



1 Introduction and state of the art

In the pharmaceutical industry, oral tablets represent one of the most common drug delivery forms. Due to efficiency demands and cost pressures, tablet production is highly automated, typically using rotary tablet presses. Modern presses can achieve throughputs of up to 1.6 million tablets¹ per hour while maintaining a high pharmaceutical quality standard.

Ensuring consistent tablet quality depends not only on the machinery but also on the properties of the powder to be compressed, particularly its flow characteristics and its homogeneity. The powder must flow freely into the die cavities of the press to ensure a uniform fill and consistent tablet mass.

Pharmaceutical powders are often available as very fine particles. This fine particle size offers advantages such as a high surface area, which promotes rapid dissolution in water and within the human body, and improved homogeneity when mixing with other ingredients. However, fine powders typically exhibit poor flowability due to the increasing relative importance of cohesive forces such as electrostatic interactions and van der Waals attractions.

Granulation is the most common approach to overcome poor flowability. In this key particle technology process, multiple primary particles are bound together to form larger granules. Depending on the material, various granulation methods can be used, some involving binders or other additives, and others operating without additional materials.

One such method is roller compaction granulation, a continuous process that is of particular interest in the context of continuous manufacturing in the pharmaceutical industry. Once established, the process is robust to control. However, for new formulations and novel active pharmaceutical ingredients, determining the optimal process parameters often requires extensive experimentation, which can be costly, especially when working with expensive and/or limited-availability compounds like newly developed active pharmaceutical ingredients.

¹Taken from product data sheet of FE75 by Fette Compacting GmbH.



Numerical simulations of the roller compaction process can help to replace, or at least reduce, the number of experiments required, thereby saving both time and resources. This can be achieved either by predicting process outcomes or by improving the understanding of the underlying mechanisms.

1.1 Aim and structure of this work

This thesis's aim was to develop mechanistic and predictive models for the roller compaction process using discrete element method simulations. The work considers the key process steps, including the compression stage and the subsequent comminution stage, and aims to develop a practical, particle-based model capable of capturing the effects of roller compaction on the process itself as well as on the subsequent tablet pressing.

The central research questions guiding this work are:

1. Can DEM reproduce stress and porosity evolution during roller compaction?
2. Can the bonded-particle model predict the granule size distribution after milling?
3. Can roller compaction information be transferred to predict tablet properties?

The thesis is structured as follows: First, an overview of dry granulation processes is provided, including the underlying physics and the derived theoretical models. Alternative wet granulation processes are then discussed, as they still dominate much of the granulation market. Next, the relevant powder properties are introduced, followed by a discussion of both classical and novel modeling approaches for the roller compaction process. The discrete element method (DEM) is then presented, with emphasis on the most important cohesive DEM contact models utilized for simulating compaction. In the second part of this section, the bonded-particle model used to describe breakage phenomena is introduced. Subsequently, additions to the existing models for compaction and comminution are described, together with the calibration procedure for both. As DEM simulations almost always require post-processing steps, the following chapter on methods of analysis outlines the general post-processing procedures applied in this work, alongside the experimental measurement techniques used for validation.

Finally, the results are presented: first for the roller compaction stage, then for the comminution stage, and lastly for a reduced-order model aimed at predicting tablet properties from dry-granulated granules.



1.2 Granulation and its applications

Granulation is a key step for the design of granular products and intermediates. Particle properties can be specifically adjusted to produce highly specialized and valuable products. An extract of industries applying granulation includes:

Crop: Plant seeds are coated with a protective and/or nutritious hull to improve growth, enhance mechanical resistance, and increase pest resistance through the application of insecticides and fungicides (Afzal et al., 2020; Kaufman, 1991). Additionally, seed flowability can be enhanced to facilitate automated planting.

Chemicals: Fertilizers often consist of multiple components that must be combined to effectively fertilize the soil. Additives can control release, surface roughness, and mechanical resistance (Hoeung et al., 2018; Guo et al., 2018; Kabiri et al., 2018).

Pharmaceuticals: For tablet production, a free-flowing and well-mixed composition is required. To ensure this, granulation locks excipients and active pharmaceutical ingredients (API) into granules (Shanmugam, 2017).

Food: Examples include granulated milk powder, encapsulated probiotics (Lim et al., 2021), sugar- and shellac-coated candies, granulated instant coffee or cacao powders, and instant soups.

Mining: Iron ore is often granulated in a kiln, where primary particles are connected via sintering. This reduces transportation losses, increases process safety, and improves final product quality (Moraes et al., 2018).

The granulation² process is generally categorized into two main types: wet and dry granulation. The two routes are schematically illustrated in Fig. 1.1. Depending on the properties of the target granules, the two types are not in direct competition, since the resulting properties are strongly influenced by the chosen method. Therefore, a decision is typically made in favor of one process over the other. The primary distinction between the two lies in the use of a liquid binder. The following sections describe these two process types in detail.

1.3 Dry granulation

In this chapter, the mechanisms of dry granulation are first analyzed, and then the most important process is introduced: roller compaction, followed by a discussion

²In German terminology, particle growth by coating or layering is referred to as *Granulation*, while particle growth by particle-particle binding is often called *Agglomeration*. In this work, the term granulation is used in line with international convention and refers specifically to the agglomeration mechanism, i.e. particle growth by particle-particle binding.

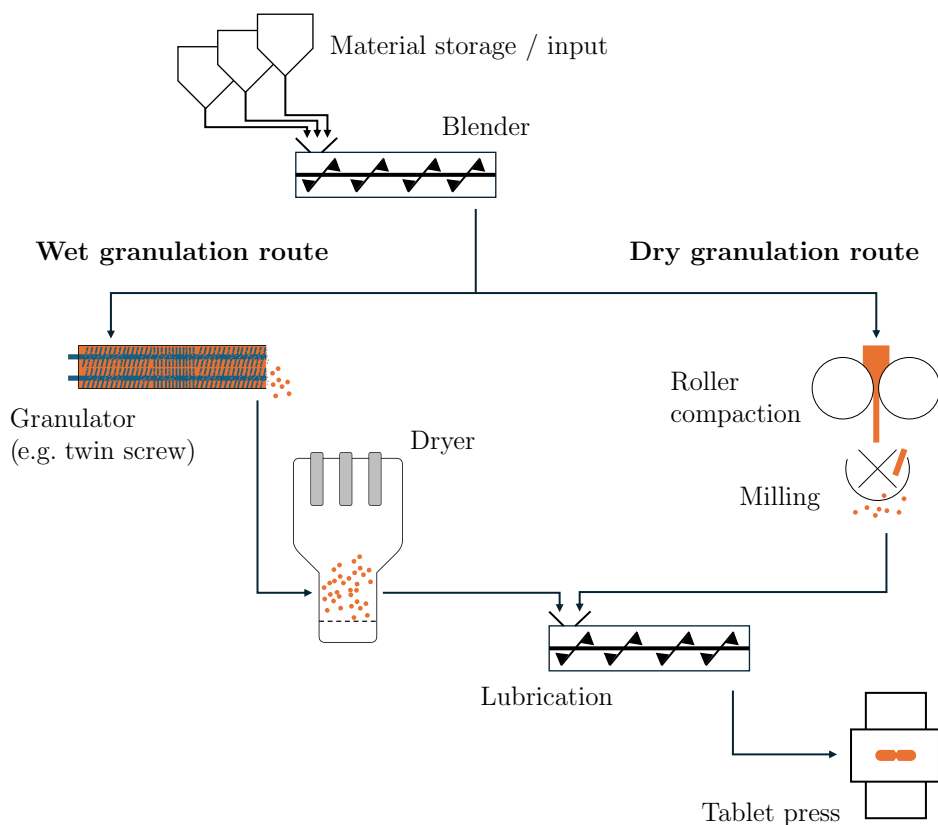


Figure 1.1: Wet and dry granulation routes for an exemplary pharmaceutical tabletting process. Following material input and blending, the wet route includes granulation and a subsequent drying step, whereas the dry route proceeds via roller compaction. Both routes lead to granules for tablet pressing.

of other relevant processes.

1.3.1 Physics in dry granulation

In dry granulation particles are brought together by rearrangement, deformation and fragmentation. Cooper et al. (1962) proposed a two staged model for ceramics, which has been transferred to more ductile materials like metals (Itoh et al., 1999) and pharmaceutical excipients and APIs (Uniyal et al., 2020; Chowhan et al., 1980; Paronen et al., 1983). Cooper & Eaton proposed that in the first stage of compaction, particles fill large gaps, a process mainly lead by particle rearrangement. In the second stage smaller gaps are closed by deformation and fragmentation of the particles. Fig. 1.2 shows the Cooper & Eaton model. The transition between

the first and second stage is fluid in reality and depends on the material. Just as material-dependent is the possibility of whether plastic deformation or fragmentation predominates in the second stage.

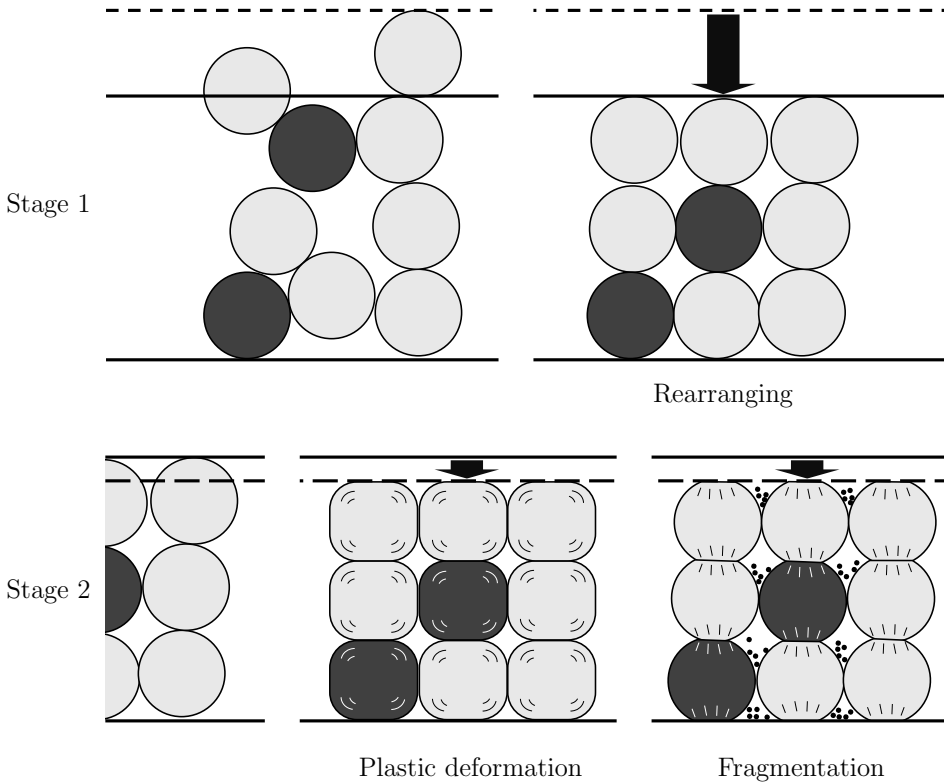


Figure 1.2: Two-stage compaction model according to Cooper & Eaton, adapted from (Cooper et al., 1962).

Examining the two-stages more closely, the resistance force against compaction in stage 1 is mainly driven by particle friction within the bed and is non-reversible. In addition, particles begin to deform elastically. In the second stage, the particles' yield strength is exceeded, and they begin to deform plastically, likely until fracturing occurs. Fig. 1.3 shows an idealized, exemplary compression of a single particle, progressing from elastic to plastic deformation, and ultimately to failure. Depending on the complex geometry of a single grain and possible weaknesses in the grain's structure (e.g., nooks), the grain's yield strength and maximum strain can vary widely. Therefore, empirical models with parameterized coefficients are commonly used to describe powder compaction.

The classic models, which are still in use today, were published by Heckel, Kawakita,

and Cooper & Eaton in the 1960s. They describe, in different ways, the behavior of the porosity ε of the powder bed as a function of the applied compression pressure σ . These models are described in the following sections.

1.3.1.1 Heckel model

Heckel applied a model with two constant parameters, A and K (Heckel, 1961a; Heckel, 1961b), which had been previously postulated (Denny, 2002), but it is referred to as the Heckel equation or model in this work, as this terminology is commonly used:

$$\varepsilon = \exp(-\sigma \cdot K - A) . \quad (1.1)$$

Heckel found an empirical relation between the parameter K and the yield strength σ_0 to be (Heckel, 1961b; Heckel, 1961a):

$$K = \frac{1}{3 \cdot \sigma_0} . \quad (1.2)$$

The relation was initially conceived for metal powders. However, since then, it has been applied to other materials as well. The empirical relation of Eq. 1.2 works for ductile materials, which tend to deform plastically. This is often the case for pharmaceutical materials. Thus, the Heckel model is widely applied in this field (Paronen, 1986; Vreeman et al., 2021; Sun et al., 2001; Patel et al., 2022; Sonnergaard, 1999; Khomane et al., 2012).

Differences between materials can be effectively visualized using the 'Heckel plot', which displays the compaction pressure σ against the negative logarithmic porosity $-\ln(\varepsilon)$, as shown in Fig. 1.4. Typically, one can distinguish between three regions

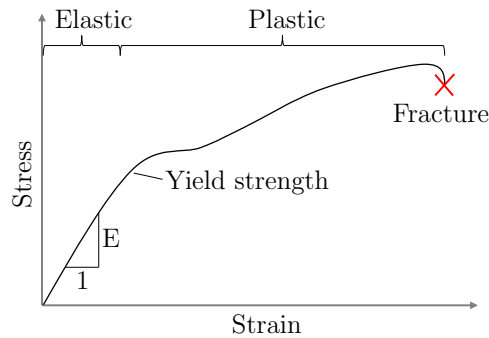


Figure 1.3: Exemplary stress-strain behavior during compression of a single, cubic particle; E refers to the Young's modulus.

of the plot based on the underlying compaction mechanisms. In the second region, plastic deformation dominates, leading to a linear slope of the curve, where Eq. 1.1 can be applied in a transformed form.

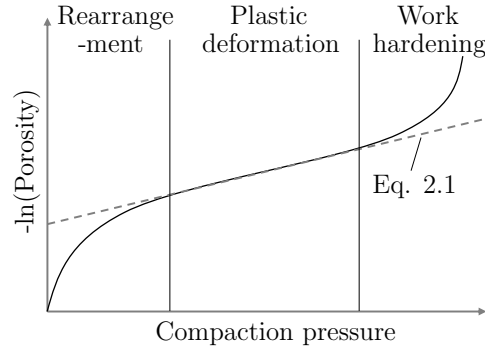


Figure 1.4: Heckel-plot, exemplary compression of a ductile material.

In the third region, Heckel proposed the work hardening of the material, which can even lead to a higher crystal density by updating the lattice order, reducing stacking faults, and limiting dislocation movement (He et al., 2021; Shun et al., 1992). This is understandable for metals and ceramics, and work hardening is also a plastic process. However, studies on pharmaceutical materials have shown that the porosity change in the right-hand region of the Heckel plot is highly reversible. In other words, there is a growing elastic component in this region.

This finding was observed through the elastic springback of the tablets after tabletting, where Sun et al. (2001) determined the in-die Heckel plot, where the porosity is calculated based on the remaining space inside the press matrix (the curve resembles the one in Fig. 1.4). These values were compared to the out-die porosities, determined from the final tablets' dimensions. At high compaction pressures within the right-hand region, the linear relationship of Eq. 1.1 remains valid for the out-die values, while the in-die curve exhibits an increasing slope, indicating elastic recovery.

1.3.1.2 Kawakita model

Besides Heckel, another popular model is the Kawakita model (Kawakita et al., 1966; Kawakita et al., 1971; Mazel et al., 2011; Denny, 2002; Sato et al., 2024; Nordström et al., 2009), which is empirical in nature and describes the relationship between porosity and pressure of compacted powders. It involves two empirical material parameters, a and b , and is given by:

$$\varepsilon = \frac{(1 - \varepsilon_0)(1 + b\sigma)}{ab\sigma - b\sigma - 1} + 1 . \quad (1.3)$$

Here, ε_0 is the initial porosity inside the press matrix, which can be approximated by the bulk porosity.

Similar to the Heckel plot, a Kawakita plot also exists, in which the porosity is related to the compression force in a way that yields a linear relationship in the data. This graph can be found in Appendix A, Fig. A.1.

1.3.1.3 Cooper & Eaton model

Cooper et al. (1962) developed a model to predict the filling of voids inside the bulk. They introduced the concept of fractional volume compaction and built their model on the idea of a shrinking relative void volume V^* , originally designed for ceramics (see Eq. 1.4). For comparison with the previously mentioned models, the Cooper & Eaton model is here rearranged to express porosity as a function of compaction pressure, as shown in Eq. 1.5. This model accounts for particle rearrangement and plastic deformation using two separate terms and includes the tapped porosity³ ε_0 and four empirical parameters (a_1 , a_2 , k_1 , k_2) for adjustment:

$$V^* = a_1 \exp\left(-\frac{k_1}{\sigma}\right) + a_2 \exp\left(-\frac{k_2}{\sigma}\right) , \quad (1.4)$$

$$\varepsilon = 1 - \left[\frac{1}{1 - \varepsilon_0} - \left(\frac{1}{1 - \varepsilon_0} - 1 \right) V^* \right]^{-1} . \quad (1.5)$$

Since this model contains the most parameters, its accuracy is the highest. However, depending on the use case, the other models also have their *raison d'être*, as they are still widely used and material parameters have already been determined for many substances. Due to its high fitting capability, the model of Cooper & Eaton is also applied to pharmaceutical materials (Wünsch et al., 2019; Mallick et al., 2011).

1.3.1.4 Model comparison

The accuracy of the three models is compared in the following section using two materials: micro-crystalline cellulose (MCC) and sodium chloride (NaCl). The data for MCC were obtained using a Styl'One tablet press, while the data for sodium chloride were taken from (Sonnergaard, 1999). Fig. 1.5 shows the experimental data and the different model fits. Fig. 1.5A displays porosity versus compaction pressure,

³Tapped porosity = 1 - relative tapped density .

and Fig. 1.5B presents the corresponding Heckel plot, which shows $-\ln(\text{Porosity})$ versus compaction pressure.

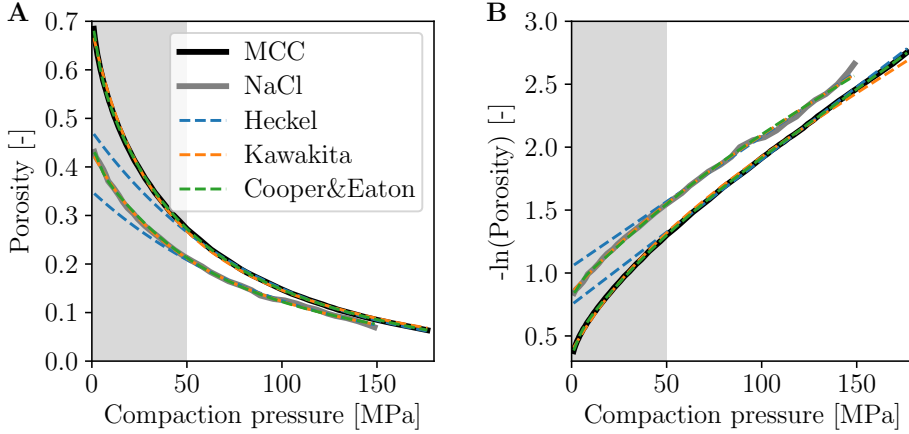


Figure 1.5: Comparison of compaction behavior for MCC and NaCl using the models of Heckel, Kawakita, and Cooper&Eaton. The initial porosity ε_0 was taken from the experimental data, and the remaining parameters were fitted. For the Heckel model, only data from the white region were used, whereas for Kawakita and Cooper & Eaton, all data points were included.

The initial porosity ε_0 was taken from the experimental data, and the remaining parameters were fitted. For the Heckel model, only data from the white region were used, whereas for Kawakita and Cooper&Eaton, all data points were included. In both graphs, the high accuracy of the Kawakita and Cooper & Eaton models is clearly visible to the reader. Heckel's equation fits well for compaction pressures above 50 MPa but lacks accuracy at lower pressures. Therefore, the model parameters A and K were fitted only to the data within the white background area of the plots. In contrast, for the Kawakita and Cooper & Eaton models, all experimental data were used for fitting.

The Heckel plot is particularly useful for identifying the linear portion of the compaction curve, which helps in selecting the appropriate data range for model parameter estimation. For both MCC and NaCl, the linear behavior coincidentally begins around 50 MPa.

The fitted parameters for all models and materials are listed in Tab. 1.1, along with the mean absolute percentage error (MAPE), defined as

$$\text{MAPE} = 100\% \cdot \frac{1}{N} \sum \left| \frac{x_{\text{true}} - x}{x_{\text{true}}} \right|. \quad (1.6)$$

In all cases, the fitting error is below 2%. The Kawakita and Cooper & Eaton models show comparable accuracy, whereas, by definition, Heckel's model exhibits a significant lack of predictive accuracy at lower compaction pressures, leading to higher errors.

The performance of the Cooper & Eaton model with MCC is significantly more accurate than that of the Kawakita model. This can also be seen in Fig. A.1, where the measured data are well represented, especially at higher resolution at lower compaction pressures. For NaCl, the MAPE is at a similar level for both models, likely due to greater uncertainty in the measured data.

When analyzing low compaction pressures, the Cooper & Eaton model offers a clear advantage over the Kawakita model. At higher pressures, the difference in model performance becomes negligible. In particular, if the parameters are fitted to in-die data and no further interpretation is required from the model, the Cooper & Eaton model can be applied universally. The additional effort of fitting four parameters instead of two (or five instead of three if ε_0 is unknown) is considered insignificant.

Table 1.1: Fitted model parameters for the data presented in Fig. 1.5. Mean absolute percentage error (MAPE) compares the models' predicted porosity with experimental data. MAPE was also used as the fitting objective. Values in brackets for Heckel represent the fitting error.

Model	Parameter	Fitted Values		MAPE	
		MCC	NaCl	MCC	NaCl
Heckel	A	0.748	1.05	25%	38%
	K	$1.15 \cdot 10^{-8} \text{ Pa}^{-1}$	$1.03 \cdot 10^{-8} \text{ Pa}^{-1}$	(1.0%)	(1.8%)
Kawakita	a	0.707	0.476	1.5%	1.3%
	b	$8.30 \cdot 10^{-8} \text{ Pa}^{-1}$	$2.81 \cdot 10^{-8} \text{ Pa}^{-1}$		
	ε_0	0.685	0.431		
Cooper&Eaton	a_1	0.347	0.631	0.36%	1.6%
	k_1	$3.19 \cdot 10^7 \text{ Pa}$	$4.71 \cdot 10^7 \text{ Pa}$		
	a_2	0.693	0.448		
	k_2	$3.66 \cdot 10^6 \text{ Pa}$	$6.01 \cdot 10^6 \text{ Pa}$		
	ε_0	0.685	0.431		

1.3.1.5 Attraction mechanisms of particles

After discussing the resistance or force required for dry granulation and presenting corresponding models, this section addresses why primary particles adhere to each other in the first place, which is the main objective of this form of granulation. By reducing porosity, particles are brought into closer contact (see Fig. 1.2). According