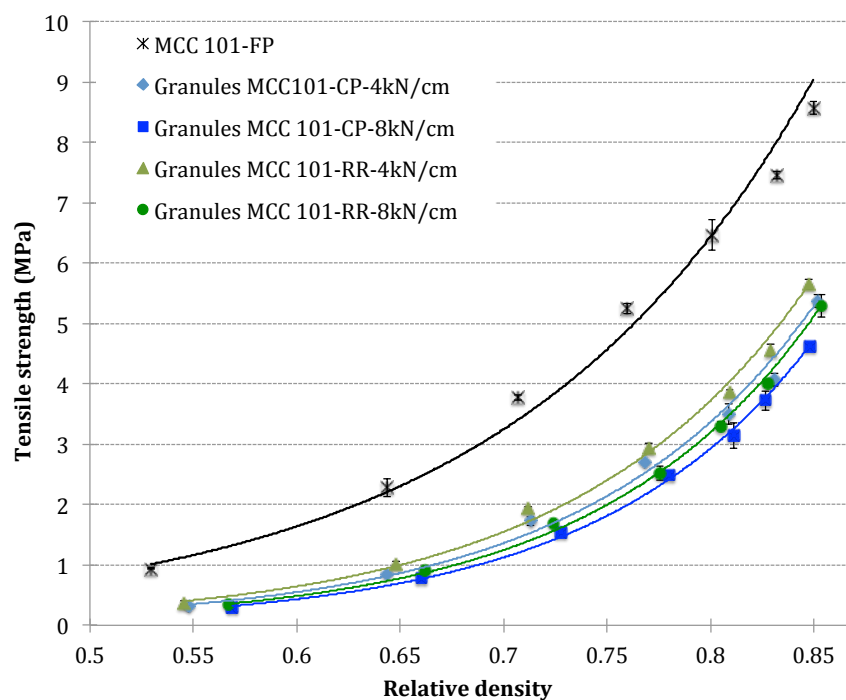


Fig. 3.10. Tensile strength as a function of relative density for MCC (CP= Check Plates, RR= Rimmed-roll; Roll compaction forces: 4 and 8kN/cm).

Regarding the effect of roll-compaction process on the tensile strength of the tablets, it can be observed that lower tensile strength is achieved for granules than for original

feed powders, mainly for MCC. This phenomenon of reduction of tensile strength after roll-compaction is known as “loss of reworkability” and it has been previously reported in the literature (Malkowska and Khan, 1983). Plastic materials are more sensitive to this phenomenon than brittle materials, as it was reported by Wu and Sun (2007). The tablets made with mannitol show very low mechanical resistance and the variation of the values of the tensile strength depending on the conditions is less significant.

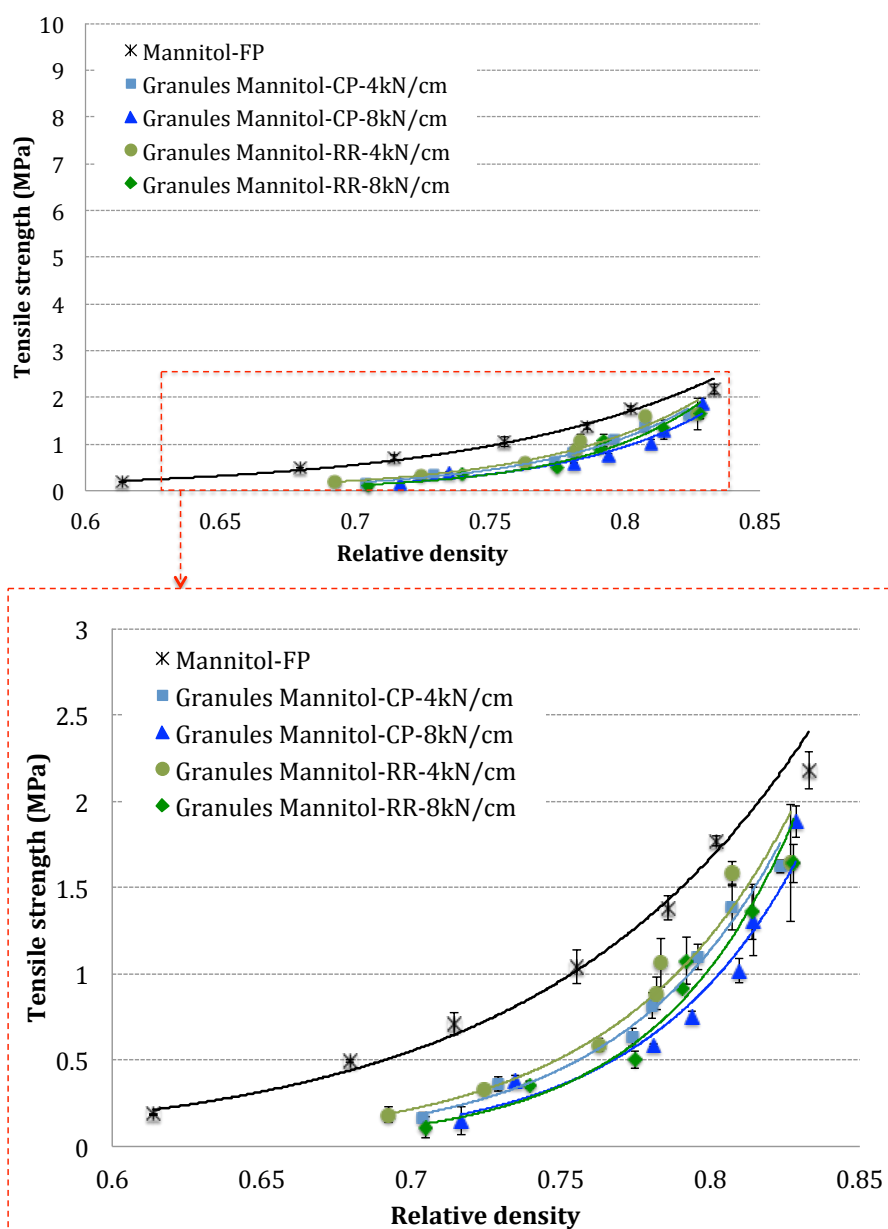


Fig. 3.11. Tensile strength as a function of relative density for mannitol (CP= Cheek Plates, RR= Rimmed-roll; Roll compaction forces: 4 and 8kN/cm).

For both excipients, results showed that the lowest tensile strength was obtained when the powders were roll compacted with cheek plates. On the one hand, as it was seen in

section 3.4, working with rimmed-roll reduced the amount of fines. On the other hand, the rimmed-roll system had less “loss of reworkability” than cheek plates. This is probably resulting from the mode of how stresses are applied on the ribbon. Indeed, in the cheek-plates case, the ribbon undertakes shearing stresses due to the friction between the powder and the seal wall whereas in the rimmed-roll system, the ribbon is more confined as in die compaction.

Regarding the roll-force, the higher is the level of compaction, the harder are the granules and, hence, more significant is loss of reworkability. Nevertheless, the tensile strength of tablets produced under different roll-compaction conditions has similar values.

The same statistical analysis as before was done for these results. The coefficient plot (Fig. 3.12) shows a non-significant effect of the roll-compaction conditions on the tensile strength (specific compaction force and sealing system assembled). The reduction of tensile strength after roll-compaction is evident when granules are compared to feed powder, but slightly different values are obtained for granules obtained under different roll-compaction conditions. Obviously, the die-compaction pressure (DCP) and the material behaviour under compression are the most noteworthy factors.

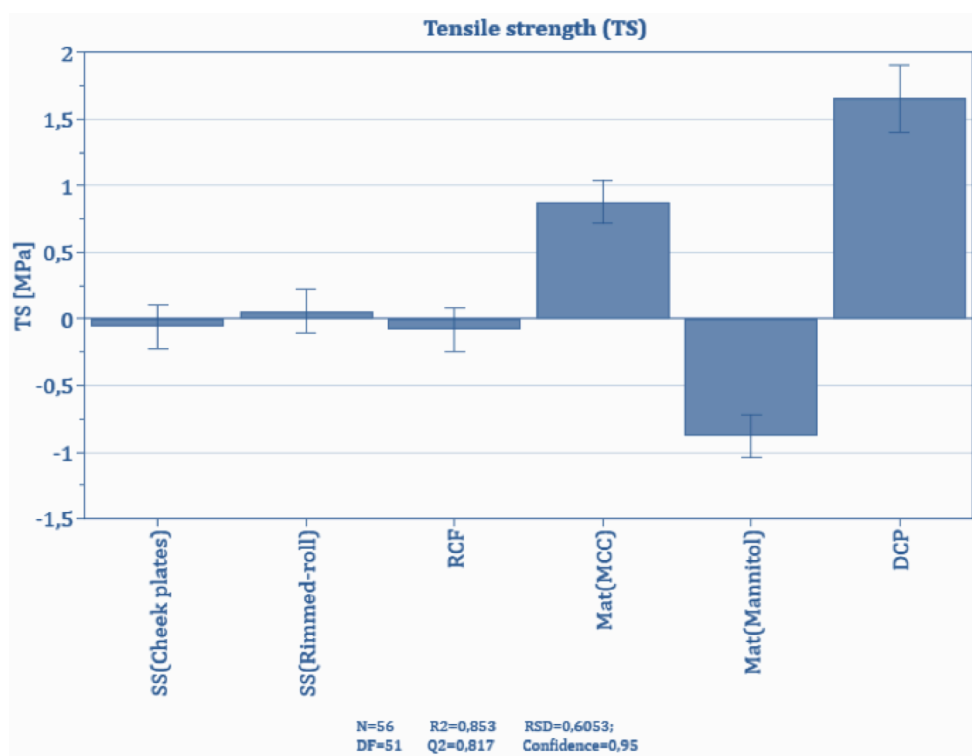


Fig. 3.12. Coefficient plot for tensile strength (TS) for different roll-compaction conditions (SS= sealing system, RCF= Roll-compaction force; Ang= angle of rotation; DCP= die-compaction pressure).



- *How do milling-conditions affect the compactability of tablets?*

As it was seen in section 3.2.3, different milling conditions can lead to different particle size distributions. It was reported in the literature that different milling systems and impellers can induce different milling mechanisms (Samanta et al., 2012), and therefore, to different size distributions.

The question asked here is, if due to the differences of the milling mechanisms (such as compression against the screen for example), is there any effect of the milling system on the mechanical properties of granules under compression? For that reason, the compactability of granules was used to evaluate the effect of various milling parameters on the mechanical properties of granules.

As we did before, the differences due to the roll-compaction step should be minimized and only the granules obtained under the same roll-compaction conditions but different milling conditions were tableted. Ribbons of MCC and mannitol compacted under 4 kN/cm of roll compaction force and using cheek plates as sealing system were milled under different conditions, detailed in section 3.1.1. Also, the range of size was reduced to [200-500  $\mu\text{m}$ ]. Table 3.2 and Table 3.3 show the tensile strength of tablets for granules of MCC and mannitol obtained under different milling conditions (clockwise and oscillating) for two different die compaction pressures: 40 and 100 MPa.

Table 3.2. Tensile strength of tablets for granules of MCC obtained under different milling conditions (CW= Clockwise; OSC= Oscillating) for two different die compaction forces.

Tensile strength (MPa)				
Milling system	Angle of rotation	Speed (rpm)	Die compaction pressure	
			40 MPa	100MPa
Star granulator	Clockwise 360°	30	1.33 ± 0.02	4.11 ± 0.07
		120	1.41 ± 0.04	4.43 ± 0.16
	Oscillating 150°	30	1.42 ± 0.04	4.55 ± 0.10
		120	1.43 ± 0.15	4.51 ± 0.04
Pocket mould-grooved	Clockwise 360°	30	1.43 ± 0.05	4.57 ± 0.11
		120	1.34 ± 0.05	4.64 ± 0.11
	Oscillating 150°	30	1.42 ± 0.05	4.49 ± 0.14
		120	1.39 ± 0.02	4.45 ± 0.20

Table 3.3. Tensile strength of tablets for granules of mannitol obtained under different milling conditions (CW= Clockwise; OSC= Oscillating) for two different die compaction forces.

Tensile strength (MPa)				
Milling system	Angle of rotation	Speed (rpm)	Die compaction pressure	
			40 MPa	100MPa
Star granulator	Clockwise 360°	30	0.36 ± 0.04	1.10 ± 0.07
		120	0.45 ± 0.02	1.06 ± 0.20
	Oscillating 150°	30	0.39 ± 0.04	1.21 ± 0.12
		120	0.40 ± 0.01	1.28 ± 0.16
Pocket mould-grooved	Clockwise 360°	30	0.32 ± 0.03	1.25 ± 0.09
		120	0.31 ± 0.02	1.25 ± 0.10
	Oscillating 150°	30	0.35 ± 0.02	1.31 ± 0.16
		120	0.33 ± 0.02	1.27 ± 0.07

As it was shown before, the tensile strength obtained for mannitol tablets is lower than for MCC. Regarding the milling parameters, results show that tensile strength of tablets produced at the same die compaction pressure has similar values, regardless of the mill type, speed and angle of rotation.

The coefficient plot (Fig. 3.13) confirms this statement, showing a non-significant effect of the milling conditions on the tensile strength. It is in agreement with what was confirmed by Vendola et al. (2008) that the mill type and the obtained granule size distribution did not greatly influence the compactability. As it was shown before, obviously, the die-compaction pressure (DCP) and the material behaviour under compression are the most relevant factors. Thus, it can be concluded in this study, that there is no significant effect of milling conditions on the mechanical properties of granules under die compaction.

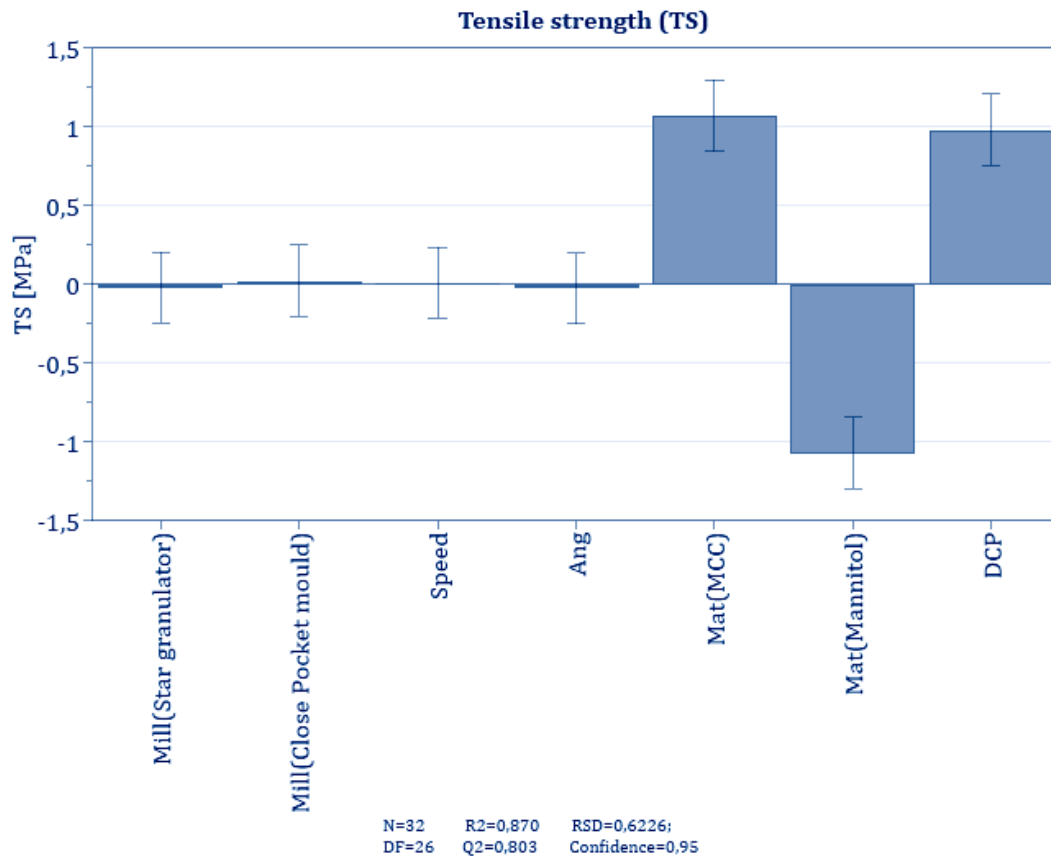


Fig. 3.13. Coefficient plot for tensile strength (TS) for different milling conditions (Ang= angle of rotation; DCP= die-compaction pressure).

### 3.2.5. Conclusions

It can be concluded that the roll-compaction effect is predominant over the milling effect for the generation of fines. According to the minimal production of fines approach ( $d_{10}$ ), it is preferable to work at a high roll-compaction force and use rimmed-roll as the sealing system in order to reduce the amount of fines produced, mainly for plastic materials. The statistical analysis confirmed this statement, but also the angle of oscillation resulted to have a direct influence of mill. In contrast, the type of mill and the speed are considered non-significant factors on  $d_{10}$ .

The characterization of loss of compactability confirms the loss of reworkability after roll-compaction and that is more significant for plastic materials. Nevertheless, the subsequent statistical analysis showed that the parameters are not significant factors on the tensile strength, mainly controlled by the material characteristics and the die-compaction pressure.

### 3.3. SEALING SYSTEM AND RIBBON DENSITY DISTRIBUTION

In the previous section, it was investigated how the sealing system design affects the production of fines and, slightly, the compactability of tablets. The statistical analysis confirmed that the sealing system has significant effect on the amount of fines. Moreover, it was concluded that the rimmed-roll as the sealing system is preferred in order to reduce the amount of fines produced. On the other hand, the sealing system showed small differences in the results of tensile strength and the statistical analysis pointed out that the effect of the sealing system on the tensile strength of tablets was not significant. So, the sealing system has a significant effect mainly on the granules attributes.

These statements led us to wonder:

- Is there a difference in the ribbon density distribution depending on the type of sealing system used?
- In that case, what will be the influence of the different density distributions on the milling performance?

Therefore, these questions will be discussed in this section, through the analysis of the effect of the sealing system on the ribbon density distribution (measurements of density distribution along the ribbon width using different techniques) and the milling performance of pieces placed in different position of the ribbon width through the analysis of mass throughput (mass of ribbons milled as a function of the milling time) and granule size distribution.

#### 3.3.1. Density distribution

The relative density distributions along the ribbon width for cheek plates and rimmed-roll are represented, respectively, in Fig. 3.14 and Fig. 3.15 only for MCC 101 (As it was seen in Fig. 3.2, for mannitol it was only possible to obtain small fragments with irregular shapes. Therefore, the density distribution cannot be measured for this excipient). Ribbon width pieces were sectioned into four rectangular pieces (0.6 x 1 cm) and the density was measured for each piece. Therefore, the profiles of density distribution were created representing the relative density value of each sectioned piece over the  $x$  axis, which represents the position along the width, being the position  $x=0$  the central point of the ribbon width (2.5 cm of total width).

At first sight, it can be remarked that all the profiles show similar patterns for each type of sealing systems, independently of the method of characterization. Nevertheless,

the accuracy of the methods differs. It is clear that increasing the roll-compaction force, the average relative density is higher. Regarding the sealing systems, two different patterns are obtained.

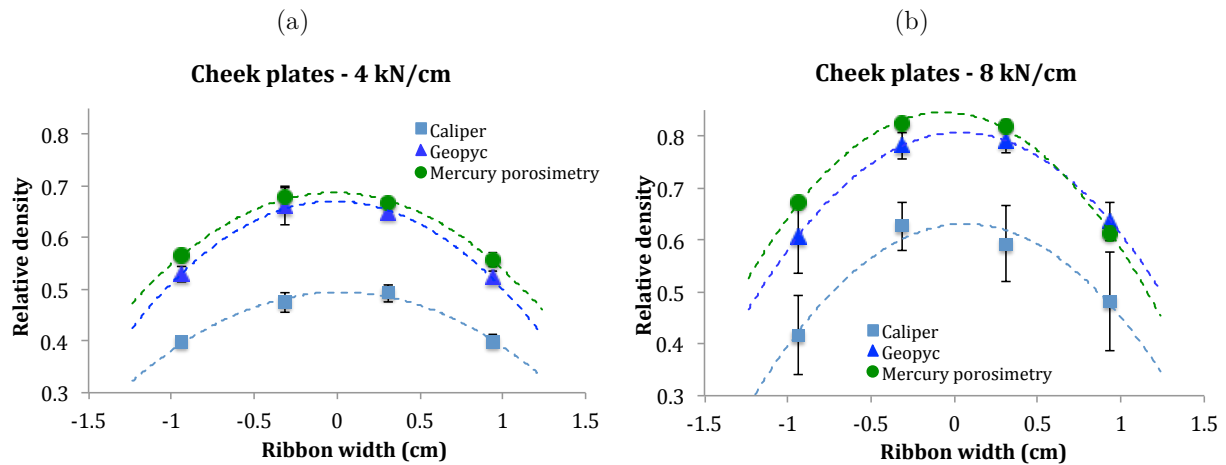


Fig. 3.14. Density distribution along the ribbon width for cheek plates as sealing system for a roll-compaction roll force of (a) 4 kN/cm and (b) 8 kN/cm.

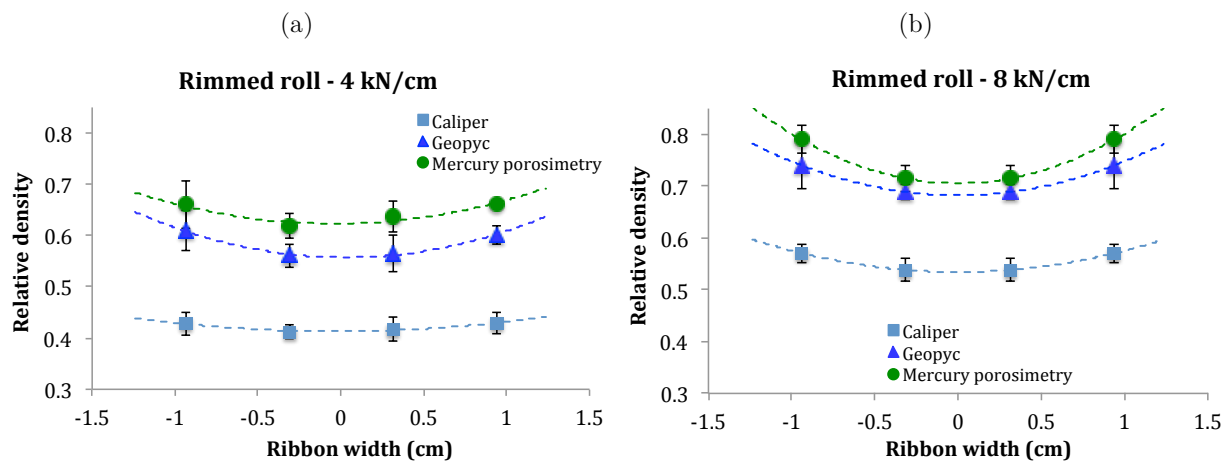


Fig. 3.15. Density distribution along the ribbon width for rimmed roll as sealing system for a roll-compaction roll force of (a) 4 kN/cm and (b) 8 kN/cm

Results for cheek plates (Fig. 3.14) showed that a lower density is obtained at the edges than in the middle of the ribbon width. This is due to the friction of the powder with the plates, which act as resistance to the powder flow, resulting in a non-uniform flow of powder into the compaction zone and, as consequence, non-uniform pressure is applied and a density variation is obtained. These patterns for cheek plates are in agreement with those obtained previously in the literature for roll-compaction with stationary cheek plates (Miguélez-Morán et al., 2009).

On the other hand, using the rimmed-roll system (Fig. 3.15), it can be observed that more uniform profiles are obtained. The rimmed-roll allows the conveying of powder to the gap in a more uniform manner. However, slightly higher density zones are developed at the edges of the ribbons. This heterogeneity can be explained by comparison to what happens when the powder is die-compacted. During die compaction, a higher density zone is obtained at the top edge of the tablet due to the friction between the powder, the die and the punch (Wu et al., 2005; Kadiri and Michrafy, 2013). Similar behaviour can be assumed when using rimmed-roll system: the upper roll acts as an upper punch and the bottom roll together with the rims act as the die. Then, the friction prevents the powder from moving forward along the interfaces of upper roll and rims. Notwithstanding, the differences of density between the center and the edges are smaller than those obtained with the cheek plates.

These results are comparable with the modelling results obtained by Mazor et al. 2016 with Finite Element Analysis. In this work, a 3D Finite Elements Method (FEM) modelling is used to analyse the roll compaction process and the effect of sealing system designs on the compacted ribbon's density distribution. A density dependent Drucker–Prager Cap (DPC) constitutive model for MCC101 was calibrated and implemented in Abaqus. The results of the state variable relative density distribution of the powder between the rolls using both sealing systems are visualized in Fig. 3.16. Similar patterns to the experimental ones were obtained, with the highest values of density in the middle and the lowest in the edges for cheek plates and the opposite for the rimmed-roll system. Nevertheless, the ribbon density at the edges for the cheek plates sealing system was overestimated due to the assumptions of mass conservation made in the FEM.

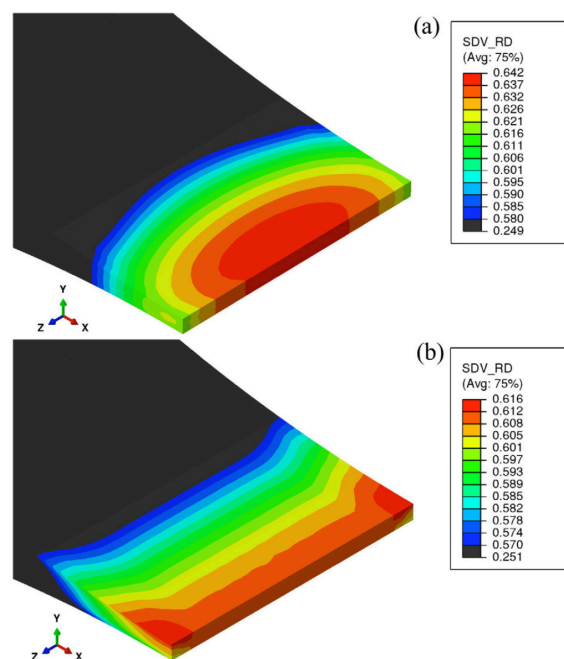


Fig. 3.16. Modelling results of the relative density of ribbons produced with (a) cheek plates and (b) rimmed-roll (Mazor et al., 2016)

Comparing the three techniques, Fig. 3.14 and Fig. 3.15 show that the three of them are capable of measuring the variation of density depending on the width position and the same types of profiles are obtained, but with different accuracy. The simplest technique is the determination of density through the measurement of the dimensions with a calliper. In this case, the lowest values of density are obtained due to the fact that the volume is overestimated. The ribbon sections are irregular pieces and the assumption of its shape as perfect rectangles induced to an overestimation of the volume and, hence, underestimation of the density. This technique is easy and fast to use and it is able to predict the profile of density variation but it is difficult to get precise density information. Instead, the density values obtained with the Geopyc pycnometer and mercure porosimetry are closer and differ slightly, showing less variability. The Geopyc analyser measures the ribbon volume by covering it with a very fine powder (DryFlo®) with a wide particle size distribution that contours the ribbon shape (Zinchuk et al., 2004). It is a reliable method, easy to use and the results are reproducible. Nevertheless, the DryFlo® is not able to arrive to the small interstices, when the pore diameter is smaller than the DryFlo® diameter. On the contrary, intruded mercury is able to arrive to small pores and, hence, the obtained apparent volume is lower and higher values of density are obtained.

The three techniques used in this work are able to determine the pattern of the density distribution depending on the sealing system and have the advantage of not requiring calibration. Nevertheless, they are destructive techniques and are not able to detect

local heterogeneities. In order to assure the quality of ribbon during production (in-line), density distribution should be controlled with non-destructive techniques such as X-ray tomography (Miguélez-Morán et al., 2009; Akseli et al., 2011), ultrasonic (Akseli et al., 2011), near infrared chemical imaging (Lim et al., 2011; Khorasani et al., 2015; Souihi et al., 2015) or terahertz (Zhang et al. 2016), that can provide spatial information of the ribbon density without cutting the sample. However, these techniques require calibration to correlate the signals with the bulk density.

### 3.3.2. Milling performance

The ribbon pieces (regrouped into edges or center pieces) were milled separately in the oscillating Erweka milling device at 100 rpm with a 2 mm sieve and the mass throughput and the granule size distribution were measured.

#### 3.3.2.1. Mass throughput

The milling performance of the different sections (edges and center) was evaluated through the evolution of the milled mass (mass throughput, %) as a function of the time. Results are shown in Fig. 3.17 and Fig. 3.18 and they are in direct relation to the density distribution profiles.

The size reduction is directly correlated with the degree of densification of the ribbons. In general, ribbons pieces with lower density are milled easily than the denser ones. That is why, in the case of cheek plates (Fig. 3.17), it was observed that more throughput was obtained from the edges than from the center parts for a certain time.

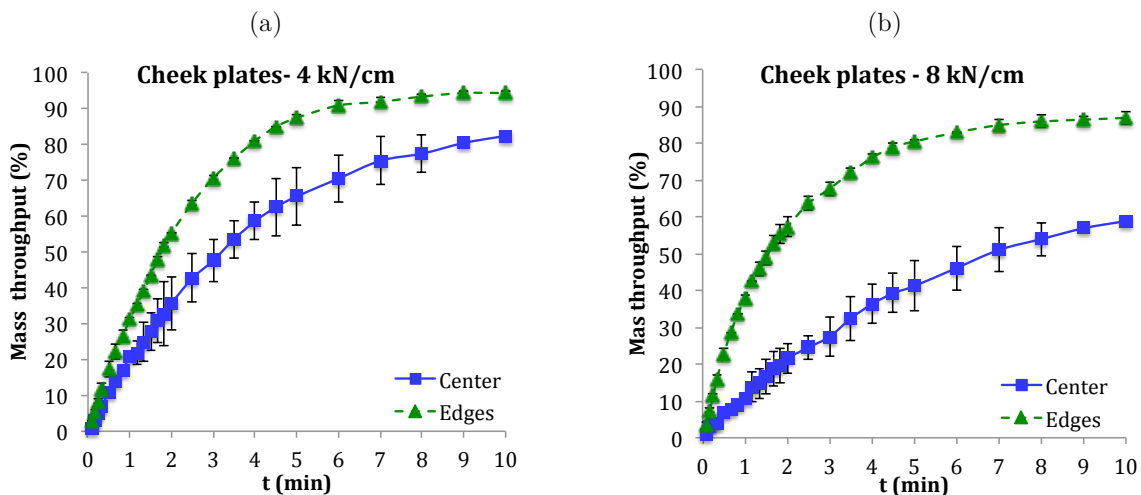


Fig. 3.17. Mass throughput after milling ribbons produced with cheek-plates for a roll-compaction force of (a) 4 kN/cm and (b) 8 kN/cm.



For 4kN/cm of roll-compaction force, a ribbon granulation of 85% was obtained for the center after 10 minutes while the edges were milled up to 95% in that time. Moreover, when the roll-compaction force was increased (8 kN/cm), the difference between the mass throughputs obtained from the edges (87%) and from the center (54%) is more significant after 10 minutes of milling. Denser ribbons are harder and, hence, more difficult to deagglomerate.

The curves obtained when the rimmed-roll system was used showed the opposite effect than cheek plates. Ribbons produced using rimmed-roll at 4 kN/cm had a density profile quite homogeneous (Fig. 3.18) and the mass throughputs curves from the edges and the center are almost overlapping, arriving to 97% after 10 minutes.

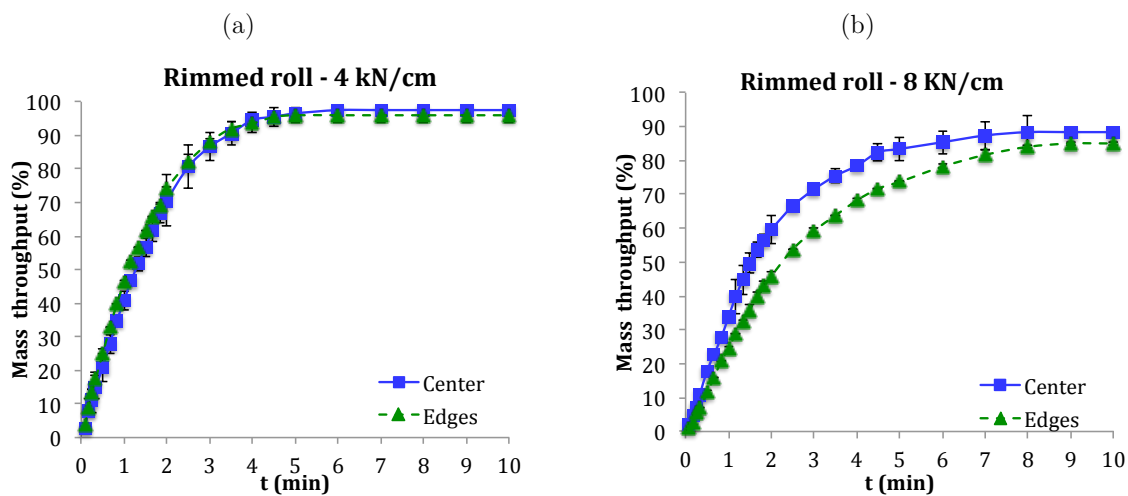


Fig. 3.18. Mass throughput after milling ribbons produced with rimmed-roll system for a roll-compaction force of (a) 4 kN/cm and (b) 8 kN/cm.

At high roll-compaction force, the mass throughput curves are inverted compared to the ones obtained from cheek plates. This is, the edges were slightly denser and, therefore, more difficult to mill and the mass throughput is inferior for the edges than for the center sections, but the curves are closer to each other than in the case of cheek-plates. So, when rimmed-roll is used higher throughput is obtained from both, edges and center sections, mainly at low roll-compaction force (4kN/cm).

### 3.3.2.2. Granule Size distribution

The granule size distributions were obtained using sieve and are represented Fig. 3.19 and Fig. 3.20. The question here was if the differences on the density distribution profiles would be translated into different size distributions of granules obtained from the different sections.

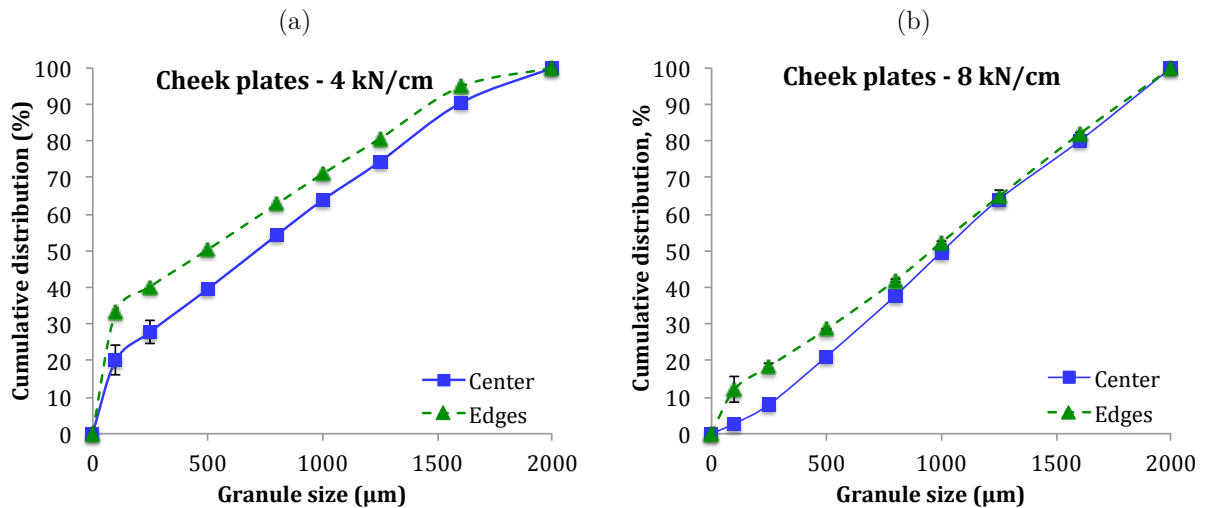


Fig. 3.19. Granule size distributions obtained from milling ribbons produced with the cheek-plates system for a roll-compactation force of (a) 4 kN/cm and (b) 8 kN/cm.

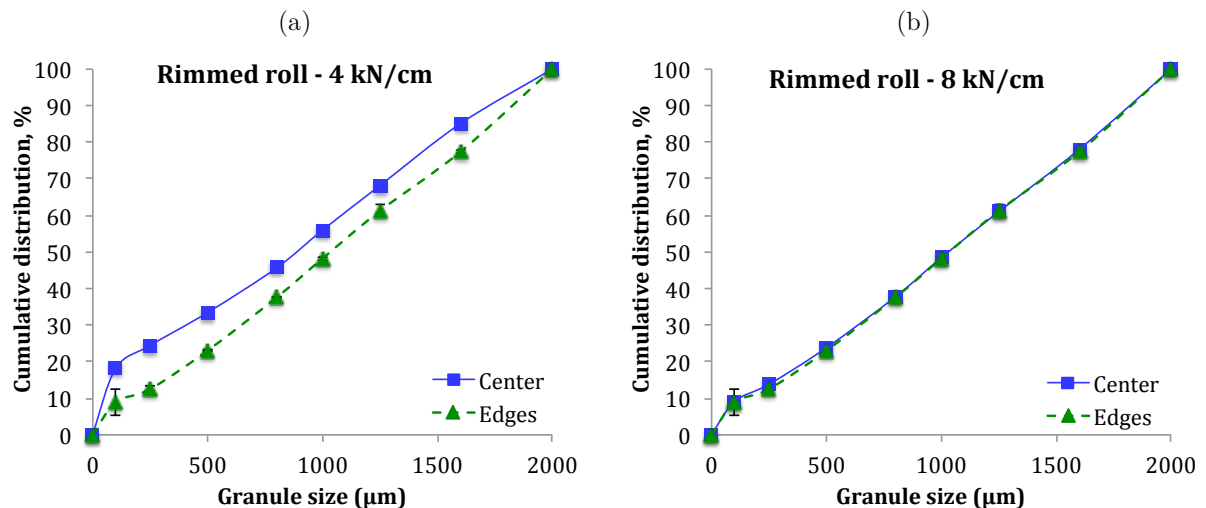


Fig. 3.20 Granule size distributions obtained from milling ribbons produced with the rimmed-roll system for a roll-compactation force of (a) 4 kN/cm and (b) 8 kN/cm.

These differences between the size distribution curves were found and they are due to three factors: the roll-compaction force, the use of a sealing system and the position of the milled piece along the ribbon width (edges or center), as it is described next.

I. Roll-compaction force. The roll-compaction force used to produce ribbons had a direct effect on the size of granules. The granule size increased when the roll-compaction force was increased. This is represented by the shifting of the curves from left (Fig. 3.19a and Fig. 3.20a) to right (Fig. 3.19b and Fig. 3.20b). At 8kN/cm, the degree of ribbon densification is higher and it is harder to deagglomerate and, therefore, coarser particles are obtained. This is in agreement with our results of the previous section and with other research works (Herting and Kleinebudde, 2008; Omar, et al., 2015).

II. Sealing system. Ribbons produced with cheek plates produced more fines comparing to the ones produced with rimmed-roll system at the same compaction force. As it was shown in the previous section, the rimmed-roll as sealing system have a proportional influence on  $d_{10}$ , i.e. the use of rimmed-roll system induced a decrease in the amount of fine.

III. Position of the milled piece along the ribbon width. In this study, the granule size distribution of the granules from different pieces along the ribbon width has been studied. In section 3.3.1 the density distribution showed evident differences among the samples and Fig.7 confirms the influence of the ribbon density distribution on the quality of granules. For cheek plates (Fig. 3.19), the denser pieces (center) give coarser particles than the edges. On the other hand, for rimmed-roll system (Fig. 3.20), coarser particles are obtained from the edges (edges curves shifted to the right compared to the center pieces curve). Moreover, at 8kN/cm using the rimmed-roll system (d), the curves are overlapping. So in terms of control of homogeneity of granule size, these conditions are preferred.

### 3.3.3. Conclusions

In this section, the influence of the sealing system on the ribbon density distribution has been analysed. The ribbon relative density is an important property that gives valuable information about the quality of the ribbon and the roll-compaction process. In addition, a study on the milling performance (in terms of mass throughput and granules size distribution) showed the effect of the ribbon density distributions on the granules properties.

Results indicated that, the ribbon relative density values depend on both the roll-compaction force applied and the sealing system design. The use of cheek plates results in non-uniform density distribution along the ribbon width, with higher densities in the

middle of the ribbon and lower densities at the edges. The density distribution obtained when using the rimmed-roll system is more homogenous, although values of density are slightly higher at the edges, mainly at high roll-compaction force.

In order to see the effect of these heterogeneities on the quality of granules, the milling performance was evaluated. Regarding the mass throughput, results highlighted that, for cheek plates, the centre parts of the ribbon were harder to mill. The opposite effect was found for rimmed-rolls.

Regarding the granule size distribution, for ribbons produced with cheek plates, coarser particles are obtained from the centre than from the edges. On the other hand, for the rimmed-roll system, coarser particles are obtained from the edges. In other words, coarser particles are obtained from denser agglomerates. It was found that is preferred to work at 8kN/cm using rimmed-roll system, obtaining the same particle size distribution from the edges than in the centre. This latest statement agrees with the previous section, where less fines were obtained under these conditions.

### 3.4. CONCLUSIONS

The objective of this chapter was to discuss the results of the effects of different roll-compaction and milling conditions (roll-force, sealing system design and milling system and milling parameters) on the produced ribbons, granules and tablets of MCC and mannitol. In this study, two roll-forces (4 and 8 kN/cm) were applied and two different sealing conditions (cheek plates and rimmed-roll) were used to produce ribbons. After, the ribbons were milled using two milling systems (star and pocket mould-grooved) with different operating conditions (milling speed: 30 and 120 rpm; rotation mode: clockwise-360° and oscillating-150°) to generate granules, used further in tableting process. The ultimate interest was to determine and discuss of the results of varying the operating conditions that can improve the quality of ribbons, granules and tablets.

To reach that goal, it is necessary to find a balance between a good flowability (reducing the amount of fines produced during the milling step) and the loss of reworkability during die compaction (caused by roll compaction). Therefore, the analysis of results was done based on the amount of fines (through the value of  $d_{10}$ ) and the tensile strength of tablets produced with roll-compacted granules compared to the feed powder. In addition, an

First, the minimal fines approach results showed that for MCC, the minimum percentage of fines (higher value of  $d_{10}$ ) is produced when ribbons are produced at 8 kN/cm using rimmed-roll and milled at 30 rpm clockwise using star granulator as milling system. On the contrary, for mannitol, the higher value of  $d_{10}$  is obtained for ribbons produced at 8 kN/cm with rimmed-roll system milled at 30 rpm clockwise with the pocket mould-grooved granulator. So, it was evidenced that is preferable to work at high roll-compaction force and rimmed-roll as sealing system in order to reduce the amount of fines produced. On the other hand, the milling conditions differ between the two excipients. However, the statistical analysis pointed out that the roll-compaction effect is predominant over the milling effect for the generation of fines, mainly for plastic materials. Moreover, the specific roll-compaction force and the rimmed-roll as sealing system have a significant proportional influence on  $d_{10}$ .

The characterization of loss of compactability confirms the loss of reworkability after roll-compaction and that is more significant for plastic materials. Nevertheless, the subsequent statistical analysis showed the parameters are not significant factors on the tensile strength, mainly controlled by the material character and the die-compaction pressure. On the other hand, the characterization of loss of compactability of granules under die compaction showed that with the rimmed-roll system at low roll-compaction force slightly stronger tablets are produced. Nevertheless, the roll-compaction and

milling conditions resulted as non-significant factors on the tensile strength, based on the statistical analysis.

Based on these results, we considered pertinent to further investigate the relation between ribbon properties and granules size when these two parameters (roll-compaction force and sealing system) are varied. For that, in the second section of the chapter, the influence of the sealing system on the ribbon density distribution was first measured and, then, the milling performance was evaluated.

It has been shown that, the use of cheek plates results in non-uniform density distribution along the ribbon width, being obtained higher densities in the middle of the ribbon than at the edges. The patterns obtained when using cheek plates are in accordance with the literature. On the other hand, the density distribution obtained when using the rimmed-roll system is more homogenous, although values of density are slightly higher at the edges, mainly at high roll-compaction force.

Results highlighted the importance of controlling the density distribution profiles along the ribbon width in order to narrow the dispersion of the particle size distributions. Under the same milling conditions, it has been reported that the granules properties resulted an extrapolation of the ribbon characteristics.

Furthermore, it was proved that the density distribution of the ribbons has an important impact on the milling performance. Mass throughput measurements showed that ribbons compacted at high force were harder to mill. This means that the central part for ribbons produced with cheek plates and edges of ribbons produced with rimmed-roll system remained more time in the milling chamber. Moreover, for cheek plates, the center parts of the ribbon give coarser particles than the edges and for the rimmed-roll system coarser particles are obtained from the edges. It was found that at 8 kN/cm using rimmed-roll system the same particle size distribution is obtained from the edges and from the center pieces. Therefore, from a quality by design point-of view, these conditions are preferable in order to assure a homogeneous particle size distribution.

To summarize, different operating conditions of roll-compaction and milling were evaluated in order to improve the quality of the products, including ribbons (through density distribution results), granules (through the evaluation of  $d_{10}$  and milling performance) and tablets (tensile strength). The results allowed recognizing the most significant parameters: material character, sealing system and roll-compaction force.



## Chapter 4.

# Die-compaction results and modelling

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### Abstract

*In this chapter, the compaction behaviour of feed powder and roll-compacted granules was investigated. In the first part, the analysis was conducted for MCC and was based on the Drucker-Prager Cap (DPC) model. The material parameters of virgin material and granules were determined based on standard procedure experiments for DPC calibration.*

*In the second part, the analysis focused on the role of the composition of dry granulated binary mixtures of lactose and MCC and the effect of the granule size distribution on the compaction behaviour. In particular, compressibility, compactability and stress transmission measurements during the compaction were analysed and discussed.*

### Resumé

*Ce chapitre fait l'objet de l'étude de la compréhension des différences de comportement en compression de poudres granulées et non-granulées de poudre de cellulose microcristalline (MCC). L'analyse est menée à l'échelle locale en considérant la poudre comme un milieu poreux continu avec une seule phase solide. Le comportement en compression est représenté par le modèle Drucker-Prager Cap (DPC). Les paramètres du matériau vierge (poudres non-granulées) et ceux du matériau composé de poudres granulées sont déterminés en se basant sur la procédure standard de calibration. Une discussion sur le lien des résultats obtenus et les mécanismes sous-jacents de densification est proposée. Dans cette analyse, l'effet de la taille des granulés sur les paramètres du modèle DPC est aussi identifié et analysée.*

*Dans la deuxième partie de ce chapitre, l'étude a porté sur le comportement en compression d'un mélange binaire de lactose et de MCC. Les résultats concernent le mélange binaire avant et après granulation pour 3 proportions de dosage. Les effets de la granulation, de la taille des particules ainsi que les proportions de dosage sur les propriétés de compressibilité et de compactabilité sont présentés et analysés. Par ailleurs, une analyse de la transmission des*



*contraintes pendant le cycle de compression est menée pour mettre en exergue l'hétérogénéité générée.*

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## 4.1. INTRODUCTION

The most challenging limitation of the dry granulation by roll-compaction process is the ‘loss of reworkability’ or ‘loss of tabletability’, which leads to an inferior tensile strength of tablets compared with direct compression. In order to better understand this phenomenon, the compaction behaviour of roll-compacted granules was evaluated through the calibration of the DPC model for MCC 101. The results will be correlated to the deformation mechanisms of the granules.

Furthermore, many researchers have worked on the understanding of the influence of the raw material properties on this phenomenon (Malkoska and Khan, 1983; Sun and Himmelpach, 2006; Herting and Kleinebudde, 2007; Bacher et al., 2008; Šantl et al., 2011) and two critical attributes were highlighted to be critical for this phenomenon: the mechanical behaviour of the powder (the loss in compactability is more significant for plastic materials than for brittle materials) and the granule size (an increase in the granule size reduces the tensile strength). For this reason, a study was carried out and the effect of the composition (binary mixtures of a plastic and a brittle material) and the granule size effect were evaluated together with an analysis of the stress transmission during the process.

## 4.2. COMPACTION BEHAVIOUR OF GRANULATED POWDER BASED ON DPC ANALYSIS

How granulated powders behave during die compaction and why they exhibit different behaviours from those showed by raw material is still a challenge. Currently, there is no credible procedure able to explain the above challenge. A tentative to explore the differences of compaction behaviour for raw and granulated material was to conduct a study on the behaviour, under stressing, of the main parameters of particulate solids, proposed by DPC model, which is commonly used in the field.

To go further in the investigation of the compaction behaviour of granules a pure excipient (MCC 101) was used to produce ribbons that were milled into granules (with the Komarek roll-compactor and the Erweka oscillating milling as described in in Chapter 2 ). The ribbon relative density was 0.57. Then, granules were sieved and two size classes were selected [250-500 $\mu\text{m}$ ] and [1250-1600  $\mu\text{m}$ ], to study the effect of granule size on the results. SEM images of each type granules can be observed in Fig. 4.1. Although these granules are coming from the same type of ribbons, it can be observed that coarser granules look more densified than the small ones.

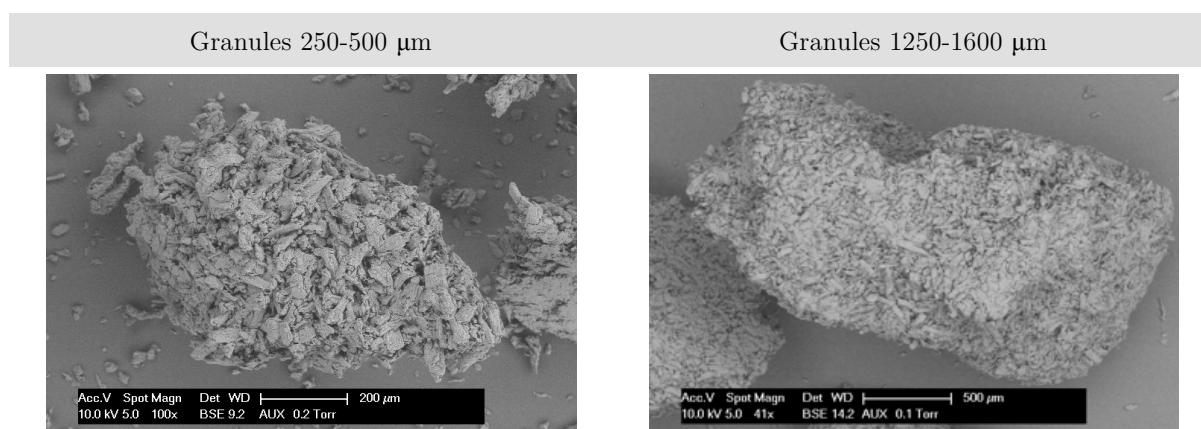


Fig. 4.1. SEM images of roll-compacted granules

To identify the material parameters based on the DPC model, the standard procedure of experiments was used (as described in Chapter 2) and tablets were prepared for uniaxial and diametrical strength test using the Instron press and the Frogerais press to measure the radial stress. The study was based on the analysis at different tablet densities: 0.4, 0.5, 0.6, 0.7, 0.8, 0.85 and 0.9. Thus, the material parameters will be analysed for a large range of relative density (low and high) for the feed powder and for the two granule size ranges.

Fig. 4.2 shows optical images of tablets (9 mm of height) prepared at different relative densities (from 0.4 to 0.9) using the granules of the two size ranges. The images are the top and side views of the tablets. Differences in the surface can be observed. On the one hand, at low relative density (0.4 and 0.5), it can be observed rough surfaces where the granules boundaries can be distinguished, mainly for large granules. At this level of compaction, the granules have passed the stage of rearrangement and start to deform plastically. On the other hand, at higher density, the surfaces becomes smother and more homogeneous. At a relative density of 0.8 and 0.9, the granular structure is not visible. This suggests that, during compaction, the granules fractured into smaller particles that were again rearranged filling the voids and deformed.

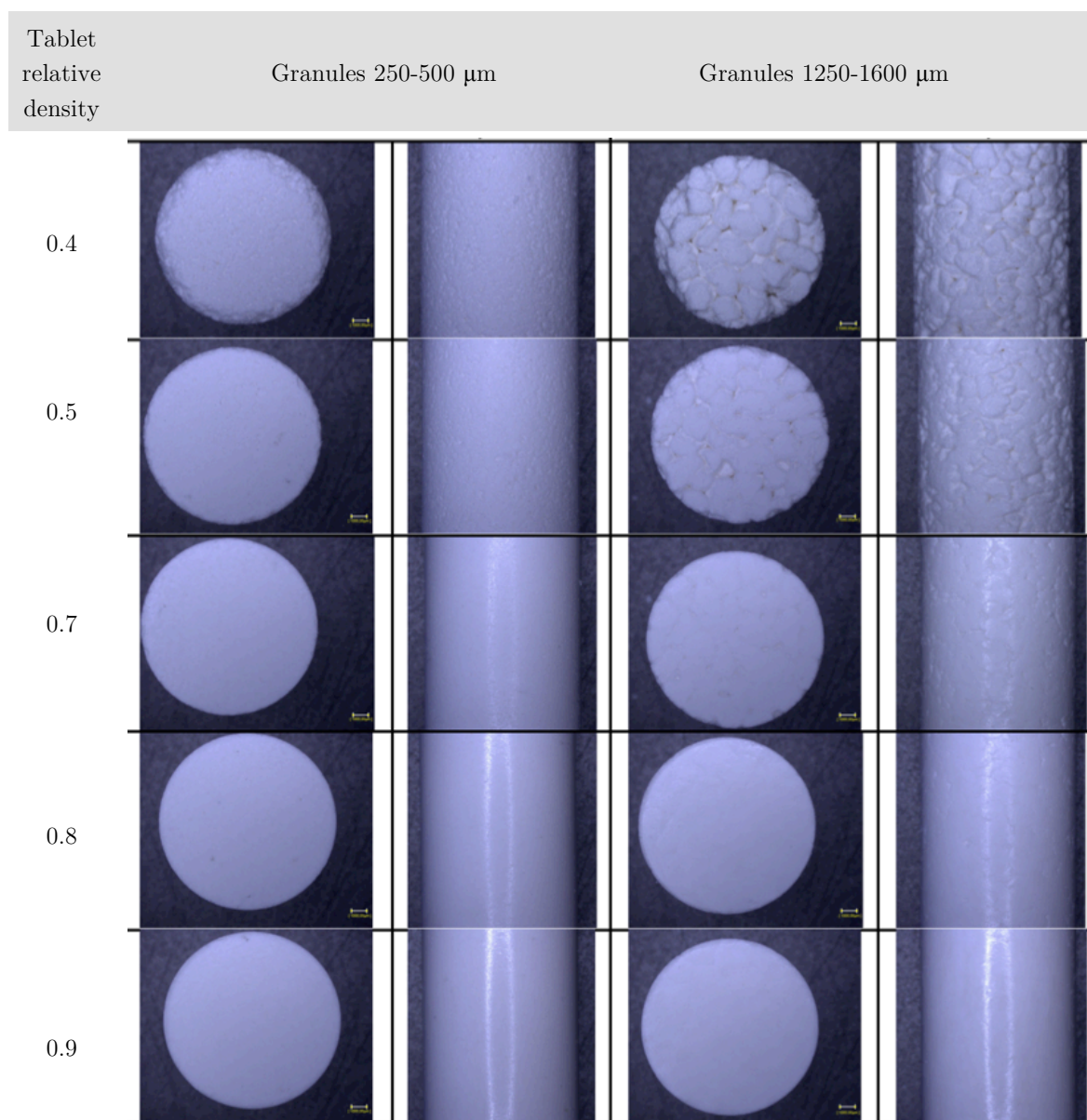


Fig. 4.2. Optical images of tablets at different tablet relative density (Height=22 mm)

### 4.2.1. Cohesion and internal friction coefficient

In order to determine the shear failure line of the DPC model and to calculate the cohesion and the angle internal friction parameters, the uniaxial compression strength and the diametrical tensile strength were obtained. Both strengths results are plotted in Fig. 4.3 and Fig. 4.4 as a function of the tablet relative densities.

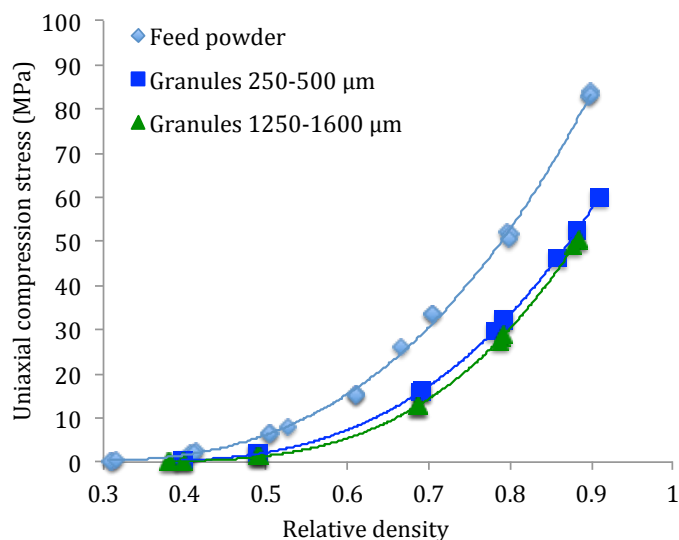


Fig. 4.3. Uniaxial compression strength of tablets

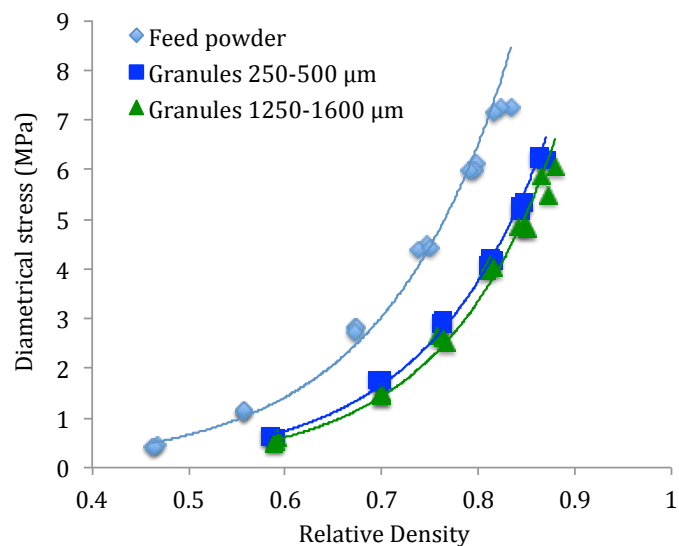


Fig. 4.4. Diametrical tensile strength of tablets

For uniaxial compression, it was possible to reach densities lower than 0.4 due to the dimensions of the tablets (9mm of height), which give tablets strong enough to be handled. On the other hand, for diametrical test, the tablets were compacted at different compaction pressures, being the minimum pressure 20 MPa, which gave

minimum relative densities of 0.46 for feed powder and 0.59 for granules. For later calculations of the shear failure parameters at lower densities, the results were fitted in exponential regressions. In both cases, we can observe that there is a decrease of the strength when comparing the feed powder with the granules, as it was observed for other materials in previous sections of this thesis. Also, both strengths decrease when the granule size increase.

The results of the diametrical and uniaxial compression strengths were plotted in the plane  $p$ - $q$  and the shear lines were fitted, obtaining the values of cohesion (intersection with  $q$  plane) and angle of internal friction (slope of the line) for relative densities of 0.4, 0.5, 0.6, 0.7, 0.8 0.85 and 0.95.

Results of the cohesion ( $d$ ) versus tablet the relative density are represented in Fig. 4.5. Despite its name, the cohesion is not a measurement of the binding forces between particles, but a measure of a compact's shear strength (LaMarche et al., 2014). In Fig. 4.5, it is shown that the cohesion increased exponentially when the relative density of tablets is increased. Nevertheless, it is decreased when the granules size is increased, although the difference of values for different granule size is not really significant.

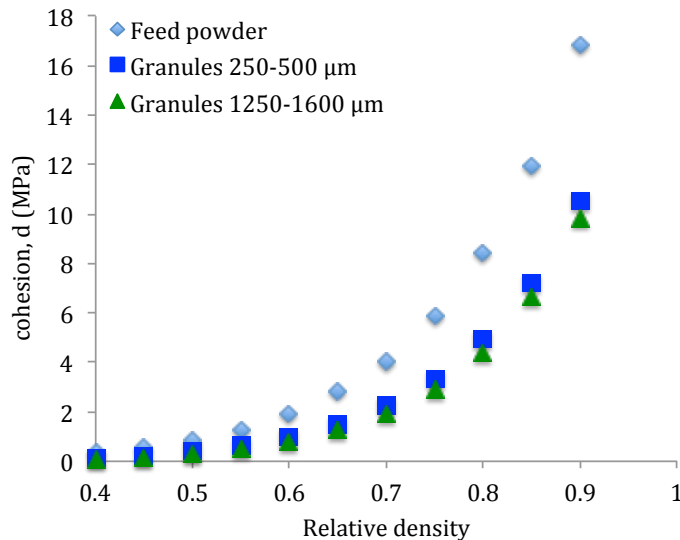


Fig. 4.5. Cohesion,  $d$

In the same way as the cohesion, the angle of internal friction ( $\beta$ ) is plotted against the tablet relative density in Fig. 4.6. The internal friction angle shows a nonlinear behaviour, with a slight increase at low relative densities until reaching a more or less constant value of 70 degrees.

For high tablet density (from 0.7 to 0.9), the angle  $\beta$  resulted to be insensitive to roll-compaction process and to granule size, with values of approximately 68°. This is classical value reported in the literature, in general constant and in the range from

around  $60^\circ$  to  $70^\circ$  either for a metal or pharmaceutical materials (Han et al., 2008; Kadiri and Michrafy, 2013; Krok et al. 2014). On the other hand, it can be observed that at low densities (from 0.4 to 0.6), the value of  $\beta$  is lower when the granule size increases.

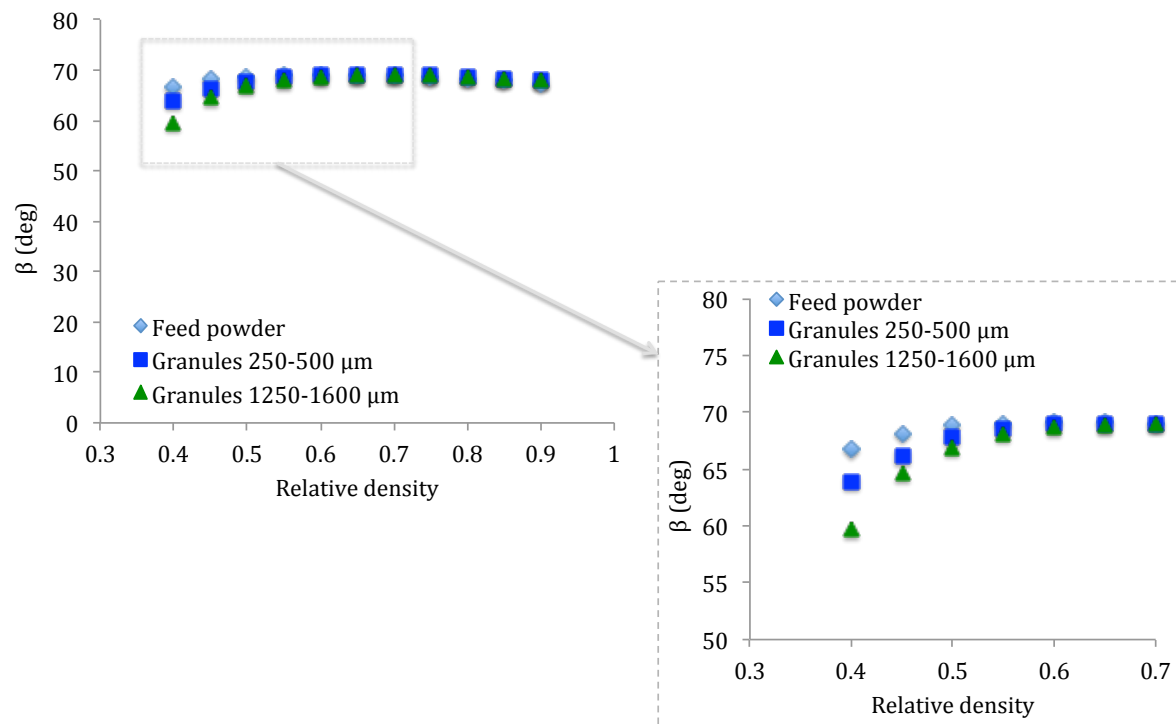


Fig. 4.6. Angle of internal friction,  $\beta$

Mitra et al. (2016a) also analysed the shear failure parameters for feed powder and granules and they found results for cohesion similar to our results, showing that the dry granulation significantly affected the results. The cohesion was higher for the feed powder than for the granules. It decreased as the granule solid fraction decreased. The authors stated that the cohesion is the only DPC parameter that is impacted by the dry granulation process. On the other hand, no variation was found in the angle of internal friction, resulting independent of the granule solid fraction or the tablet density. But it has to be remarked that they measured  $\beta$  at high tablet relative density (from 0.69 to 0.89), so the region of low density where we found the differences between feed powder and granules (zoomed area in Fig. 4.6) was not studied.

#### 4.2.2. Cap parameters

The cap parameters are the cap eccentricity  $R$  (eccentricity of the ellipse representing the cap) and the hydrostatic yield strength  $P_b$  (point of intersection of the cap with the  $p$ -axis). They are calculated using the equations described in Chapter 2 (Eq. 2.15 and 2.16).

The cap eccentricity ( $R$ ) determines the shape of the cap line. It controls the ratio of hydrostatic to shear stress required to densify a compact (LaMarche et al., 2014). In Fig. 4.7, the cap eccentricity ( $R$ ) is plotted against the tablet relative density. It can be observed that  $R$  varied from 0.75 to 0.95, reaching the highest values for the feed powder compared to the granules. Similar values are reported in the literature (Cunningham et al. 2004; LaMarche et al. 2014; Garner et al., 2015; Mazor et al., 2016;).

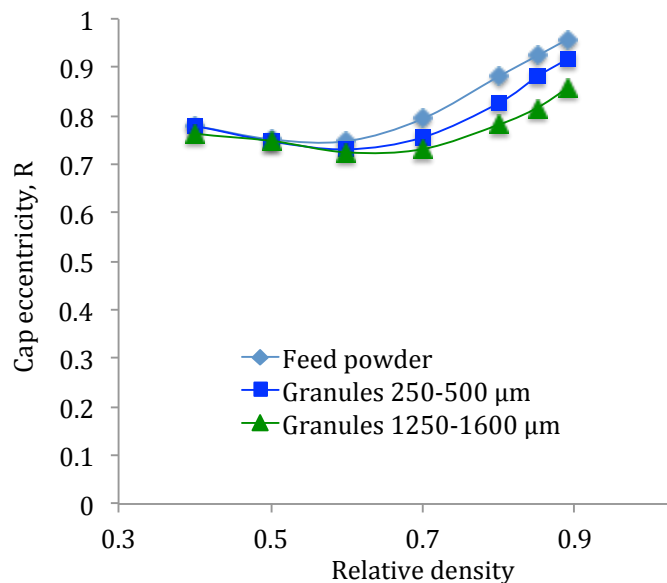


Fig. 4.7. Cap eccentricity,  $R$

In our case, in the evolution of the eccentricity can be distinguished two tendencies. At low tablet relative density, the eccentricity slightly decreases when increasing the density. In this region, there is no significant effect of the granule size on the values of  $R$ . On the other hand, from 0.6 of relative density, the eccentricity increases when the relative density increases and it is lower for larger granules. Therefore, it is highlighted that it is important to consider the DPC parameters from its initial loose-packed state (low tablet relative density) to a high-densified state (high tablet relative density).

Similar evolution was found in Brewin et al., (2008) for low and high-pressure closed-die compaction tests of zirconia ( $\text{ZrO}_2$ ) powder (Fig. 4.8). The obtained data of eccentricity depended on the pressure regime: at low pressure, the eccentricity decreased and at high pressure, it increased. Nevertheless, at low density there was a high dispersion of the data and the evolution was fitted to a linear equation.



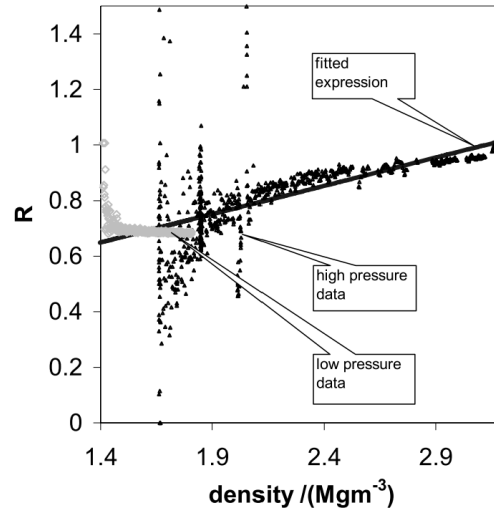


Fig. 4.8. Evolution of eccentricity with density from low- and high-pressure compaction (from Brewin et al., 2008-Fig. A.1.38)

The hydrostatic yield stress  $P_b$  is the stress needed to compact a material only when hydrostatic stress is applied. It is represented in Fig. 4.9 as a function of the tablet relative density.

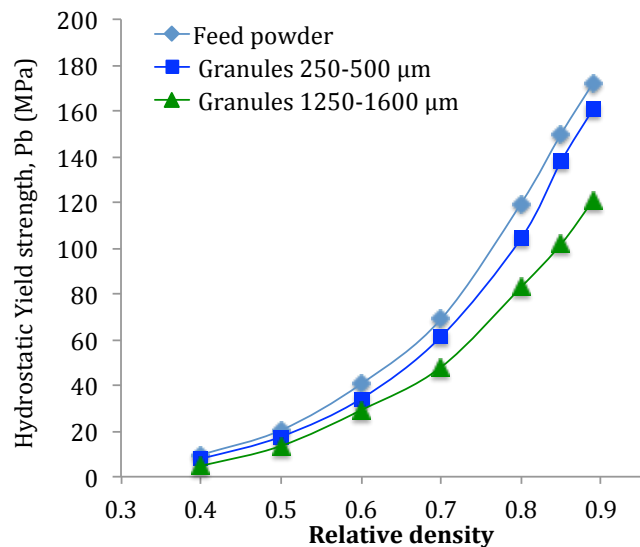


Fig. 4.9. Hydrostatic yield strength,  $P_b$

$P_b$  increases exponentially when the tablet density increases. At low stresses, the compaction of low apparent density powders is characterized by large plastic deformations while, when the relative density increases, the hydrostatic yield stress approaches infinity asymptotically at RD=1 (Cunningham et al., 2004).

Regarding the roll-compaction effect, it can be observed that  $P_b$  decreases significantly when the granule size increases. This means that less hydrostatic stress needs to be

applied to compact the granules to a certain tablet relative density. Contrary to this, Mitra et al. (2016) found that the feed powder and the granules, independent of the densification status, required the same amount of hydrostatic stress to be densified to a specific tablet density. This is, no differences in  $P_b$  were found comparing the feed powder and the granules of different solid fractions.

In the implementation of the DPC parameters in a FEM model (with ABAQUS® for example), only the hardening parameter  $P_b$  depends on the volumetric strain (which is equivalent to the density, obtaining also an exponential relation), while other parameters such as the eccentricity, the cohesion or the angle of internal friction are considered, in general, as constants.

All the Cap parameters showed to be density-dependent and also granule size dependent. These parameters evolutions as a function of the density will affect the shape of the yield surfaces, as it will be seen in the next section.

### 4.2.3. Yield surfaces

The parameters obtained in the previous sections were compiled and the DPC yield surfaces in the plane  $p$ - $q$  were plotted.

First, the iso-density yield surfaces for the feed powder and the granules are plotted in Fig. 4.10. As expected, for the three types of particulate materials (feed powder and granules of 250-500 and 1250-1600  $\mu\text{m}$ ), when relative density increases, the yield surface expands in the stress space, which means a greater resistance to further plastic deformation

The curves are not self- similar, due to the variation of the parameters such as cohesion and internal friction angle, which increase during compaction for all the materials (Cunningham et al., 2004). In the same manner, there is an evolution of the shape and size of the ellipse (determined by the variation of  $R$  and  $P_b$ ). It can be observed the maximum hydrostatic pressure decrease from feed powder (172 MPa) to granules (160 for granules of 250-500  $\mu\text{m}$  and 120 for granules of 1250-1600  $\mu\text{m}$ ).

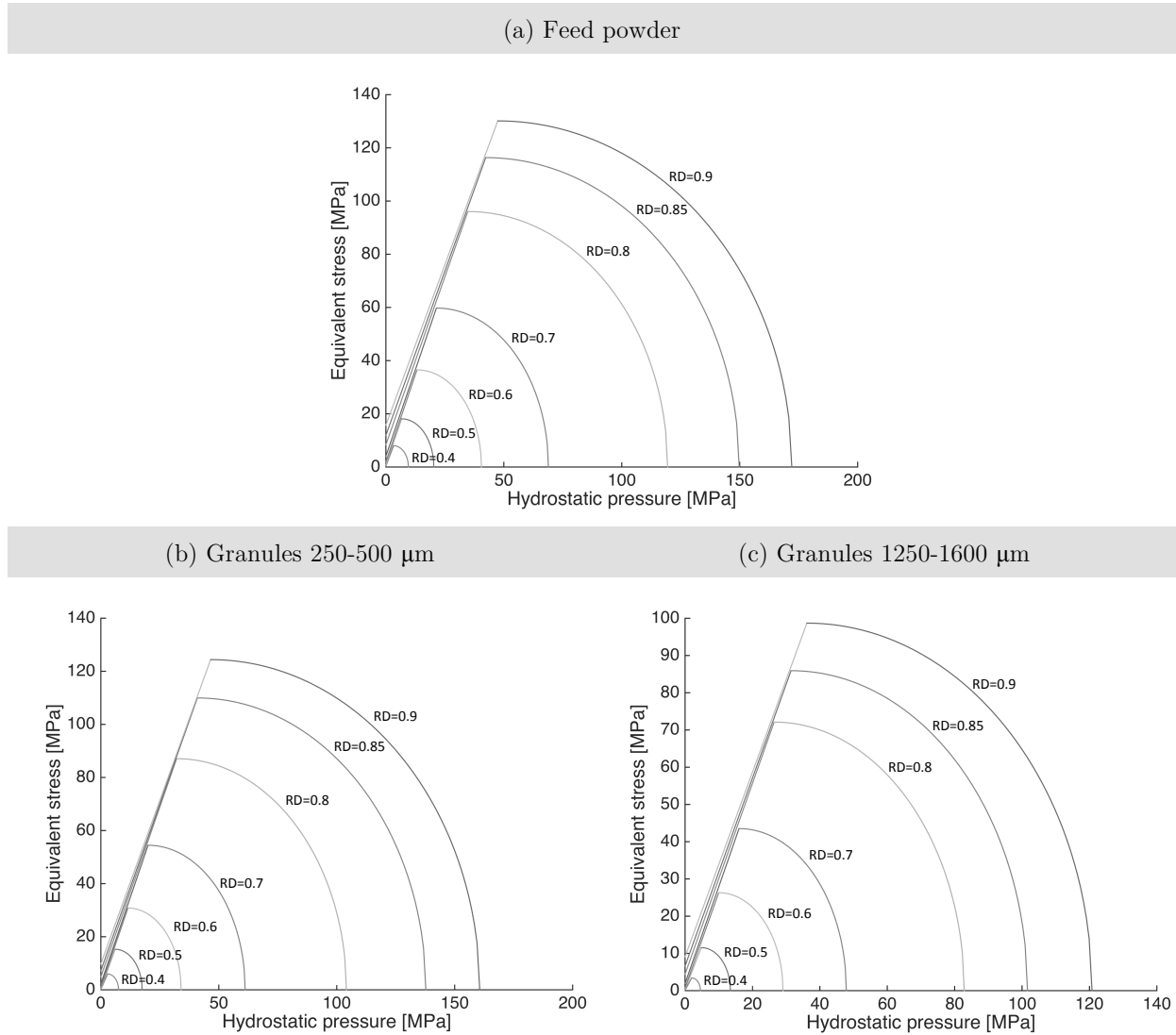


Fig. 4.10. Iso-density yield surfaces for different tablet densities for (a) feed powder, (b) Granules 250-500  $\mu\text{m}$  and (c) Granules 1250-1600  $\mu\text{m}$

The main interest of this study is to compare the DPC results for the different particulate materials (feed powder and granules). For this reason, the yield surfaces of the three material are plotted together at two different tablet densities: RD=0.4 (low density) and RD=0.9 (high density) in Fig. 4.11. This allows us to compare the results considering low and high density and see if under these states of stresses the behaviours differ.

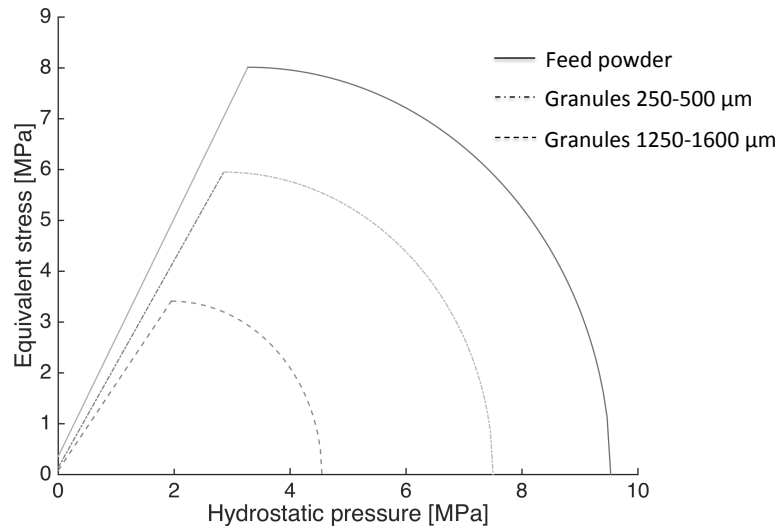
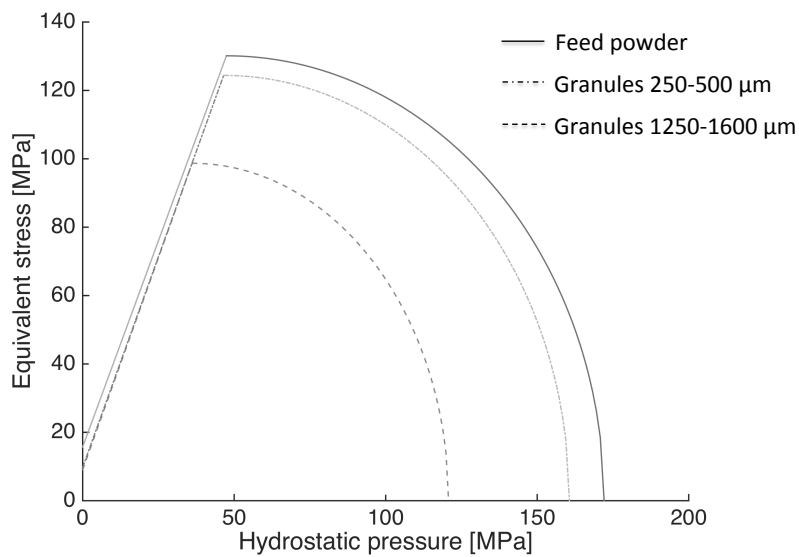
(a) Low tablet density ( $RD=0.4$ )(b) High tablet density ( $RD=0.9$ )

Fig. 4.11. Comparison of DPC yield surfaces of feed powder and granules at (a) Low relative density,  $RD=0.4$  and (b) High relative density,  $RD=0.9$

It can be observed that, for both densities, the granules have smaller yield surface than the feed powder. Moreover, when the granule size increases, the yield surface contracts. For the granules, the yielded (flowing) region is smaller than for the feed powder. This means that, not all the materials required the same amount of pressure to produce tablets with the same density. A higher stress needs to be applied to the feed powder in order to deform it. On the other hand, the granules require lower stress to reach such density. As the granules have been previously compacted in the roll-press, part of the

stress was applied in a previous step, and during die compaction, less stress is required to reach the same level of densification.

Regarding the shear failure line, it can be observed that, at high density, it is overlapping (same cohesion and internal friction) for both sizes of granules, while for feed powder, the line has the same slope but different cohesion. This is, at high relative density, the only parameter differing in the shear failure is the cohesion and not the angle of internal friction, as it was seen previously in Section 4.2.1. On the other hand, at low density, not only the cohesion but also the angle of internal friction is affected by the kind of material. Higher values of cohesion and angle of internal friction (case of feed powder) give the sharpest line, and therefore increase the area of the yield surface. For both densities, the shear failure line for feed powder is over the granules' lines, which that tablets produced with feed powder can resist higher stress before fracture. These differences in the shear failure line are due to the "loss of reworkability" after roll-compaction.

In contrast to our results, Mitra et al. (2016) found that the yield cap curves for all the materials (feed powder and granules) were overlapping for the same tablet density. The feed powder and granules required the same amount of stress to densify to a certain tablet density. Nevertheless, they used monodisperse granules, higher densified than the granules in our study (the ribbons relative density in our study was 0.57) and with cylindrical shape and the results may be different to the ones of roll-compacted granules.

#### 4.2.4. Conclusions

In this section, we showed the difference of the compaction behaviours between raw material (MCC) and granulated powders by roll compaction. We based this analysis on the elastic-plastic model of Drucker Prager Cap, which takes into account the main properties of compacted material (cohesion, internal friction, hardening and breaking under shearing stress) according to the relative density as a microstructural variable that controls the densification state.

The results provided a deeper understanding on the effect of roll-compaction process on the compaction behaviour of granules. It was found that all the parameters ( $d$ ,  $\beta$ ,  $R$  and  $P_b$ ) differ from feed powder to granules, mainly at low levels of densification. In addition, also the increase of the granule size had an effect on the DPC parameters. This led to the attainment of different yield surfaces curves for the different materials. The yield surface was expanded for the feed powder and it was contracted when the granule size increased. Additional studies should be pertinent, evaluating other materials and granules of different size, density and compositions.

### 4.3. COMPACTION BEHAVIOUR OF ROLL-COMPACTED BINARY MIXTURES \*

The above analysis of the compaction behaviour of granules was conducted on a simple material (MCC). Following we examine the compaction behaviour of granulated binary mixtures composed from a brittle material (lactose) and a plastic one (MCC), based on previous research works that reported that the sensitivity of materials with different mechanical behaviour is different (plastic materials are more sensitive to roll compaction process due to the consumption of binding potential in the first compression step while brittle materials are less sensitive to granule size enlargement). The focus here will be on the stress transmission through a granulated powder bed of binary mixtures and their compressibility and compactability according to the composition and the particle size of the granules.

The densification behaviour of binary mixtures of MCC and lactose was analysed in Michrafy et al. (2009) based on stress transmission and wall friction during compaction in axial and radial directions. Results provided further insight on the impact of the individual components during the process. Size enlargement by dry granulation of the mixtures should improve the behaviour rather than the blended mixtures. In this paragraph, we present the results of this study by highlighting the deformation mechanisms of the granules.

Experiments were performed using the Komarek® B050PH laboratory. The gap was kept constant at 1.5 mm. The speed of rolls was 3.75 rpm and the screw speed was varied in order to produce ribbons with the same relative density. Resulting ribbons were milled in an oscillating mill (Erweka, AR402) at 60 rpm using a 1.25 mm sieve.. In order to evaluate the granule size effect, the granules were sieved and three size ranges were separated: 315-500, 630-800 and 800-1000  $\mu\text{m}$ . Tablets were produced with the Instron press for feed powder and granules, as detailed in Chapter 2.

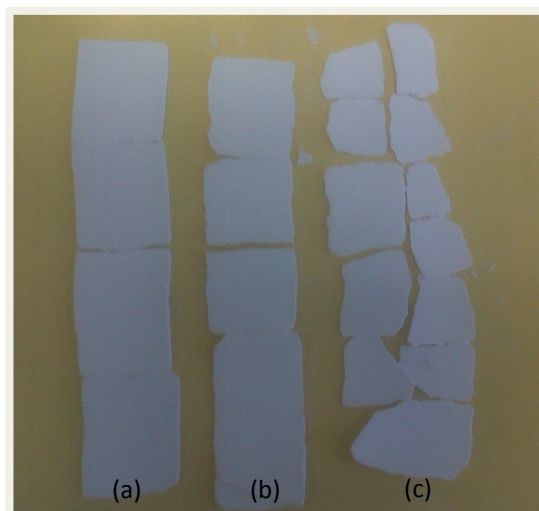
#### 4.3.1. Ribbon appearance and density

In Fig. 4.12, it can be observed the quality of the obtained ribbons and the resulted ribbon relative density (calculated from measured weight and dimensions). Ribbons of good quality are produced for a high percentage of MCC in the mixture. On the other hand, when the percentage of lactose increases, the roll-compaction becomes more difficult due to the brittle behaviour of lactose and smaller pieces are obtained.

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\*This section has been published under the reference: *Perez-Gandarillas, L., A. Mazor, D. Souriou, O. Lecoq, and A. Michrafy. 2015. "Compaction Behaviour of Dry Granulated Binary Mixtures." Powder Technology 285. Elsevier B.V.: 61–66. doi:10.1016/j.powtec.2015.05.003.*

However, the produced ribbons had similar solid fraction, SF, for the three binary mixtures.



Materials	Ribbon relative density
(a) 75%MCC/25% Lactose	$0.60 \pm 0.02$
(b) 50%MCC/50%Lactose	$0.60 \pm 0.05$
(c) 25%MCC/75%Lactose	$0.59 \pm 0.03$

Fig. 4.12. Characteristics of the ribbons

### 4.3.2. Granules size and shape

Particle size and particle shape may play an important role in the densification process, affecting the interparticulate interaction. In this study, the granules were obtained under similar conditions of roll compaction and milling, therefore only small differences among the granule size distributions for the different compositions were observed (Fig. 4.13).

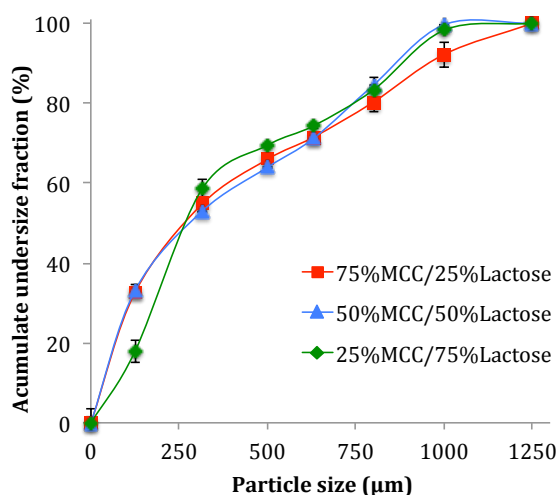


Fig. 4.13. Granule size distributions of roll-compacted binary mixtures

Granules were imaged using a scanning electron microscope (SEM, Philips XL30). In Fig. 4.14, the SEM pictures of the granules for the three mixtures show that the granules have an irregular shape. In general, an irregular shape and a rough surface,

improve the bonds between particles and, therefore, the compactability of tablets. It can be remarked that the granules are not spherical. From the pictures, it can be also noticed that the higher is the percentage of lactose in the mixture, the smoother the surface becomes (Fig. 4.14c). Surface roughness has been reported to influence the mechanical behaviour of the excipients and the mechanical properties of the tablet. Brittle materials result in smoother granules and, therefore, smoother compacts with high surface variability due to particle fracture.

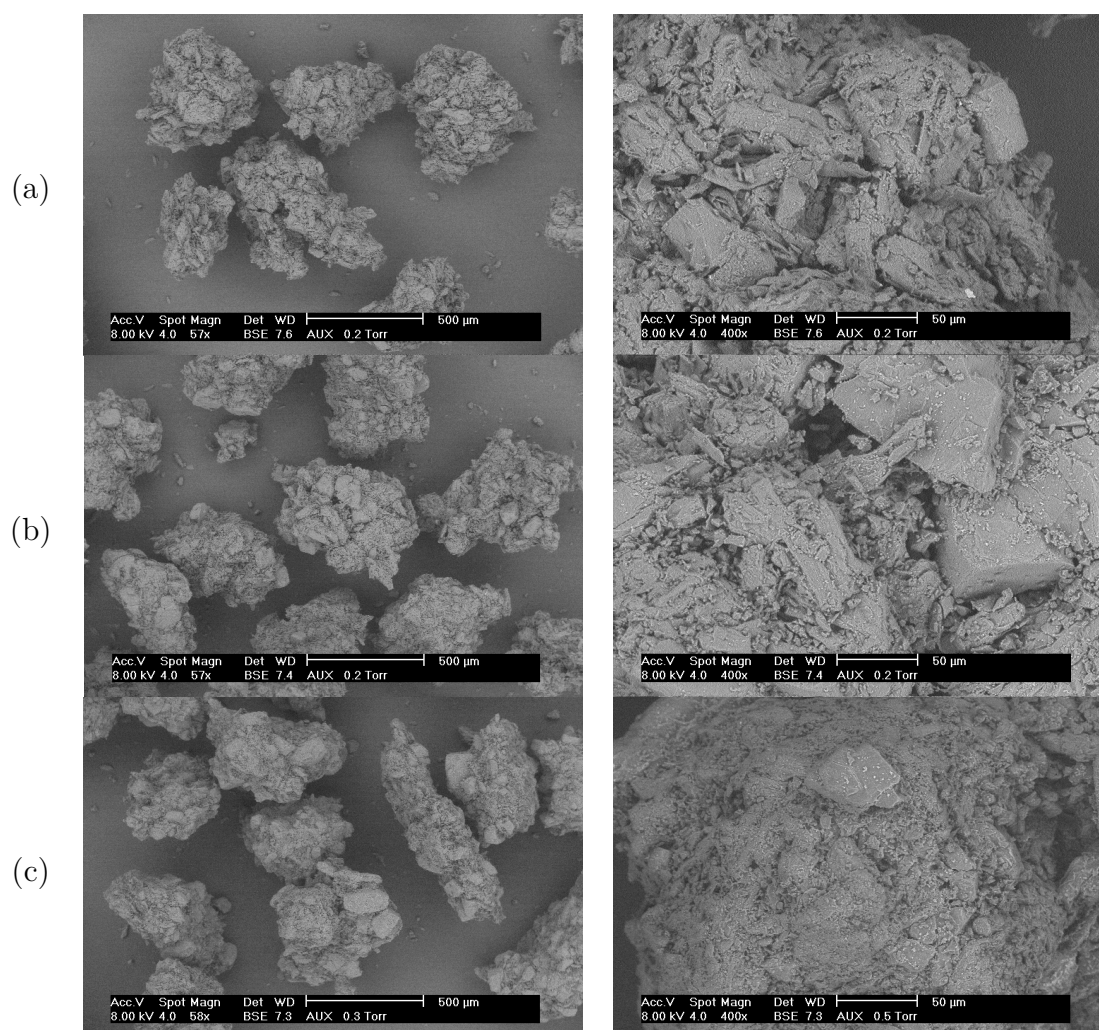


Fig. 4.14. Scanning electron microscopy images of granules: (a) 75%MCC/25%Lactose, (b) 50%MCC/50%Lactose and (c) 25% MCC/75%Lactose.

### 4.3.3. Compressibility

Results of the Heckel analysis are summarized in Table 4.1.  $K$  represents the Heckel coefficient (slope of the straight line portion of the Heckel plot) and  $P_y$  (reciprocal



value of the slope) represents the yield pressure. The model was applied in a range of pressures from 20 MPa to 140 MPa.

Regarding the composition, the results show that a high proportion of lactose increases the compressibility. Comparing the compressibilities of original feed powder and granules, it was found that feed powders are more compressible than granules, mainly for the proportion 25%MCC/75% lactose. On the other hand, roll-compacted granules were relatively denser than feed powder, resulting in a lower compressibility. Feed powders can be rearranged more easily during compression, resulting in a larger compressibility.

Table 4.1. Compressibility using Heckel model

Mixture		$K \times 10^3 \text{ (MPa}^{-1}\text{)}$	$P_y$	$R^2$
75MCC/ 25Lactose	Non-roll compacted mixture	7.5	133	0.969
	Granules 315-500 $\mu\text{m}$	6.9	145	0.979
	Granules 630-800 $\mu\text{m}$	7.1	141	0.987
	Granules 800-1000 $\mu\text{m}$	7.3	137	0.983
50MCC/ 50Lactose	Non-roll compacted mixture	8.1	123	0.977
	Granules 315-500 $\mu\text{m}$	7.7	130	0.971
	Granules 630-800 $\mu\text{m}$	7.6	132	0.976
	Granules 800-1000 $\mu\text{m}$	7.2	139	0.971
25MCC/ 75Lactose	Non-roll compacted mixture	9.5	105	0.929
	Granules 315-500 $\mu\text{m}$	8.4	120	0.954
	Granules 630-800 $\mu\text{m}$	8.2	122	0.984
	Granules 800-1000 $\mu\text{m}$	8.4	119	0.968

Among the granule sizes, it was not found a pronounced difference in compressibility between granule size fractions. As it was described by Šantl (2012), at low pressure granules fragment into smaller particles and when the compression is increased, the extensive fragmentation nullifies the effect of particle size on compressibility. The yield pressure ( $P_y$ ), has lower values for a high percentage of lactose and it is lower for the original feed powder than for granules, although the values do not differ significantly from one mixture to another.

#### 4.3.4. Compactability

The diametrical crushing load of tablets was measured with a diametric strength tester and the tensile strength of the compacts ( $\sigma_t$ ) was calculated according to Eq. 2.4. The tablet tensile strengths as a function of the relative densities are shown in Fig. 4.15, Fig. 4.16 and Fig. 4.17.

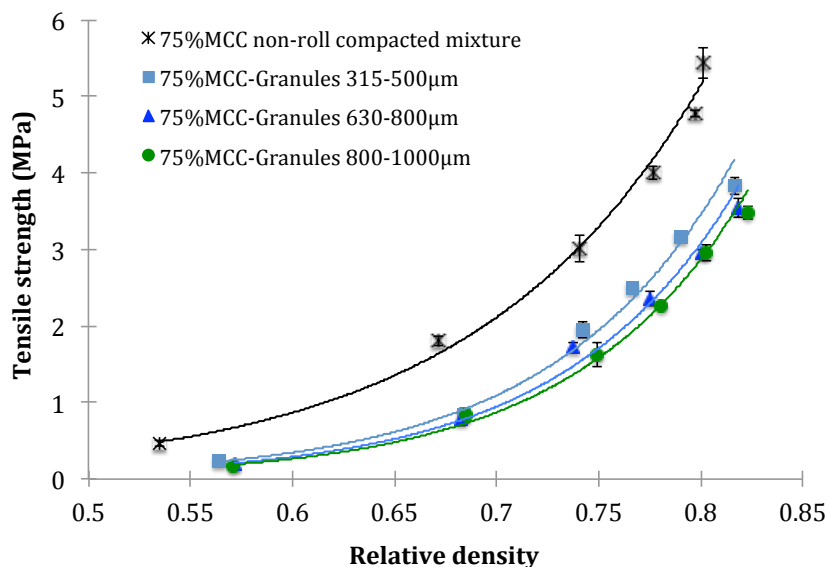


Fig. 4.15. Tensile strength of tablets as function of relative density for the composition 75%MCC/25%Lactose

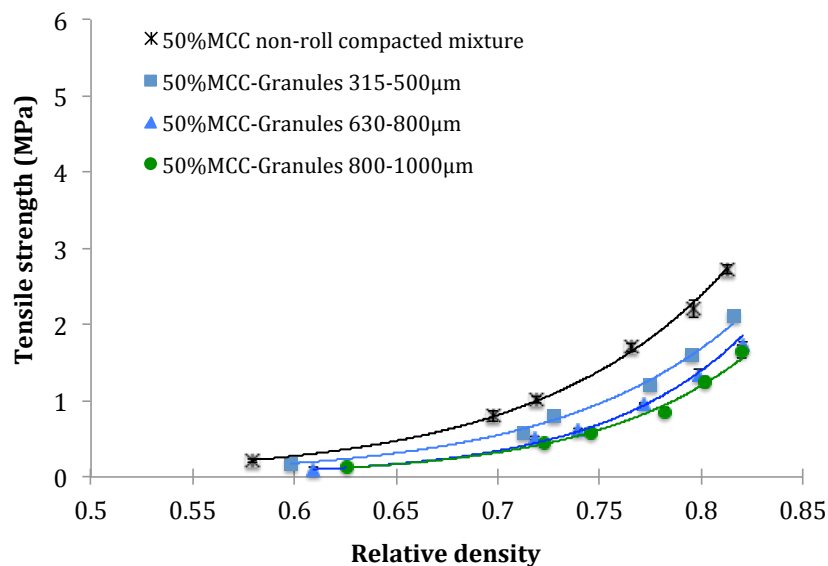


Fig. 4.16. Tensile strength of tablets as function of relative density for the composition 50%MCC/50%Lactose

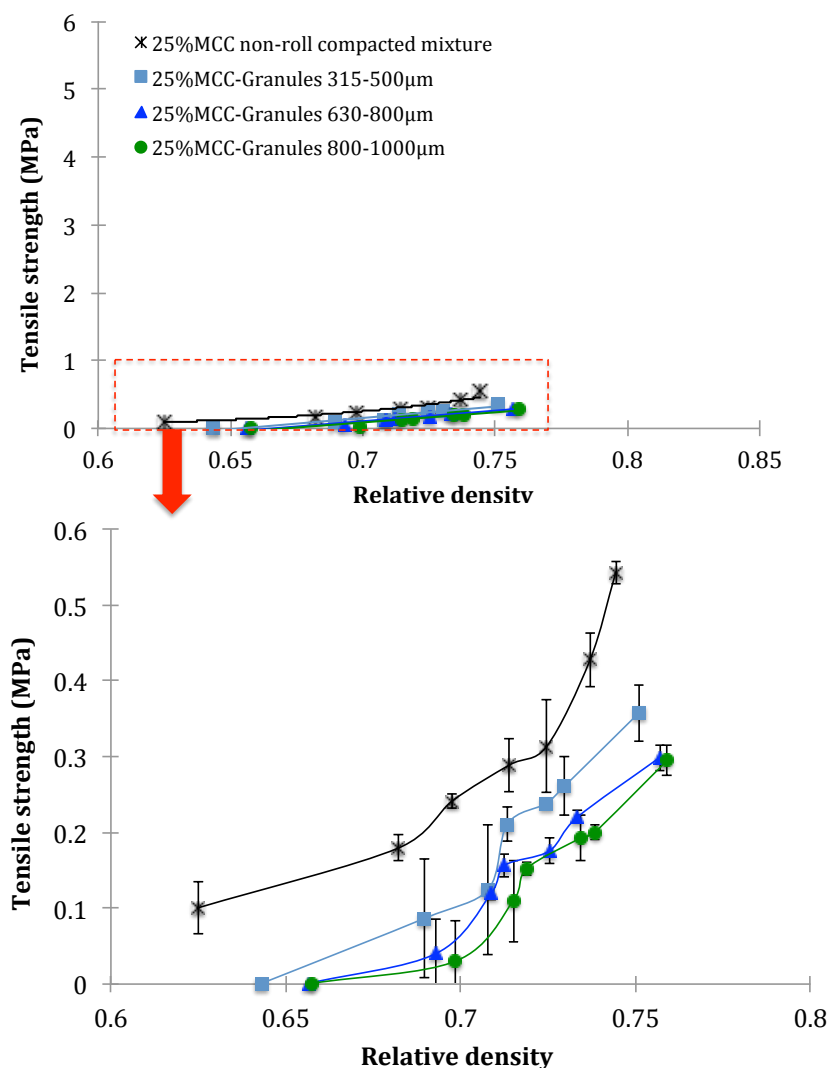


Fig. 4.17 Tensile strength of tablets as function of relative density for the composition 25% MCC/75%Lactose.

Regarding the composition, as ductile materials result into higher tablet tensile strength, the tablets produced with high percentage of MCC have higher tensile strength. On the other hand, a high percentage of lactose in the mixture means lower tensile strength.

Attending to the effect of roll compaction on the tensile strength, it can be observed that the tablets produced with granules from roll-compacted mixtures show lower tensile strength than the tablets produced with the original binary mixtures. In the case of 75% of MMC in the mixture, the reduction of tablet strength after roll compaction is more significant than for the others compositions. When a brittle material is incorporated in the formulation, the effect of loss of tabletability is less pronounced at identical compaction conditions, obtaining closer results to those

obtained with the original binary mixtures. The granules are an agglomeration of particles and, when the pressure is applied, the granules break into smaller particles, assimilating their behaviour to a brittle material under densification. These results confirm that incorporating an adequate amount of brittle excipient can minimize the effect of size enlargement process by roll compaction, as it was reported by Wu and Sun (2007). In order to reduce the effect of loss of reworkability, quality by design should be applied in the formulation of the mixture.

The particle size plays also an important role in the final tableability. An increase in the granule size is translated into a reduction of tensile strength of tablet. The granules with a size of 800-1000  $\mu\text{m}$  have the lowest tensile strength, although the differences of tensile strength among the different granule sizes is more pronounced for a high percentage of MCC in the mixture. For materials with a fragmentary behaviour, the granule size is less important than for plastic materials, and therefore, tablet strength is less affected by the particle size.

#### **4.3.5. Conclusions**

It was confirmed that tablets produced with granules from roll- compacted mixtures show lower tensile strength than the tablets produced with the original binary mixtures. However, the reduction of tensile strength is more relevant for a high percentage of ductile material in the mixture. Attending the granule size, an increase in the size leads to a reduction of tensile strength of tablet. These results confirm that incorporating an adequate amount of brittle excipient and controlling the granule size, the effect of size enlargement process by roll compaction can be minimised. Quality by design should be applied in the formulation and parameters to predict the optimal final properties.

## 4.4. STRESS TRANSMISSION ANALYSIS

As it could be observed before, roll-compaction process has an effect on the strength of tablets. This effect has been reported in the literature as “loss of reworkability”. In order to better understand why this phenomenon takes place, a stress transmission analysis was done. During the die compaction of a powder bed, the capacity of the mass to convert the applied pressure to the axial and radial densification is an intrinsic characteristic of the behaviour of that powder. The force is applied with the upper punch and, hence, the stress is transmitted from the top to the bottom of the powder causing its densification in the axial direction whereas a stress is developed in die cavity by expansion in the normal direction to the die wall and the densification in the radial direction takes place (Michrafy et al., 2009).

For this study, the materials used were the same as in the previous section. This is, the binary mixtures of MCC and lactose and their granules of different size ranges. As explained in Section 2.3.3.3, the behaviour of the binary mixtures and their granules during die compaction was analysed through the axial and radial stress transmissions (Eq. 2.5 and 2.6).

### 4.4.1. Axial transmission

Fig. 4.18, Fig. 4.19 and Fig. 4.20 show the axial transmission (defined as the ratio of pressure transmitted from the top to the bottom of the powder bed) as a function of the applied pressure and the displacement of the upper punch. The data obtained under 5 MPa of applied pressure was considered as noise due to the sensor's sensitivity. It can be observed that, at the beginning of the compaction cycle, the axial transmission is very low for the three compositions. Less than 20% of the applied pressure is transmitted to the bottom of the powder bed, for the three binary mixtures and their granules. After 5 MPa, the axial transmission starts to increase reaching, at the maximum pressure, a value that varies from 50% (for high percentage of lactose in the mixture) to 60% of transmission (for high percentage of MCC) depending on the composition and granule size. This suggests that, at the beginning of the compaction, the applied pressure is consumed on the rearrangement of particles and is not completely transmitted to the lower punch. When the particles start to densify, the axial transmission increases until reaching a final constant value.

It can be noticed as well, that when the percentage of lactose in the mixture is increased, the axial transmission values decrease. This can be explained through the brittle behaviour of lactose, which pass for a stage of fragmentation before densify. Therefore, part of the energy applied is consumed on fragmenting the particles and, as a consequence, is not transmitted to the lower punch.

The consequences of the non-uniform axial stress are the generation of density gradients along the height of the tablet with higher density values around the top of the tablet (Kadiri and Michrafy, 2013). This effect renders the tablet less robust.

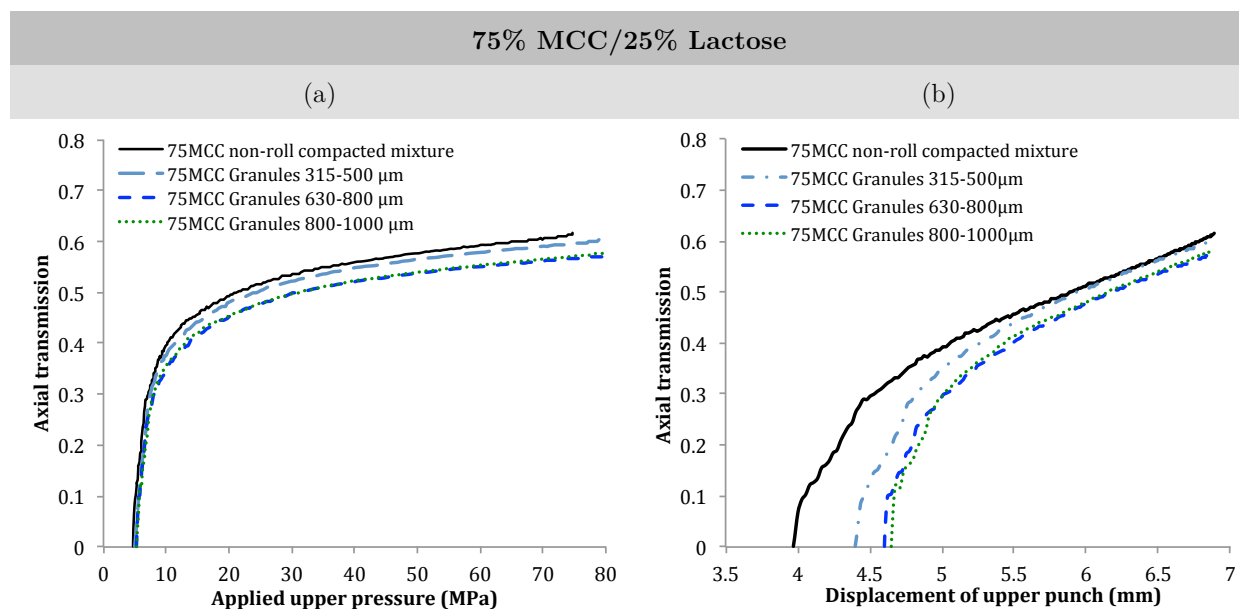


Fig. 4.18. Axial transmission versus (a) applied pressure and (b) punch displacement for 75% MCC/25% lactose.

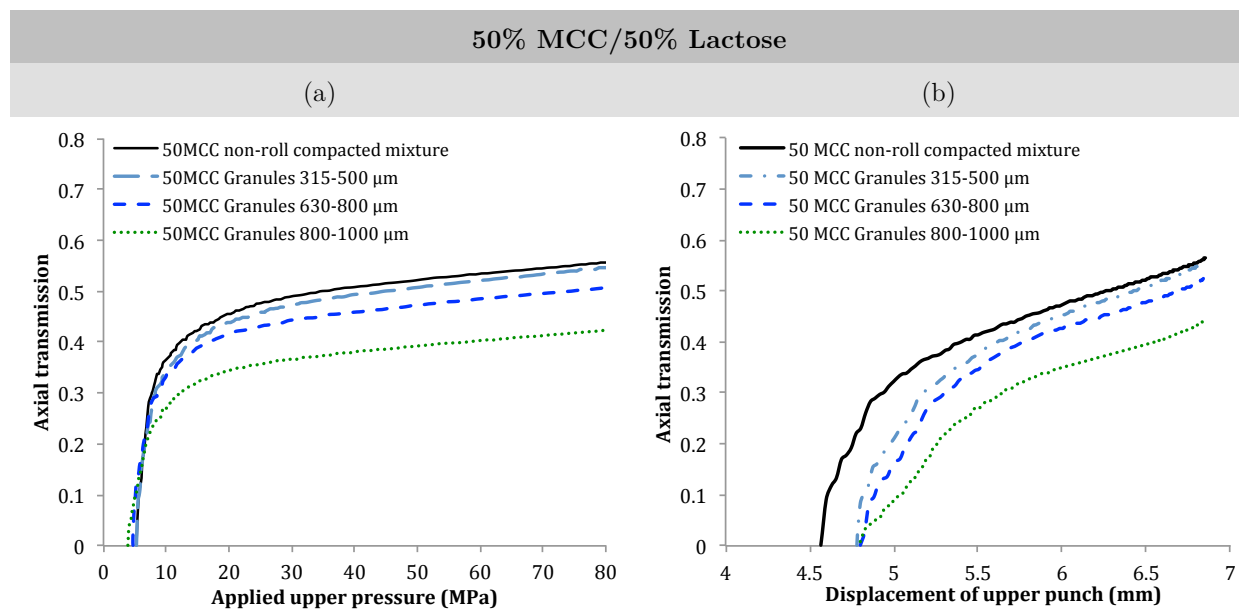


Fig. 4.19. Axial transmission versus (a) applied pressure and (b) punch displacement for 50% MCC/50% lactose

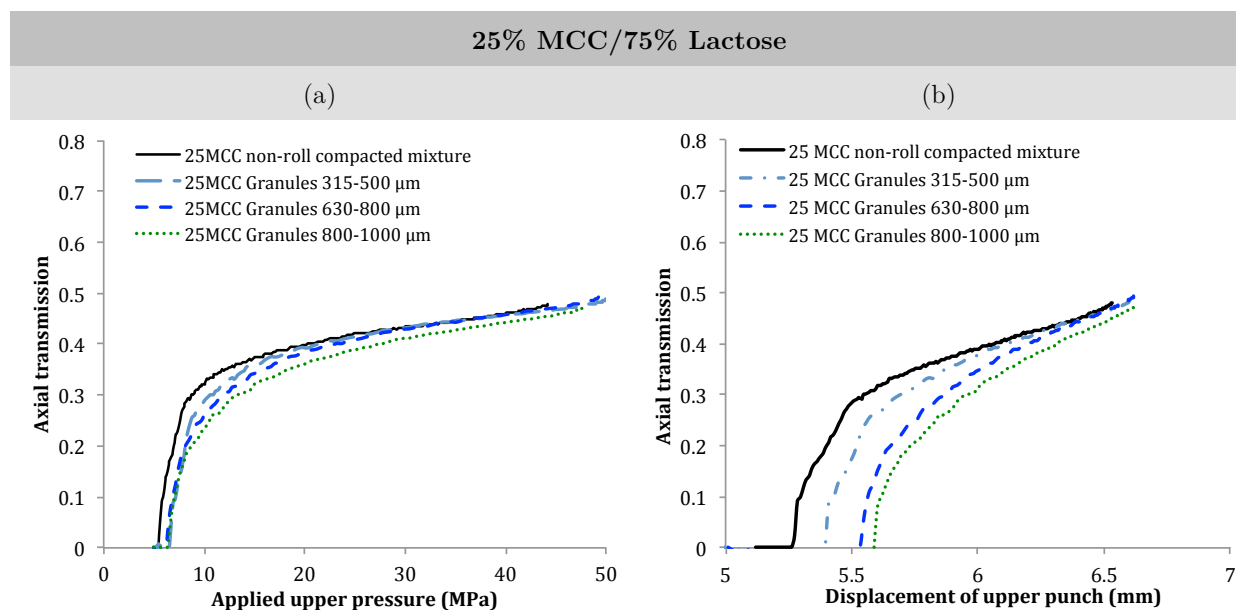


Fig. 4.20. Axial transmission versus (a) applied pressure and (b) punch displacement for 25%MCC/75% lactose.

Regarding the effect of roll-compaction, it was noticed that for a specific applied pressure, less pressure is transmitted for the granules than for the original feed powder. Regarding the granule size, transmission has also lower values when the granule size is increased. Due to their fragmentary behaviour, the granules consume part of the applied pressure in an intermediate densification step that consists on the breakage into smaller particles and the rearrangement of these new particles. Hence, in the densification of granules, less energy is consumed to form inter-particulate bonds, which can explain the reduction of their tablet tensile strength.

#### 4.4.2. Radial transmission

The stress on the wall of the die was also measured and the radial transmission ratio was calculated. The final radial transmission at the maximum applied pressure is listed in Table 4.2.

During the compaction cycle, the radial stress resulted independent from the granule size, obtaining the same values for feed powders than for granules of different sizes for a certain composition. However, it could be noticed that the radial stress ratio increases slightly according to the increase of lactose proportion in the mixture. Indeed, lactose is considered as a cohesive powder, particle-particle and particle-surface, and lubrication is commonly used for the compaction of this excipient.

Table 4.2. Densification behaviour: maximum displacement, applied upper pressure at maximum displacement and radial stress transmission at maximum displacement

Mixture		Maximum displacement of upper punch, $d_{max}$ (mm)	Maximum applied pressure at $d_{max}$ , $\sigma_{u,max}$ (MPa)	Radial Stress transmission ( $\sigma_{radial}$ ) at $\sigma_{u,max}$
0.75MCC/ 0.25Lactose	Non-roll compacted mixture	$6.890 \pm 0.006$	$74.341 \pm 2.838$	$0.265 \pm 0.005$
	Granules 315-500 $\mu\text{m}$	$6.875 \pm 0.003$	$79.717 \pm 1.143$	$0.270 \pm 0.003$
	Granules 630-800 $\mu\text{m}$	$6.870 \pm 0.002$	$80.770 \pm 0.801$	$0.271 \pm 0.004$
	Granules 800-1000 $\mu\text{m}$	$6.861 \pm 0.003$	$80.607 \pm 0.947$	$0.266 \pm 0.015$
0.50MCC/ 0.50Lactose	Non-roll compacted mixture	$6.853 \pm 0.004$	$83.491 \pm 0.724$	$0.283 \pm 0.007$
	Granules 315-500 $\mu\text{m}$	$6.851 \pm 0.003$	$85.536 \pm 0.398$	$0.286 \pm 0.002$
	Granules 630-800 $\mu\text{m}$	$6.842 \pm 0.003$	$87.199 \pm 0.832$	$0.272 \pm 0.004$
	Granules 800-1000 $\mu\text{m}$	$6.845 \pm 0.003$	$88.191 \pm 0.922$	$0.272 \pm 0.004$
0.25MCC/ 0.75Lactose	Non-roll compacted mixture	$6.596 \pm 0.056$	$48.223 \pm 3.573$	$0.330 \pm 0.004$
	Granules 315-500 $\mu\text{m}$	$6.627 \pm 0.012$	$47.409 \pm 3.647$	$0.337 \pm 0.011$
	Granules 630-800 $\mu\text{m}$	$6.624 \pm 0.014$	$47.081 \pm 3.032$	$0.338 \pm 0.009$
	Granules 800-1000 $\mu\text{m}$	$6.629 \pm 0.012$	$44.121 \pm 5.384$	$0.351 \pm 0.019$

#### 4.4.3. Conclusions

The results showed that the transmission stress in axial direction differs depending on the powder behaviour. This suggests that the differences on how the stress is transmitted can cause heterogeneities on the tablets properties such as the tablet density distribution, which affects the mechanical resistance of the compacts.



## 4.5. CONCLUSIONS

The goal of this chapter was to analyze the compaction behavior of dry granulated material in order to gain some understanding on the macroscopic aspects of tableting roll-compacted granules.

In the previous chapter, the results had highlighted the effect of the roll-compaction process on the compaction behaviour of granules compared to feed powder. In order to further investigate the mechanical response of the granules, the Drucker-Prager model was calibrated. The DPC parameters were calculated for pure MCC 101 and roll-compacted granules of two different size ranges: [250-500] and [1250-1600]  $\mu\text{m}$ . Results showed that all the parameters ( $d$ ,  $\beta$ ,  $R$ , and  $P_b$ ) differ from feed powder to granules, mainly at low levels of densification. Comparing the yield surfaces, it was observed that, for low and high density, the granules have smaller yield surface than the feed powder. Moreover, when the granule size increases, the yield surface contracts. Differences in the shear failure line were found, due to the “loss of reworkability” after roll-compaction.

After, an analysis of the effect of the composition (binary mixtures of MCC and lactose) and the granule size on the tablet properties was done. In this research, it was confirmed that tablets produced with granules from roll-compacted mixtures show lower tensile strength than the tablets produced with the original binary mixtures. This phenomenon is known in the literature as “loss of re-workability. However, the reduction of tensile strength is more relevant for a high percentage of ductile material (MCC) in the mixture. Attending the granule size, an increase in the size is translated into a reduction of tensile strength of tablet. These results confirm that incorporating an adequate amount of brittle excipient and controlling the granule size, the effect of size enlargement process by roll compaction can be minimised. Quality by design should be applied in the formulation and parameters to predict the optimal final properties.

In order to better understand the loss of re-workability, an analytical technique based on the stress transmission measurement was proposed and used to study the densification behaviour of binary mixtures and granules. It was shown that the transmission stress in axial direction differs depending on the powder bed behaviour. It was observed that roll compacted granules work against the axial transmission due to their fragmenting behaviour under pressure. Indeed, a part of the applied pressure is consumed in the breakage of granules into smaller particles, improving the volume reduction but reducing the available energy to form strong inter-particulate bonding. This is typically the densification mechanism of brittle materials and that is why brittle excipients are less sensitive to the effect of loss or re-workability after roll

compaction. On the other hand, the radial transmission was slightly affected by the increase of lactose in the mixture and it resulted indifferent to the increase of granule size.



# General conclusions and perspectives

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Dry granulation of pharmaceutical ingredients is a complex process in which multiple operations are involved, making necessary the control of parameters and product quality. In this context, this thesis has presented a study that covers different aspects of the production chain “roll-compaction, milling and die-compaction”. Therefore, the results and conclusions drawn from this thesis can be grouped into five points:

- ✓ Analysis of roll-compaction and milling conditions on the ribbons, granules and tablet properties
- ✓ Evaluation of the role of the sealing system in terms of ribbon density distribution and milling performance
- ✓ Investigation of the densification mechanisms of granulated powder based on the Drucker-Prager Cap model.
- ✓ Assessment of the role of the composition and the size effect on the compaction of dry granulated binary mixtures.
- ✓ Analysis of the stress transmission through a powder bed of roll-compacted materials.

Firstly, a study on the effect of the operational parameters (roll-compaction force, sealing system, mill type, mill speed and angle of rotation) was evaluated in terms of ribbon density, granules morphology, particle size distribution (through the measurement of the percentage of fines), and tablet tensile strength. Previous results in the literature showed that the percentage of fines is a critical attribute during the production and that is highly affected by the roll-compaction and milling conditions. The results allowed recognizing the most significant parameters: material character, sealing system and roll-compaction force. Therefore, it is concluded that the roll-compaction effect is predominant over the milling effect for the generation of fines. In particular, it is preferable to work at high roll-compaction force and using rimmed-roll as sealing system in order to minimize the amount of fines. In addition, the results were evaluated through a statistical analysis that confirmed these facts. Regarding the compactability of granules, small differences among the granules produced under different conditions were found, which was also confirmed through the statistical

analysis. Nevertheless, the characterization of loss of compactability confirms the loss of reworkability after roll-compaction and that is more significant for plastic materials.

Arrived until this point, it was proved that the sealing system played an important role on the granule size distribution. This statement led us to wonder what was the relation between the ribbon properties obtained using the two different sealing systems (cheek plates and rimmed-roll) and the granules properties. For that, the density distribution of ribbons was analyzed using different techniques (measurement of dimensions, envelope analyzer and mercury porosimetry). It was found that the ribbon relative density values highly depended the sealing system design. Results showed that, the use of cheek plates results in non-uniform density distribution along the ribbon width, with higher densities in the middle of the ribbon and lower densities at the edges. On the other hand, the density distribution obtained when using the rimmed-roll system is more homogenous, although values of density are slightly higher at the edges, mainly at high roll-compaction force. This is valuable information because in the literature only profiles of density distribution for cheek plates were found.

Once it was demonstrated that the sealing systems generate heterogeneities on the ribbon density profiles, the question that arose was whether the granules properties were affected by the density heterogeneities. To investigate this, the milling performance of the ribbon was evaluated in terms of mass throughput and granule size distribution, cutting and milling apart the central part and the edges of the ribbon. Regarding the mass throughput, results highlighted that, for cheek plates, the centre parts of the ribbon were harder to mill. The opposite effect was found for rimmed-rolls. Concerning the granule size distribution, for ribbons produced with cheek plates, coarser particles are obtained from the centre than from the edges. On the other hand, for the rimmed-roll system, coarser particles are obtained from the edges. It was also found that is preferred to work at high roll-compaction force using rimmed-roll system, obtaining the same particle size distribution from the edges than in the centre. This latest statement agrees with the previous experimental results and the statistical analysis. These results revealed, for the first time, the direct impact of the ribbon density distribution on the milling performance and specifically, on the granule size distribution.

After, in the last chapter of this thesis, the compaction behavior of granulated powder was investigated. Previously, literature results, and even our results from Chapter 3, showed that there is a loss of compactability (reduction of tensile strength) after roll-compaction. Nevertheless, there is not a single mechanism that could explain these observations and the understanding of this phenomenon is still a challenge. For that reason, it was included in this thesis a deep study of how granulated powders behave during die compaction and why they exhibit behaviours different from those showed by the raw material. The goal of chapter 4 was to analyze the compaction behavior of dry

granulated material in order to gain some understanding on the macroscopic aspects of tableting roll-compacted granules.

First, the analysis of the compaction behaviour of feed powder and roll-compacted granules of MCC was conducted based on the Drucker-Prager Cap (DPC) model, which proposes the main parameters of particulate solids (cohesion, internal friction, hardening and breaking under shearing stress) according to the relative density as a microstructural variable that controls the densification state. It was found that all the parameters ( $d$ ,  $\beta$ ,  $R$  and  $P_b$ ) differ from feed powder to granules, mainly at low levels of densification. In addition, also the increase of the granule size had an effect on the DPC parameters. This led to the attainment of different yield surfaces curves for the different materials. The yield surface was expanded for the feed powder and it was contracted when the granule size increased. Differences in the shear failure line were found, due to the “loss of reworkability” after roll-compaction. These results provided a deeper understanding on the effect of roll-compaction process on the compaction behaviour of granules. However, additional studies should be pertinent, evaluating other materials and granules of different size, density and compositions.

The above conclusions of the compaction behaviour of granules were limited to a single material. But, based on previous literature researches that reported the sensitivity of the compactability results to the mechanical behaviour of the materials, we found pertinent to explore what happens when materials with different mechanical behaviours are mixed, roll-compacted and further tableted. The analysis was focused on the role of the composition of dry granulated binary mixtures of lactose and MCC and the effect of the granule size distribution on compaction behaviour (compressibility and compactability). Results confirmed that tablets produced with granules from roll-compacted mixtures show lower tensile strength than the tablets produced with the original binary mixtures. However, the reduction of tensile strength is more relevant for a high percentage of ductile material in the mixture. Attending the granule size, an increase in the size leads to a reduction of tensile strength of tablet. These results confirm that incorporating an adequate amount of brittle excipient and controlling the granule size, the effect of size enlargement process by roll compaction can be minimised.

In order to better understand these facts, an analytical technique based on the stress transmission measurement was proposed and used to study the densification behaviour of binary mixtures and granules. The results from the densification behaviour analysis show heterogeneity of the stress distributions in the tablets. The transmission stress in the axial direction differed depending on the granule size and the composition (higher for smaller particles and higher percentage of ductile material). It was observed that roll compacted granules work against the axial transmission due to their fragmenting behaviour under pressure. Indeed, a part of the applied pressure is consumed in the breakage of granules into smaller particles, improving the volume reduction but

reducing the available energy to form strong inter-particulate bonding. This is typically the densification mechanism of brittle materials and that is why brittle excipients are less sensitive to the effect of loss or re-workability after roll compaction. On the other hand, the radial transmission was slightly affected by the increase of lactose in the mixture and it resulted indifferent to the increase of granule size.

Part of the work included in this thesis has been published under the following references and it has been presented in three international conferences with oral presentations:

**Perez-Gandarillas, L.**, A. Perez-Gago, A. Mazor, P. Kleinebudde, O. Lecoq, and A. Michrafy. 2016. "Effect of Roll-Compaction and Milling Conditions on Granules and Tablets Properties." *European Journal of Pharmaceutics and Biopharmaceutics* 106: 38-49.

**Perez-Gandarillas, L.**, A. Mazor, D. Souriou, O. Lecoq, and A. Michrafy. 2015. "Compaction Behaviour of Dry Granulated Binary Mixtures." *Powder Technology* 285: 61-66.

**Particulate Processes in the Pharmaceutical Industry IV** (September, 2014, Potsdam, Germany). "Compaction behavior of dry granulated binary mixtures".

**Granulation Workshop** (June 2015, Sheffield, UK). "Impact of milling process conditions on the granule's properties: effect of milling speed and rotation".

**PARTEC: International Congress on Particle Technology** (April 2016, Nuremberg, Germany) "The impact of roll compaction on die filling and die compaction"

Moreover, this thesis has opened interesting perspectives of work that could be further developed:

- ✓ The measurement of the ribbon density distribution should be further investigated by using in-line and non-destructive techniques such as X-ray tomography, ultrasonic, near infrared chemical imaging or terahertz. These techniques can provide spatial information of the ribbon density without cutting the sample
- ✓ Deeper investigation on the understanding of how to relate the milling mechanisms with the granules properties could be done. Up to date, there is a lack of mechanistic understanding of the milling operation.
- ✓ Additional studies of the compaction behavior of granulated powder based on DPC model can be done considering materials with different mechanical behavior. In this thesis, only MCC was considered (plastic behavior), but the study can be extended to other excipients such as mannitol and/or lactose which have a brittle behavior under compression. This will allow the evaluation of the insensitivity of brittle materials to the loss of reworkability described in the literature.

## **Résumé en français**

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Dans l'industrie pharmaceutique, les comprimés sont les formes galéniques les plus utilisés. Afin de produire des comprimés avec des propriétés d'usage contrôlées à l'aide de presses rotatives, il est essentiel que la formulation pharmaceutique ait certaines propriétés, telles qu'une bonne coulabilité et une granulométrie uniforme. Ce qui assure le remplissage de la matrice, l'homogénéité de la composition et le dosage du principe actif. Comme les formulations pharmaceutiques sont souvent des mélanges de poudres avec des particules de tailles et de formes différentes, une étape de granulation est souvent nécessaire pour améliorer leurs propriétés, notamment la coulabilité et l'homogénéité.

Les procédés de granulation consistent principalement à agrandir la taille des particules par agglomération. La granulation peut être effectuée par voie humide (en ajoutant d'un liant liquide suivi d'une opération de séchage) ou par voie sèche (sans l'utilisation d'un liant liquide). L'avantage majeur de la granulation en voie sèche réside dans la production continue et sans l'utilisation de solvants, ce qui est bien adapté aux principes actifs qui sont sensibles à l'eau ou à d'autres solvants.

La granulation en voie sèche est réalisée à l'aide d'une presse à rouleaux. Son fonctionnement est basée sur le transport de poudres par vis sans fin ou par gravité entre deux rouleaux séparés par un entrefer et qui tournent en contre sens. La poudre est ensuite entraînée par les rouleaux dans la zone de l'entrefer pour être compactée en plaquette à l'aide de la pression des rouleaux. Ensuite, à l'aide d'un granulateur, les plaquettes sont réduites sous forme de granulés dont les tailles sont normalement supérieures à celles des particules d'origine. Ces granulés sont ensuite utilisés dans le procédé de compression pour produire des comprimés. Cette chaîne de procédés qui permet de modifier les propriétés des poudres à l'échelle du grain et à l'échelle de



l'assemblage (amélioration de la coulabilité, l'homogénéité et la réduction des fines...etc) est schématisée dans la figure 1.

Depuis dix ans, on assiste à une forte activité scientifique et technologique au niveau international, dans le domaine de la granulation sèche par compactage à rouleaux. C'est le caractère continue et économique (pas de séchage) qui suscitent cet engouement. Cependant, comme on le verra plus loin, au-delà de l'utilisation courante de ce procédé, le procédé de granulation sèche par compactage à rouleaux pose des questions fondamentales et technologiques.

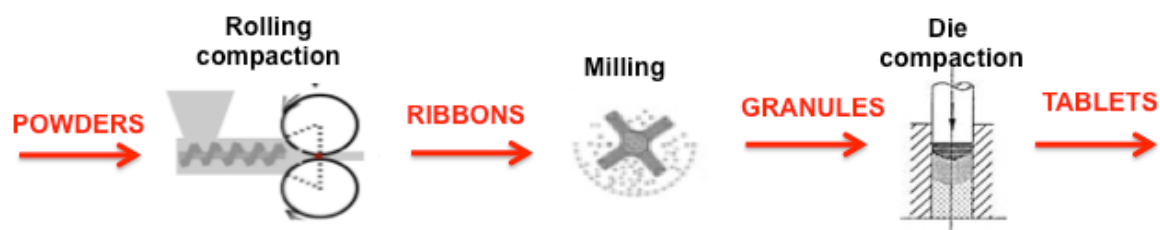


Figure 1. Schéma de la succession de procédés mis en jeu lors de la production de comprimés (granulation sèche par compactage à rouleaux; broyage/granulation et compression).

Parmi les challenges, il y a :

- (i) la compréhension des modifications structurales à l'échelle des granules permettant d'améliorer les propriétés d'usage. En effet, durant le processus de compactage à rouleaux et de broyage, la structuration de la poudre est complexe car elle dépend à la fois des paramètres des procédés (pression de compactage, vitesse d'alimentation, vitesse des rouleaux, entrefer, surface des rouleaux), du design de la presse (design du confinement au niveau des rouleaux) et des propriétés des poudres. L'amélioration des propriétés d'usage comme la coulabilité et l'homogénéité sont peu compris. En parallèle à cette amélioration, d'autres problèmes sont générés comme la production de particules fines ou encore la réduction de la résistance des compacts obtenus à partir des granules (par comparaison avec ceux obtenus à partir de la poudre non granulée).
- (ii) la dépendance des propriétés finales des granules des paramètres du procédé et des propriétés de poudres primaires. Pour améliorer la compréhension du processus de granulation, il est important de comprendre, les liens

« propriétés de poudres – paramètres du procédé – propriétés du produit ». Le produit est à la fois, le compact et le granulé. Quelle est l'origine des poudres fines ? quel est l'impact des paramètres procédé sur la production de fines ? quel est l'impact des paramètres procédés du broyeur sur l'homogénéité de la distribution de densité des granulés ?

Tenter de répondre à ces questions nous aidera dans le contrôle et l'optimisation du procédé de granulation sèche.

- (iii) l'impact du design des presses à rouleaux sur la qualité des granulés. En particulier, l'effet du système de confinement entre les rouleaux (plaques fixes de confinement ou jante fixée au rouleau inférieur. La plupart des études de granulation par compactage à rouleaux sont réalisées à l'aide de presses à rouleaux équipées par des plaques de confinement de part et d'autres des rouleaux et qui permettent de limiter la perte de poudres pendant le processus d'entraînement par les rouleaux. Les résultats expérimentaux de ces études montrent une hétérogénéité de la distribution de densité du compact le long de la largeur, la longueur et l'épaisseur. Les résultats de ces travaux n'ont jamais été corrélés à la production de fines suite aux broyages des compacts. Par ailleurs, l'homogénéité de densité dans le compact peut-être améliorée en étudiant l'impact du design du confinement. C'est le cas par exemple des presses équipées d'un système de confinement « rouleaux combiné à une jante ». L'étude de l'impact du design du confinement est l'un des points pertinents analysés dans ce travail. L'analyse est réalisée à la fois expérimentalement et en se basant sur la simulation numérique par éléments fins.

En passant de la granulation sèche par compactage à rouleaux à la compression en matrice, la chaîne de modifications structurelles et fonctionnelles des poudres est complexe. La différence de comportement en compression des granulés et des poudres primaires est un problème peu compris. Différentes échelles d'analyses des modifications structurelles et fonctionnelles existent. Sans être exhaustif, cela peut aller de l'échelle moléculaire, à l'échelle macroscopique en passant par l'échelle de la particule. Pour comprendre les relations entre les propriétés initiales des poudres, les paramètres du procédé et les propriétés d'usage du compact, le choix d'une échelle

d'analyse aide à déterminer les moyens expérimentaux à mettre en place et les modèles adaptés.

Cette thèse s'intègre dans un projet Européen intitulé IPROCOTM (the development of in silico process models for roll compaction), centré sur le développement de modèles robustes pour prédire les propriétés des plaquettes en sortie de l'opération de compactage à rouleaux et du comprimé final à partir des propriétés des particules élémentaires. Ce projet a réuni 8 partenaires Européens et 3 entreprises. Dans le cadre de ce projet 15 doctorants et post-doctorants ont travaillé en synergie sur 3 aspects (1) la compréhension des procédés mis en jeu dans les procédés de granulation/compactage, (2) la modélisation multi-échelles des relations « procédés-produits » et (3) la modélisation « intelligente » basée sur les réseaux de neurones ou inspirée de la nature.

L'**objectif** proposé dans ce travail de thèse est de développer une meilleure connaissance et compréhension du procédé de granulation par compactage à rouleaux en étudiant toutes les étapes conduisant à un comprimé pharmaceutique : compactage à rouleaux, broyage et compression. De part les procédés étudiés, cette thèse se veut multidisciplinaire, expérimentale, numérique et multi-échelles.

### **La structure de la thèse se décline de la manière suivante :**

Le **Chapitre 1** présente une étude bibliographique qui présente les différents procédés utilisés dans le travail proposé : compactage à rouleaux, broyage et compression en essayant de faire ressortir les paramètres d'intérêts des couples Produits /Procédés, reportés dans la littérature, le problème de l'hétérogénéité des propriétés des plaquettes en lien avec les paramètres critique du procédé, l'impact, peu étudié du broyage sur les propriétés des granulés en relation avec les propriétés des plaquettes ou encore le rôle de la microstructure dans les processus de déformation en compression. Cette revue bibliographique se termine par la mise en évidence que les modifications structurelles et fonctionnelles tout au long des trois procédés reste un défi scientifique et technologique.

Il en sort de cette bibliographie que les études réalisées se sont intéressées à une partie de la chaîne de procédé comme le compactage à rouleaux seul en se limitant à la caractérisation des compacts, le broyage seul pour étudier la distribution de taille des granulés ou encore la compression directe sans tenir compte de la structuration des

grains par agglomération en voie sèche.

Les challenges que l'on s'est donné dans cette thèse consistent à mieux comprendre les modifications structurales et le comportement mécanique des trois procédés et d'améliorer la compréhension des relations entre la formulation initiale de poudres et le comprimé. En particulier, l'effort s'est concentré sur :

- Les relations entre les propriétés des poudres et des compacts après granulation sèche par compactage à rouleaux,
- La compréhension de l'impact du système de confinement de la poudre entre les rouleaux sur les propriétés des compacts
- L'amélioration de la compréhension des relations entre les propriétés des compacts (après granulation) et le taux de fines
- Le développement de la connaissance au niveau de la différence de comportement en compression entre la poudre granulée et non granulée.

Le **Chapitre 2** présente les excipients pharmaceutiques utilisés (MCC, lactose et mannitol) aussi comme les dispositifs pour produire des échantillons (presses à rouleaux, broyeurs et presse uni-axiale). Ensuite, les techniques de caractérisation employées dans ce travail sont décrites. Dans l'objectif de mieux comprendre le comportement mécanique en compression de poudres granulées et la différence de comportement observé expérimentalement par rapport à celui des poudres non-granulés, le modèle Drucker Prager-Cap est présenté ainsi que la procédure pour sa calibration à partir de données expérimentales. Ce modèle prend en compte plusieurs propriétés caractéristiques des solides divisés. Les résultats de son application pour les systèmes granulaires étudiés sont présentés dans le chapitre 4. Autre l'approche par ce modèle élasto-plastique, une procédure expérimentale de mesure des rapports de transmission de contraintes axiales et radiales, s'appuyant sur une presse uni-axiale instrumentée, est introduite. Le but étant de mieux comprendre l'impact de la structure du granulé sur les phases de réarrangement et de densification des poudres. Cette analyse expérimentale est appliquée au comportement d'une formulation binaire granulée et non-granulée.

Le **Chapitre 3** concerne la synthèse des résultats obtenus après compactage à rouleaux et broyage de 2 types de produits et en utilisant des conditions expérimentales

variables et maîtrisées. Ces résultats sont issus de deux presses à rouleaux de design et de confinement des rouleaux différents, de deux types de granulateurs et en faisant varier différents paramètres liés aux procédés. L'analyse des données pour l'étude des paramètres influents sur, par exemple, la production de taux de fines et la cohésion est réalisée à l'aide d'une approche statistique.

Dans une première partie du chapitre, l'effet des paramètres de fonctionnement tels que la pression de compactage, le système de confinement (plaques fixes ou jante sur rouleau inférieur) et les conditions de broyage (type de broyeur, vitesse et angle de rotation) est évalué en termes d'impact sur la distribution de densité dans les plaquettes, la morphologie des granulés, la distribution de taille des particules et la résistance mécanique des comprimés. Dans une deuxième partie du chapitre, l'analyse des résultats a concerné l'impact du type de système de confinement sur les propriétés des plaquettes et des granulés. Une attention particulière a été donnée à la distribution de densité des plaquettes. Par ailleurs, l'évaluation du système de broyage a été déterminée en termes de performances basées sur la mesure du débit massique et de la distribution granulométrique des granulés.

Il en sort de cette analyse que le système de confinement a un impact fort sur la distribution de densité des plaquettes. Il a été montré que le système de confinement par plaques fixes génère une distribution de densité non homogène sur la largeur de la plaquette avec une densité plus élevée au centre que sur les bords. Par ailleurs, le système de confinement qui consiste en une jante fixée au rouleau permet de mieux homogénéiser la distribution de densité dans la largeur des plaquettes. Ce résultat important dans ce travail, est illustré dans la figure 2. A noter que la mesure de densité a été réalisée par deux techniques différentes: la porosité au mercure et une mesure dimensionnelle à l'aide d'un appareil Geopyc. L'impact du système de confinement sur les propriétés de la plaquette a été aussi appréhendé indirectement par l'analyse du taux de fines après broyage. Le résultat obtenu confirme les résultats précédents.

Les résultats obtenus sur l'hétérogénéité des plaquettes et l'impact du système de confinement ont été aussi confirmés par une modélisation 3D de type éléments finis.

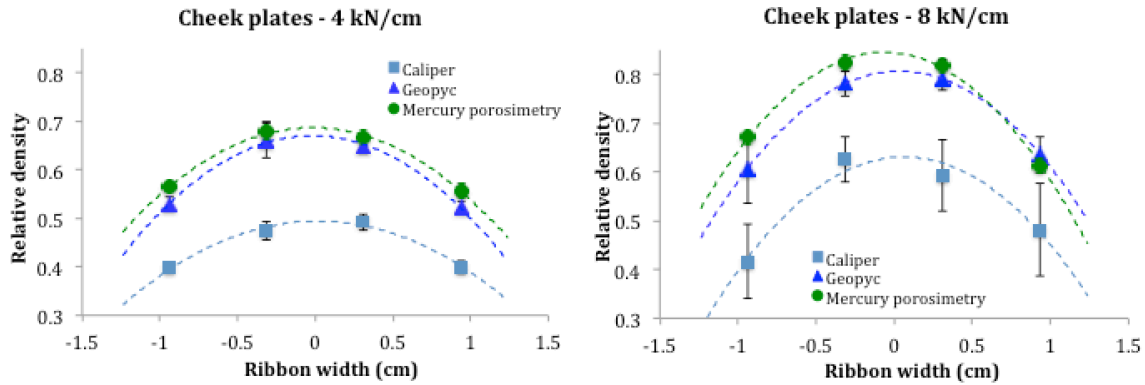


Figure 2(a) : Distribution de densité dans la largeur du compact granulé – cas du confinement par plaques de part et d’autres des rouleaux

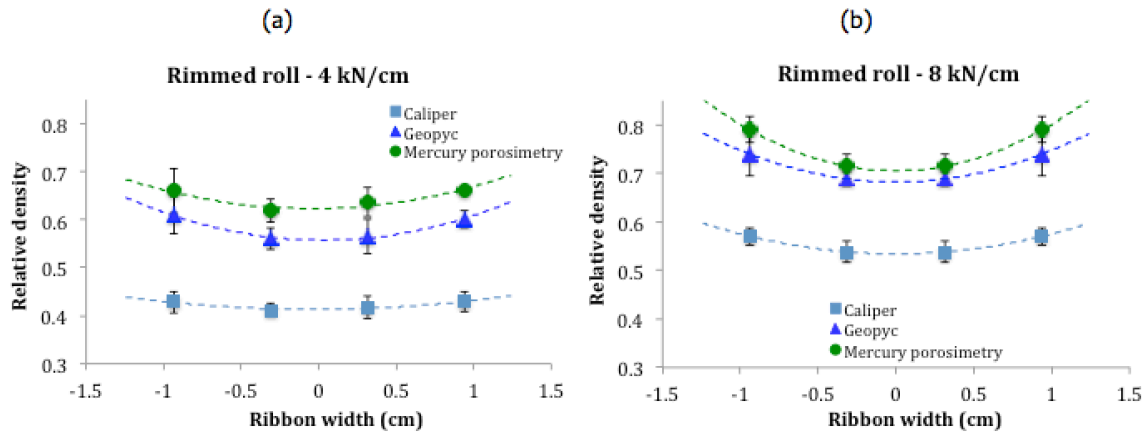


Figure 2(b) : Distribution de densité dans la largeur du compact granulé – cas du confinement « rouleau+jante ».

L’objectif du **Chapitre 4** est de (i) mieux comprendre la différence de comportement en compression d’une poudre de cellulose microcristalline non-granulés et des granulés résultant d’une granulation sèche par compactage à rouleaux (ii) étendre cette analyse à une formulation binaire composé de lactose et de cellulose microcristalline.

Dans le cas (i), l’analyse est menée à l’échelle locale en considérant la poudre comme un milieu poreux continu avec une seule phase solide. Le comportement en compression est représenté par le modèle Drucker-Prager Cap (DPC), qui propose les principaux paramètres caractérisant les poudres ( $d$ ,  $\beta$ ,  $R$  et  $P_b$ ). Les paramètres la poudre non-granulée et ceux du matériau granulé sont déterminés en se basant sur la procédure standard de calibration. Une discussion sur le lien des résultats obtenus et les mécanismes sous-jacents de densification est proposée. Dans cette analyse, l’effet de la

taille des granulés sur les paramètres du modèle DPC est aussi identifié et discutée. Les résultats obtenus montrent que les paramètres du modèle dépendent de la structure des particules (particule granulée ou non), particulièrement dans les phases de réarrangement et le début de la densification. De plus, les paramètres du modèle de DPC sont influencés par la taille des granulés. En particulier, la cohésion diminue avec l'augmentation de taille de granulés.

Les surfaces de charge, représentées dans les figures 3(a) et 3b), récapitulent les différences de comportement des poudres sous forme de granulés ou non

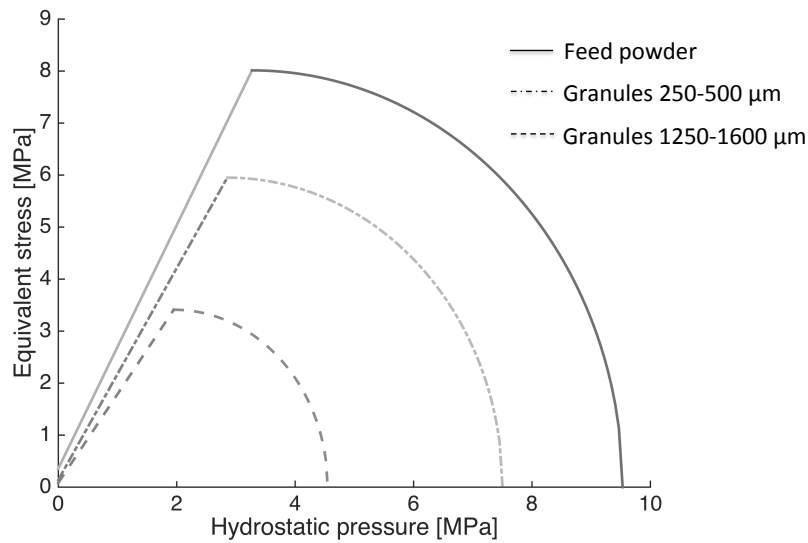


Figure 3(a) : Surfaces de charge (Drucker-Prager Cap) et effet de la granulation et de la taille des granulés (comprimés de densité relative (0.4))

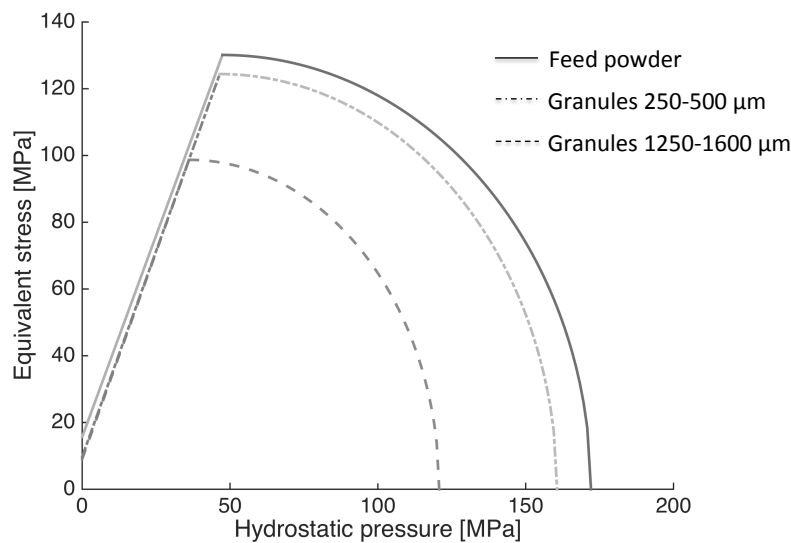


Figure 3(b) : Surfaces de charge (Drucker-Prager Cap) et effet de la granulation et de la taille des granulés (comprimés de densité relative (0.9))

Dans le cas d'étude (ii) le mélange binaire avant et après granulation pour 3 proportions de dosage (25, 50 et 75%) est analysé en terme de processus de compression en suivant l'évolution des contraintes dans le sens de la compression et dans le sens radial. Les effets de la granulation, de la taille des particules ainsi que les proportions de dosage sur les propriétés de compressibilité et de compactabilité sont analysées et les résultats discutés en qualifiant le comportement du lactose comme fragile et celui de la cellulose comme ductile. Les résultats montrent que les mélanges binaires granulés présentent une résistance mécanique à la rupture inférieure à celle des comprimés produits avec les mélanges binaires non-granulés. De plus, la baisse de résistance mécanique est plus prononcée pour un pourcentage élevé de matière ductile (MCC) dans le mélange. L'examen de l'effet de la taille des granulés a montré aussi une baisse de la résistance mécanique.

Cette thèse se termine par une **conclusion générale** et annonce l'avancée majeure de la connaissance dans ce domaine.

Du point de vue expérimental, ce travail a fournit des informations concernant la relation « paramètres – propriétés » en analysant les effets des différentes étapes de procédé, compactage, broyage, compression. Les résultats obtenus dans ce mémoire ont permis d'identifier les paramètres plus significatives et ils ont montré que :

- Les conditions du procédé de compactage à rouleaux ont l'effet le plus important sur les propriétés de produits. D'autre part, les conditions de broyage sont importantes sur la distribution de taille de granulés mais elles semblent par contre peu influentes sur la compression des granulés. Globalement, les conditions de compactage à rouleaux sont prédominantes par rapport au broyage. Ces faits ont été confirmés par l'analyse statistique.
- L'utilisation des différents types de systèmes de confinement engendre différents profils de densité dans les plaquettes. En plus, la distribution de densité dans les plaquettes est plus homogène quand le système de confinement par « jante sur rouleau » est utilisé. Ceci est une information précieuse parce que, dans la littérature, seul le profil de densités des plaquettes pour le système de confinement par « plaques fixes » est étudié. De plus, les systèmes de confinement ont montré un impact sur la performance de l'étape du broyage. En particulier



une distribution de taille plus homogène est obtenue avec le système « jante sur rouleau ». Ces résultats ont révélé, pour la première fois, l'impact direct du système de confinement sur la distribution de densité dans les plaquettes et sur la performance du broyage notamment sur la distribution de taille des granulés.

- En ce qui concerne le comportement des granulés en compression, il a été montré que la résistance mécanique des comprimés de granulés est plus faible que celle des comprimés obtenus à partir de la poudre non-granulés. De plus, cette baisse est plus significative quand le matériau a un caractère plastique. Par ailleurs, on a noté que plus la taille des granulés augmente, plus la résistance mécanique des compacts diminue.

Concernant l'aspect modélisation du compactage en matrice des matériaux granulés, les résultats du calcul des surfaces de charge pour la poudre granulé et non-granulé, ont montré que la granulation en voie sèche a un impact sur l'ensemble des paramètres du modèle DPC et notamment à faibles niveaux de densification (phase du réarrangement). De plus, il y a l'effet de la taille des granulés.

Enfin quelques perspectives à ce travail de thèse ont été dressées. En particulier l'approfondissement de la compréhension de la déformation des granulés pendant la compression et le rôle que peut jouer l'humidité dans le comportement en compression des systèmes granulaires, que ce soit au niveau de la granulation sèche ou la compression.

Une partie du travail inclus dans cette thèse a été publiée sous les références suivantes et elle a été présentée dans trois conférences internationales avec des présentations orales:

#### Articles

**Perez-Gandarillas, L.,** A. Perez-Gago, A. Mazor, P. Kleinebudde, O. Lecoq, and A. Michrafy. 2016. "Effect of Roll-Compaction and Milling Conditions on Granules and Tablets Properties." *European Journal of Pharmaceutics and Biopharmaceutics* 106: 38-49.

**Perez-Gandarillas, L.,** A. Mazor, D. Souriou, O. Lecoq, and A. Michrafy. 2015. "Compaction Behaviour of Dry Granulated Binary Mixtures." *Powder Technology* 285: 61-66.

**International conferences**

**Particulate Processes in the Pharmaceutical Industry IV** (*September, 2014, Potsdam, Germany*). “*Compaction behavior of dry granulated binary mixtures*”.

**Granulation Workshop** (*June 2015, Sheffield, United Kingdom*). “*Impact of milling process conditions on the granule’s properties: effect of milling speed and rotation*”.

**PARTEC: International Congress on Particle Technology** (*April 2016, Nuremberg, Germany*) “*The impact of roll compaction on die filling and die compaction*”



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# Annex I.

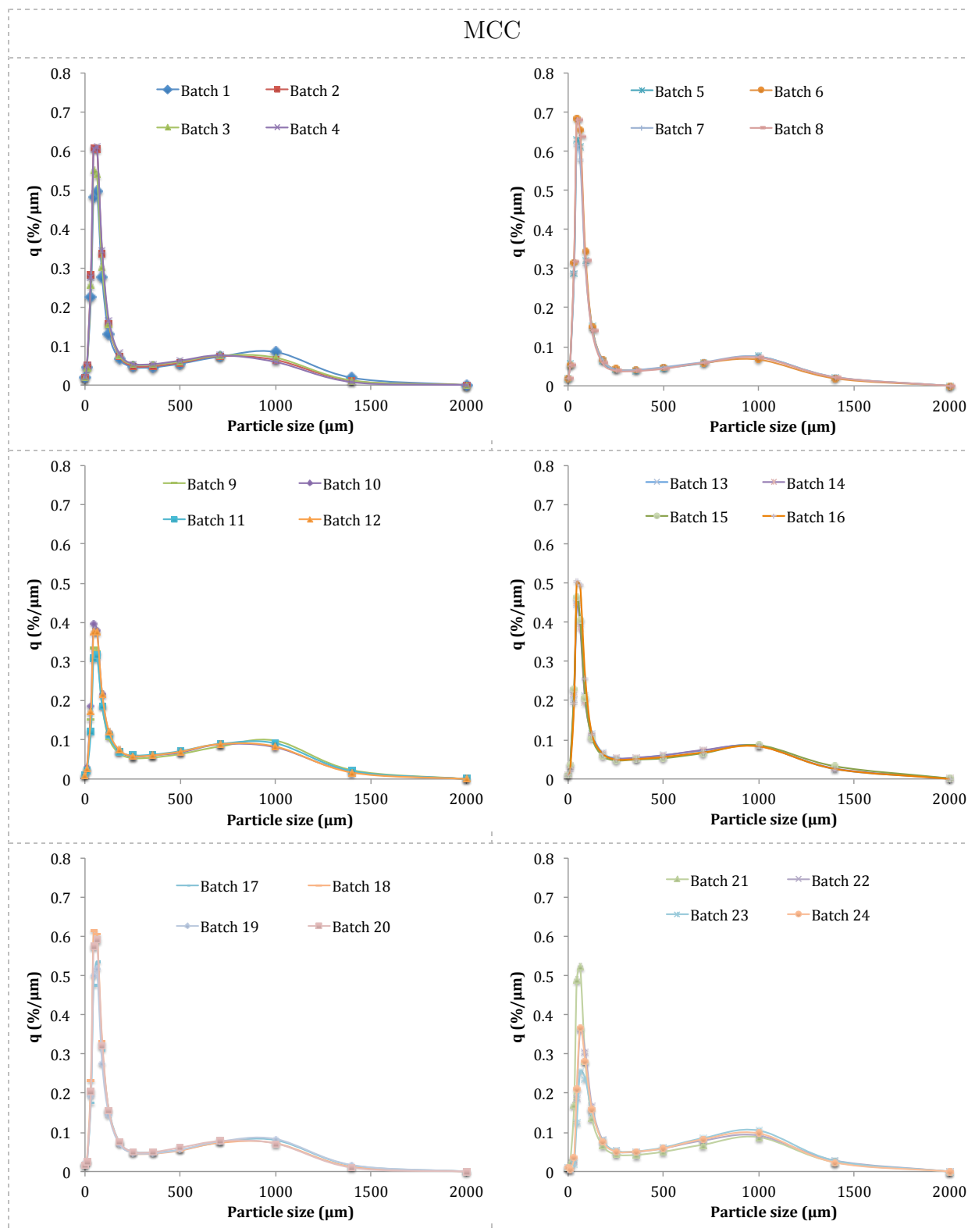
## Granule size distributions

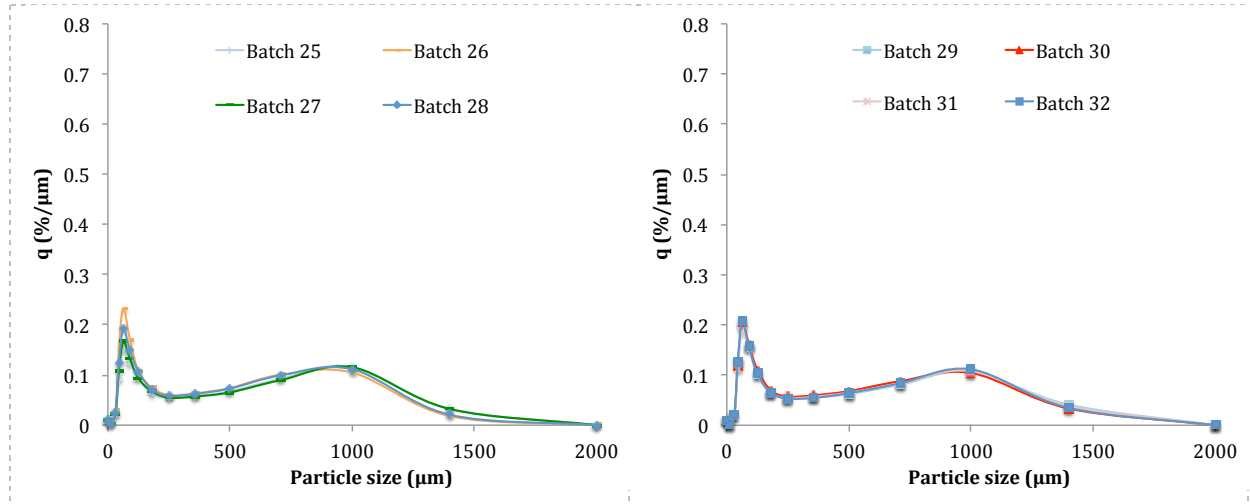
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The size distributions of the granules produced under the conditions detailed in Chapter 3 were analysed with a dynamic image analyser (Camsizer<sup>®</sup> XT, Retsch Technology GmbH). The batches are listed in Table A.1 and A.2. Due to the high amount of measurements performed (3 repetitions for each batch), the average curve was represented for each one of the 32 batches from each excipient.

The results showed that for all the batches, bimodal distributions were obtained, with the first component representing the fine particles and the second component the coarser particles.

MCC				
Batch	Roll-compaction		Milling	
	Sealing system	Compaction Force (kN/cm)	Rotor type	Speed-Angle
1	Cheek plates	4	Star granulator	Clockwise-30rpm
2	Cheek plates	4	Star granulator	Clockwise-120rpm
3	Cheek plates	4	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
4	Cheek plates	4	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
5	Cheek plates	4	Pocket mould groove	Clockwise-30rpm
6	Cheek plates	4	Pocket mould groove	Clockwise-120rpm
7	Cheek plates	4	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
8	Cheek plates	4	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°
9	Cheek plates	8	Star granulator	Clockwise-30rpm
10	Cheek plates	8	Star granulator	Clockwise-120rpm
11	Cheek plates	8	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
12	Cheek plates	8	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
13	Cheek plates	8	Pocket mould groove	Clockwise-30rpm
14	Cheek plates	8	Pocket mould groove	Clockwise-120rpm
15	Cheek plates	8	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
16	Cheek plates	8	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°
17	Rim rolls	4	Star granulator	Clockwise-30rpm
18	Rim rolls	4	Star granulator	Clockwise-120rpm
19	Rim rolls	4	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
20	Rim rolls	4	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
21	Rim rolls	4	Pocket mould groove	Clockwise-30rpm
22	Rim rolls	4	Pocket mould groove	Clockwise-120rpm
23	Rim rolls	4	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
24	Rim rolls	4	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°
25	Rim rolls	8	Star granulator	Clockwise-30rpm
26	Rim rolls	8	Star granulator	Clockwise-120rpm
27	Rim rolls	8	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
28	Rim rolls	8	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
29	Rim rolls	8	Pocket mould groove	Clockwise-30rpm
30	Rim rolls	8	Pocket mould groove	Clockwise-120rpm
31	Rim rolls	8	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
32	Rim rolls	8	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°

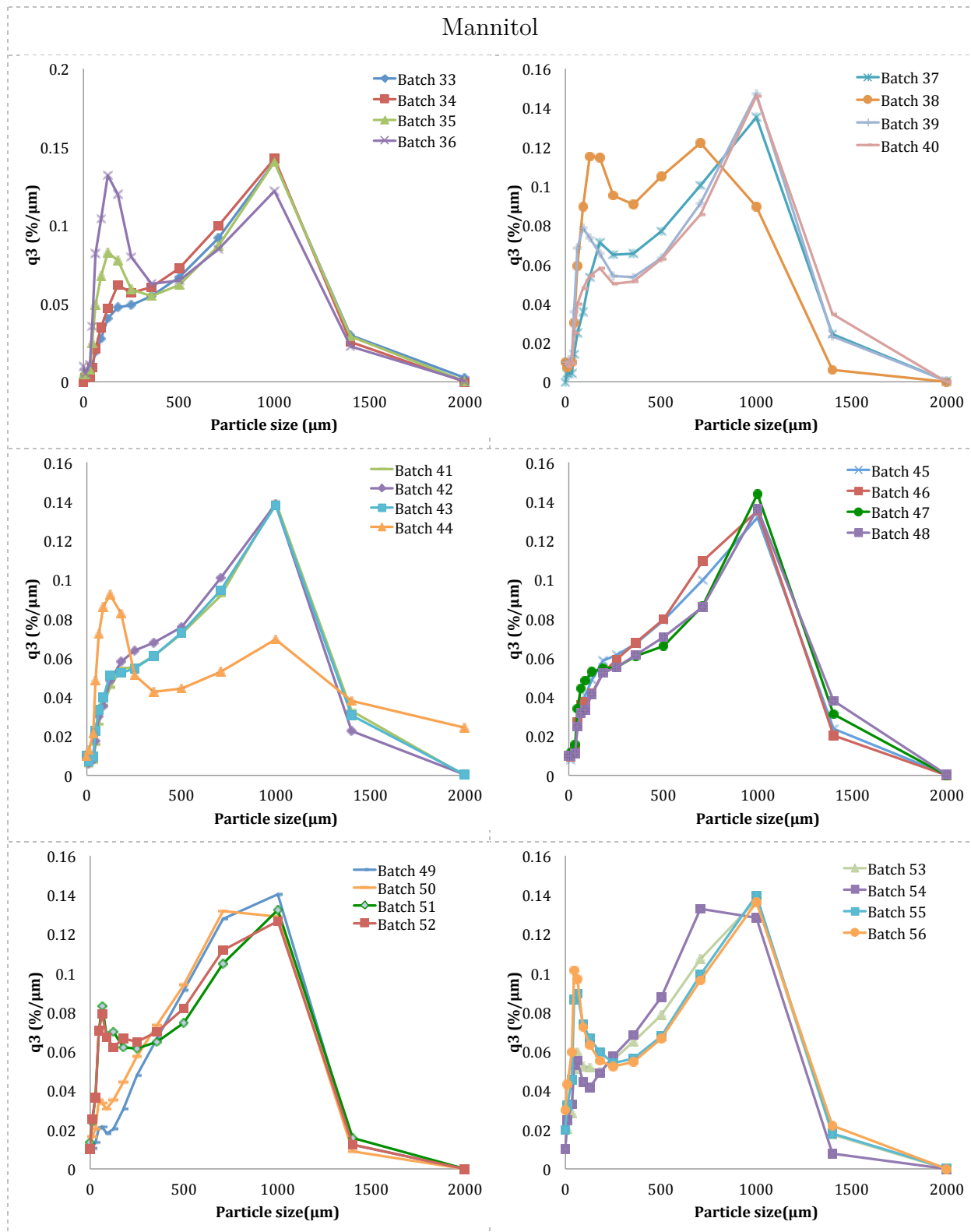


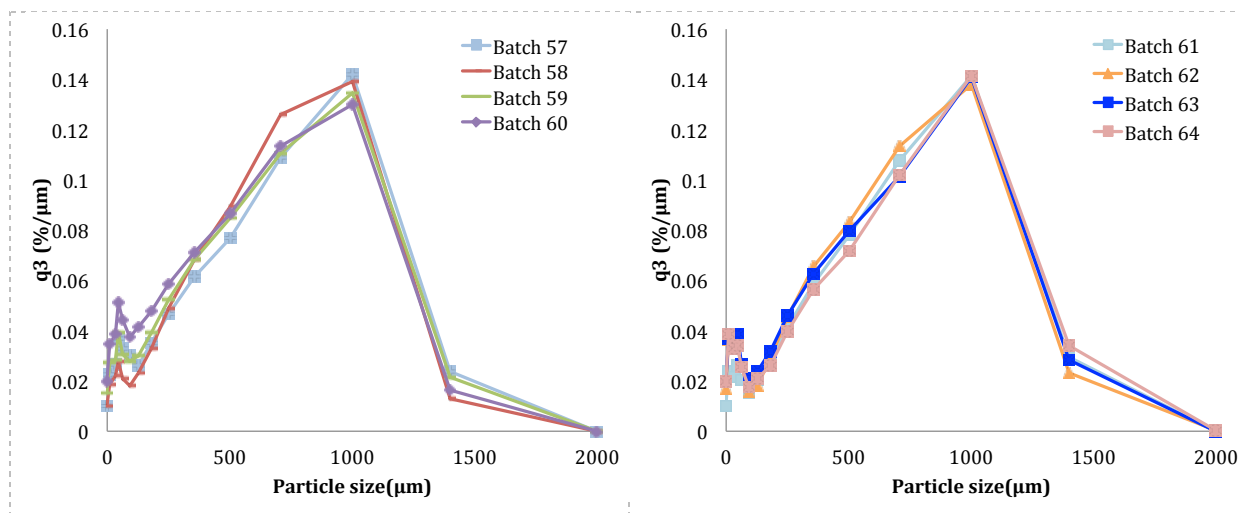


It can be seen that the component representing the fines (first component of the distribution) decrease considerably when using high roll-compaction force and rimmed-roll as sealing system (from batch 25 to 32) and the coarser particles are obtained under these conditions (second component of the distribution)

Mannitol				
Batch	Roll-compaction		Milling	
	Sealing system	Compaction Force (kN/cm)	Rotor type	Speed-Angle
33	Cheek plates	4	Star granulator	Clockwise-30rpm
34	Cheek plates	4	Star granulator	Clockwise-120rpm
35	Cheek plates	4	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
36	Cheek plates	4	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
37	Cheek plates	4	Pocket mould groove	Clockwise-30rpm
38	Cheek plates	4	Pocket mould groove	Clockwise-120rpm
39	Cheek plates	4	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
40	Cheek plates	4	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°
41	Cheek plates	8	Star granulator	Clockwise-30rpm
42	Cheek plates	8	Star granulator	Clockwise-120rpm
43	Cheek plates	8	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
44	Cheek plates	8	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
45	Cheek plates	8	Pocket mould groove	Clockwise-30rpm
46	Cheek plates	8	Pocket mould groove	Clockwise-120rpm
47	Cheek plates	8	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
48	Cheek plates	8	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°
49	Rim rolls	4	Star granulator	Clockwise-30rpm
50	Rim rolls	4	Star granulator	Clockwise-120rpm
51	Rim rolls	4	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
52	Rim rolls	4	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
53	Rim rolls	4	Pocket mould groove	Clockwise-30rpm
54	Rim rolls	4	Pocket mould groove	Clockwise-120rpm
55	Rim rolls	4	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
56	Rim rolls	4	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°
57	Rim rolls	8	Star granulator	Clockwise-30rpm
58	Rim rolls	8	Star granulator	Clockwise-120rpm
59	Rim rolls	8	Star granulator	Oscillating: 30 rpm(CW:CCW)- 150°
60	Rim rolls	8	Star granulator	Oscillating: 120 rpm(CW:CCW)- 150°
61	Rim rolls	8	Pocket mould groove	Clockwise-30rpm
62	Rim rolls	8	Pocket mould groove	Clockwise-120rpm
63	Rim rolls	8	Pocket mould groove	Oscillating: 30 rpm(CW:CCW)- 150°
64	Rim rolls	8	Pocket mould groove	Oscillating: 120 rpm(CW:CCW)- 150°







It can be noticed that the shape of the size distribution is completely different from the one of MCC granules. For mannitol, the distributions obtained differ highly depending on the conditions and different shapes of the curves are obtained. However, for mannitol, the second component of the distribution (coarser particles) is much more pronounced than for MCC, obtaining fewer amounts of fines.



## Dry granulation process and compaction behavior of granulated powders

Particulate solids such as pharmaceutical powders often require size enlargement processes to improve the manufacturing properties like flowability. For that reason, dry granulation by roll compaction has been widely used in the pharmaceutical industry. The process consists of compressing powders between two counter-rotating rolls to produce ribbons that will be subsequently milled into granules. The obtained granules are tableted for oral dosage. In this process there are two main limitations: the existence of different designs of the roll compactors, milling systems and the interaction between process parameters and raw material properties are still a challenge and the roll-compaction process leads to an inferior tensile strength of tablets compared with direct compression. These aspects are investigated in this work. In the first part of this thesis, an analysis on the effect of different roll-compaction conditions and milling process parameters on ribbons, granules and tablet properties was performed, highlighting the role of the sealing system and the ribbon density distribution characteristics. In the second part, die compaction of roll-compacted powders, as the last stage of the process, is further investigated in terms of experimental analysis (effect of the granule size and composition and stress transmission measurements) and modelling the compaction behavior of granules.

**Keywords:** *Dry granulation, Roll-compaction, Die-compaction, Ribbons, Granules, Tablets*

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## Granulation sèche par compactage à rouleaux et comportement en compression des granulés

Les solides divisés telles que les poudres pharmaceutiques nécessitent souvent des processus d'agrandissement de taille par agglomération pour améliorer leur comportement mécanique, notamment la coulabilité. Pour cette raison, le procédé de "granulation en voie sèche" est utilisé dans l'industrie pharmaceutique. Le procédé consiste à comprimer la poudre en la faisant passer entre deux rouleaux séparés par un entrefer, pour produire des plaquettes qui sont ensuite broyées en granulés et comprimés en compacts. Dans ce procédé, l'existence de différents modèles de compacteurs à rouleaux et de systèmes de broyage d'une part, et l'interaction entre les paramètres des procédés et des propriétés des produits (plaquettes, granulés et comprimés) d'autre part, rendent difficile la compréhension des phénomènes et des mécanismes sous-jacents. En particulier, le procédé entraîne une perte de résistance mécanique des comprimés formés à partir de granulés (comparativement à celles des comprimés de poudres non-granulés) et ce phénomène est encore mal compris. Ces aspects sont étudiés dans ce travail de thèse en menant des caractérisations expérimentales et des modélisations numériques permettant de mieux comprendre les modifications micro et macro structurales des poudres mises en forme par granulation sèche. Le but ultime est de progresser dans la compréhension des relations "propriétés des poudres - paramètres des procédés". Enfin, la compréhension des différences de comportement en compression de poudres granulées et non-granulées est menée à l'aide d'une modélisation du comportement dans le cadre de la mécanique des milieux continus poreux.

**Mots-Clés:** *Granulation sèche, Compactage à rouleaux, Compactage en matrice, Ribbons, Granulés, Comprimés*