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Determination of breakage rate and breakage mode of roller compacted pharmaceutical materials

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ABSTRACT

Roller compaction is a common unit operation in the manufacture of oral solid dose pharmaceutical products. The roller compactor can produce intermediate ribbons of compacted material that exhibit a range of mechanical properties. Both the breakage rate and the breakage mode of these intermediates will have an effect on the final particle size distribution (PSD), and are therefore important parameters in determining the performance of the final product in pharmaceutical manufacturing. The breakage rates of roller compacted ribbons of two pharmaceutical excipients, microcrystalline cellulose (MCC) and mannitol, were determined with two different approaches, i.e. by analysing the milling mass throughput and the change in mass in the largest granule size class. The self-similar solution of the breakage population balance equation provided an insight into size dependencies of breakage rates and the prevailing breakage mode for specific process parameters. The breakage rate was found to be dependent on the impeller speed, milling mesh aperture size and ribbon porosity, but not on grinding media fill level. For MCC ribbons the milling kinetic profile changed with the mesh aperture size, suggesting dependence of the breakage mode on screen size. Our work shows clear correlation between the amount of fines produced during milling and the underlying breakage mode. For the materials studied, it is evident that mannitol ribbons tend more toward an attrition breakage mode than MCC ribbons of equal porosity when milling with the same process settings.
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1. Introduction

Milling is one of the most extensively used unit operations in pharmaceutical manufacturing. Understanding how milling parameters affect size reduction of particles is extremely important in achieving a desired particle size distribution, which allows better product uniformity, optimization of formulation dissolution properties and improves bioavailability of the product. Despite extensive literature on the subject of milling, mechanistic insight into the milling process of pharmaceutical material still remains poorly understood. It is already established that the size reduction behaviour of particles not only depends on the material properties, but also on the milling type and process settings. In order to develop a predictive methodology for modelling size reduction processes of pharmaceutical material, the correlation among those characteristics have to be understood and quantified [1,2], in particular with respect to breakage rate and particle size distribution (PSD) of milled material.

In dry granulation processes of pharmaceutical materials the oscillating mill is a commonly used method to produce desired granules from roll compacted ribbons [3]. The principle of an oscillating granulator is to mechanically pass compacted material through a wire mesh screen using an oscillating rotor. Sakwanichol et al. [4] evaluated the granule properties obtained from an oscillating granulator using different oscillating-granulator parameters, i.e. rotor speed, oscillating angle, aperture of mesh screen and rotor type. They concluded that all the examined parameters significantly affect the granule size distribution. Moreover, it was reported that screen aperture size has the largest effect on milling time and work as well as the degree of particle size reduction whereas the impeller side arm shape has the largest effect on overall milling performance in terms of milling efficiency and energy usage [5].

In general, breakage can be achieved by impact or attrition, depending on material properties, equipment design and process parameters. Any or both of the above breakage modes may occur independently or simultaneously [6]. Bazin and Lavoie [7] found that milling proceeds by attrition when operating in the rolling and cascading regime, as the low energy intensity collisions chip off weaker edges and corners of particles.

Several methods have been developed for determination of particle breakage behaviour during milling process [6,8,9]. The aim of the current study was to determine the breakage rate of roll compacted ribbons on the underlying breakage modes during oscillating batch milling using several different approaches. In addition, the aim was to correlate the influence of process parameters and material properties, such as ribbon porosity, tensile strength, impeller speeds, input ribbon mass and screen size on the milling performance of two pharmaceutical excipients that exhibit very different mechanical properties. Specifically, microcrystalline cellulose (MCC) was selected as a material that exhibits ductile behaviour and mannitol was selected as it exhibits more brittle behaviour.

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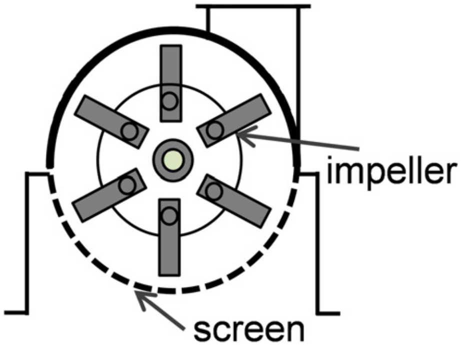

Fig. 1. Schematic representation of the oscillating granulator.

2. Experimental methods and methodology

2.1. Ribbon production

Microcrystalline cellulose (MCC) Avicel PH101 (FMC BioPolymer) and mannitol Pearlitol 200SD (Roquette)Were used to manufacture ribbons using an AlexanderWerk BT120 (Alexanderwerk, Germany) roller compactor with roll width 25 mm and smooth roll surface. To achieve different ribbon porosities, the roll force and screw speed of the roller compactor were changed. Roll gap (2.5 mm) and roll speed (3 rpm) were kept constant during experiments. Ribbon density was measured with a Geopyc (Micromeritics Ltd., US) with three repetitions. To calculate ribbon porosity the following true densities of materials were used: 1.57 and 1.47 g/cm^3 for MCC and mannitol, respectively, as determined by AccPyc 1330 Pycnometer.

2.2. Milling and particle size analysis

Before milling experiments all fines were removed from the ribbons. Ribbons were cut into smaller pieces and 50 g of ribbons were introduced into the mill for each experimental setup. The milling process was performed with a Frewitt screen mill (OscilloWitt) using oscillating mode that is schematically presented in Fig. 1.

The particle size distribution (PSD) was measured using a QicPic (Sympatec) with 0.2 bar dispersion pressure. QicPic images were processed using an EQPC (diameter of circle of equal projection area) calculation mode. In the subsequent analysis, particles of size less than 200 μm and 360 μm for MCC and mannitol, respectively, were considered as fines, based on consideration of the unprocessed material size.

2.3. Mass throughput experiment

The mass throughput of granules as a function of time was measured using a computerised balance that was placed under the mill. From the literature the exponential mass throughput was reported for batch screen milling using following equation [10]:

$$m = m_\infty \left[1 - exp\left(-\frac{N}{N_c}\right)\right] \quad (1)$$

where N is the number of cycles, m and m_∞ are the mass of granules for $N = N$ and $N = \infty$, respectively. N_c is a characteristic number of milling cycles at which $m = 1 - e^{-1}$. Smaller value of N_c corresponds to more rapid breakup of the ribbons, and a larger value corresponds to a lower fracture rate of the ribbons [10].

2.4. Study of topmost size class of PSD plots

Particle size distributions were measured at several time points during one batch milling process and the mass of granules that exited the mill was used to calculate the associated time of milling for each experiment. Breakage rate was calculated for the largest granules based on the change of mass in the topmost size class (from 3.9 to 8.0 mm) using following equation [11]

$$m_i(t) = m_f \ \exp(-S_i \ t) \quad (2)$$

where m_f is the feeding mass at the beginning of milling, S_i is breakage rate of i-th size class and t is time of milling. Based on the evolution of the PSD at different milling times, the breakage mode can be determined [12].

2.5. Self-similar solution

Kapur [8] used a self-similar solution of the breakage population balance equation to study the shape of the breakage rate function and the breakage mode where self-preserving distributions of diverse dynamic distributions collapse into a single time-invariant curve. Cumulative distribution of scaled particle size by the particle size at 80% of cumulative distribution was fitted with the following function:

$$\int z(x) = 1 - \frac{\Gamma\left[\frac{b}{a}, \left(\frac{x\Gamma\left[\frac{1+b}{a}\right]}{\Gamma\left[\frac{b}{a}\right]}\right)^a\right]}{\Gamma\left[\frac{b}{a}\right]} \quad (3)$$

where parameters a and b describe the size dependency of the breakage rate function, $S_i = Ax^a$, and fragment distribution function, $b_{i,j} = (x_i/x_j)^b$, respectively, where x_i and x_j represent daughter and mother particle size. If parameter b is higher than 1 there is more impact breakage while if parameter b is smaller than 1 the abrasion mode is predominant. From the values of breakage rates obtained from the topmost size class analysis using Eq. (2) the parameter A in breakage rate function was calculated. These parameters can be used directly in a population balance model to simulate the milled size distribution.

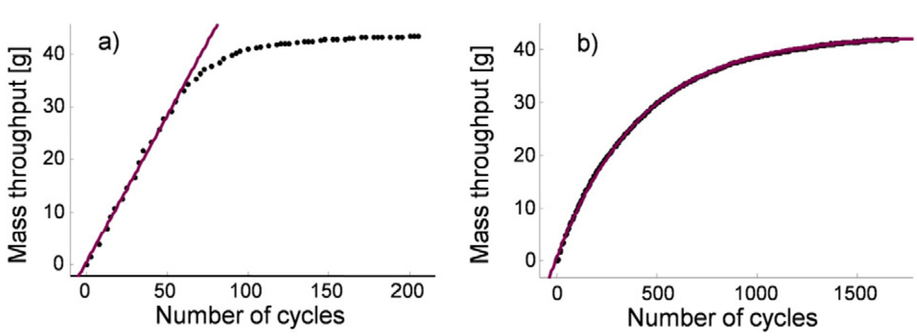

Fig. 2. Experimental (●) and fitted (—) milling mass throughput for MCC with 24% porosity when batch milling with 150 rpm impeller speed and a) 2 mm and b) 1 mm screen size.

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