European Journal of Pharmaceutics and Biopharmaceutics 106 (2016) 38–49

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Effect of roll-compaction and milling conditions on granules and tablet properties

Lucia Perez-Gandarillas [a,*], Ana Perez-Gago [b], Alon Mazor [a], Peter Kleinebudde [b], Olivier Lecoq [a], Abderrahim Michrafy [a]

[a] Université de Toulouse, Mines Albi, CNRS, Centre RAPSODEE, Albi, France
[b] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Dusseldorf, Germany

ARTICLE INFO

Article history:
Received 28 October 2015
Revised 19 May 2016
Accepted in revised form 25 May 2016
Available online 27 May 2016

Keywords:
Roll-compaction
Ribbon
Sealing system
Granule
Fines
Tablet

ABSTRACT

Dry granulation is an agglomeration process used to produce size-enlarged particles (granules), improving the handling properties of powders such as flowability. In this process, powders are compacted using a roll press to produce ribbons, which are milled in granules used further in the tableting process. The granule and tablet properties are influenced by the existence of different designs of the roll compactors, milling systems and the interaction between process parameters and raw material properties. The main objective of this work was to investigate how different roll-compaction conditions and milling process parameters impact on ribbons, granules and tablet properties, highlighting the role of the sealing system (cheek plates and rimmed roll). In this context, two common excipients differing in their mechanical behaviour (MCC and mannitol) are used. The study is based on the analysis of granule size distribution together with the characterization of loss of compactability during die compaction.

Results show that the tensile strength of tablets is lower when using granules than when the raw materials are compressed. Moreover, the plastic material (MCC) is more sensitive than the brittle one (mannitol). Regarding the roll-force, it is observed that the higher the roll force, the lower the tensile strength of tablets from granulated material is. These findings are in agreement with the literature. The comparison of sealing systems shows that the rimmed-roll system leads to slightly stronger tablets than the use of cheek plates. In addition, the use of the rimmed-roll system reduces the amount of fines, in particular when high roll force is applied. Overall, it can be concluded that roll-compaction effect is predominant over the milling effect on the production of fines but less significant on the tablet properties. This study points out that the balance between a good flowability by reducing the amount of fines and appropriate tablet strength is achieved with rimmed-roll and the highest roll-force used.

1. Introduction

Dry granulation by roll compaction is a size-enlargement technique widely used in the pharmaceutical industry. Generally, powders with poor flowability are compacted using a roll press to produce ribbons, which are milled in granules. The produced granules with improved flowability are used in further forming processes as tableting or capsule filling. The major advantage of dry granulation is the continuous production of granules without drying stage, leading to the reduction in costs [1]. This process is well suited for powders sensitive to water.

The existence of different roll-compactor designs and the diversity of operational parameters and material properties render the interpretation of the intrinsic properties of the granules and the resulting properties of tablets difficult. According to this, it is necessary to control the quality of the intermediate products (ribbons and granules) in order to optimize the properties of the final products (tablets). 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. On the other hand, the enlargement process improves the flow but the tablet tensile strength is reduced due to limited binding potential which is partially consumed in the compression step [2]. The final goal is to keep the balance between loss of reworkability (reduction in tablet's strength), caused by dry agglomeration, and good flow,

* Corresponding author.
E-mail address: lucia.gandarillas@mines-albi.fr (L. Perez-Gandarillas).

http://dx.doi.org/10.1016/j.ejpb.2016.05.020
0939-6411/

achieved through the increase in particle size. Therefore, quality of intermediate products should be maintained across the different unit operations of the process.

The effect of the roll-compaction step on the properties of ribbons and tablets has been widely reported in the literature [3–5]. Inghelbrecht and Remon [3] studied the compaction of lactose by analysing different process parameters, such as compaction pressure, roll speed, vertical and horizontal screw speed and concluded that roll-compaction pressure was the most important parameter to be controlled. During the roll-compaction step, it is also extremely important to control the non-compacted powder, which can be considered as fines if the dry granulation process takes place in a continuous mode. In this context, Wagner et al. [6,7] studied the dry granulation of different grades of mannitol and showed clearly the decrease in the amount of fines by increasing the roll pressure. In their work, the authors also analysed the compactability of the powders after roll-compaction. They concluded that the higher is the roll-compaction force, the lower is the tablet tensile strength. This effect, known as loss of reworkability, has been previously reported in the literature [8–14]. However, in contrast to this, Kuntz et al. [15] showed an increase in compactability for acetames after dry granulation.

Another parameter influencing roller compaction operation, which has received less attention, is the side sealing system that avoids the leakage of powder during the process. Roll presses are generally sealed in order to prevent the escape of powder during the compaction [16]. Two types of sealing systems are available for the commercial roll-compactors: cheek plates and rimmed-roll. The type of sealing system not only affects the amount of non-compacted powder, but also confers certain properties to the ribbons such as density distribution across the ribbon width [17–19].

After being compacted, the ribbons are subsequently milled into granules. Regarding the milling step, many variables, such as mill type, mill design, screen size, speed and mode of oscillation, have a significant influence on the quality of granules. The most important resultant property of the milling step is the particle size distribution. In order to improve the efficiency of dry granulation by roll compaction, it is required to control the granule size through the selection of appropriate milling conditions and to relate the size distribution to the properties achieved as a result of the previous roll compaction step. Some authors have reported research work on the effect of the milling on granules properties. Samanta et al. [20] evaluated the effect of conical mill process parameters and concluded that the type of impeller and the screen are the settings with the highest influence on the granule size distribution. On the other hand, Vendola and Hancock [21] compared four types of milling systems for two dry-granulated placebo formulations; the evaluation was done based on the compactability, resulting that the mill type and the granulation size distribution did not greatly influence the compactability of tablets.

The above studies highlight the complexity of the powder behaviours and the process parameter interactions in dry granulation operations. The main objective of this work was the investigation of how different roll-compaction conditions and milling parameters affect the properties of the intermediate and final products (ribbons and granules) in order to get a deeper understanding of the relationship between powder properties and process parameters during rolling, milling and die compaction. The process should be seen as a whole and the study of the downstream processes (milling and tableting) is necessary for the understanding of roll compaction. The analysis of granule size distribution together with the characterization of the compactability of granules can help in the determination of the optimal conditions for these systems and design of granules with a good quality for tableting.

2. Materials and methods

2.1. Materials

Two common pharmaceutical excipients were used: microcrystalline cellulose (MCC, Avicel® PH-101, FMC Biopolymer, USA), considered generally as plastic material and spray-dried mannitol (Pearlitol® 200SD, Roquette, France), which has higher compactability compared with the unprocessed mannitol [6]. It is the plastic or brittle character of each material that interests us in this study. These materials, known as examples of materials with different mechanical behaviours, have been investigated in previous research works. In particular, how the roll-compaction of MCC and mannitol affects the ribbon and granule properties [2,6,7,10,11]. Moreover, in their recent work, Pérez Gago and Kleinebudde [22] studied the roll-compacted mixtures of the above excipients to better understand the impact of the dosage on the ribbon microhardness and granule size distribution. The differences of mechanical behaviour under compaction were determinants in their selection in this study.

2.2. Powder characteristics

The basic characteristics of the excipients used in this study are presented in Table 1 and scanning electron microscopy images (Philips XL30, Netherlands) of these excipients are shown in Fig. 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).

2.3. Roll compaction

The preparation of ribbons was performed using a Gerteis roll compactor: Mini-Pactor® 250/25 (Gerteis Machinen + Processengineering AG, Switzerland). The configuration of this compactor consists in an inclined setup of the rolls. The Mini-Pactor® can be equipped with two side-sealing systems: cheek plates and rimmed-roll (Fig. 2). The cheek plates are two side seals, which are fixed beside the rolls. On the other hand, rimmed-roll system consists of two flat rings attached to one of the rolls and that rotate together with the roll.

Different batches of ribbons were produced under different conditions. The roll-compactor is placed in a climate room (21 °C and 45% RH) where also the powders were stored prior to compaction. 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.

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.

2.4. Milling

For continuous production, the Mini-Pactor® has integrated granulators, which consist of a moving rotor and a fixed sieve of

Table 1
Basic characteristics of excipients.

Material	Mean particle size (μm)	Bulk density (g/cm^3)	True density (g/cm^3) [n = 3]
MCC	50	0.32	1.56
Mannitol	170	0.48	1.47