# Jet milling from a particle perspective

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# Summary

Milling is a very old discipline originated in milling agricultural products to flour. Despite the enormous literature on size reduction, milling is a unit operation which has no sound underlying theory comparable to those existing for other unit operations. The design of milling equipment for a given application is based on accumulated experiences of the manufactures. It is not for lack of either interest or investigation that a quantitative theory of milling does not exist. In contrast, the number of references in the literature dealing with milling is overwhelming. This led to the belief that milling is an art which only could be learned by years of experience. From the perspective of process control this is an undesirable situation. This situation is specifically undesirable in the pharmaceutical industry where product control is critical. Hence, there has been significant emphasis on the characterization and control of the properties of active pharmaceutical ingredients (APIs). The logical consequence of this trend is to characterize and control the particle size of the API throughout pharmaceutical processing. Furthermore, in the pharmaceutical industry the successful development of new drug products is not only related to the discovery of new drugs, but also to the pharmaceutical development of an effective pharmaceutical dosage form. Depending on the intended route of administration and several properties of the drug a specific particle size of the active pharmaceutical ingredient is required. As a result pharmaceutical powders are often milled to achieve the optimum particle size. Hence, during milling control of the drug substance particle size (distribution) is essential. Jet milling is a well established technique for milling of pharmaceutically active compounds. Inherent to processing of active pharmaceutical ingredients concomitant subtle changes in the physical state may occur.

In general the milling kinetics in a mill is described by the selection function, also often referred to as the rate of breakage function. This selection function consists of two parts, representing the process parameters (the "mill function") and the material parameters (the "material function"). The mill function represents the type of mill and processing conditions. In this thesis the "material function" has been investigated more in depth and the material properties that are regarded as most important in jet milling are identified. Chapter 1 summarises literature published so far regarding the relation between material properties and particle breakage behaviour. It becomes clear that existing models used to predict particle breakage do not incorporate mechanical material properties. As a consequence it is not possible to predict the particle size distribution of the milled material a priori. In real-life pharmaceutical development it is often not possible to optimize milling conditions experimentally because the material is scarcely available.

Chapter 2 evaluates the relevant material properties involved in milling induced particle breakage. The purpose of this study was to develop a method to predict the desired milling conditions given a specific (organic) solid material. The selection function and the breakage distribution function are usually the starting points in modelling the milling process. The selection function is the parameter that includes both material and mill properties. Dimensional analysis made it possible to correlate the selection function with the material properties. The model estimates the rate of breakage function, and needs mechanical material properties like hardness and yield strength as input to calculate the rate of breakage function. A set of theories available in the literature enables prediction of the material properties. For different compounds (lactose, paracetamol, a steroidal compound, and two heterocyclic compounds) the selection functions were calculated. The calculations predict differences: lactose reduces slowly in size, while one of the heterocyclic compounds shows the most intense fracture.

Chapter 3 attempts to check the validity of the model by a series of experiments. A comparison of the experimental results with the outcomes of the model using 5 different

model compounds has been performed. It appears that the rate of breakage function can be estimated by the equation as described in chapter 2. The model is able to rank the compounds in degree of fracture as an effect of milling. It was also possible to perform a quantitative prediction of the impact of milling pressure on the particle breakage behaviour and to predict the particle size distribution after milling as well, incorporating process conditions and material properties. Finally, it appeared that the prediction of the large particles in the distribution was significantly better than small ones. Because the oversize material is usually the most critical parameter, the conclusion is that the model has acceptable practical applicability.

The model described in chapters 2 and 3 assumes that the ratio of the size of pre-existing flaws to particle size is constant. Chapter 4 evaluates the effect of the pre-existing flaws in the material to be milled. The particle rate of breakage of four samples of a model compound (sodium chloride), originating from different sources, was determined in a jet mill. It appeared that each type of sodium chloride has a distinct particle rate of breakage and breakage pattern. The numbers of flaws in the different types of sodium chloride particles have been determined by immersing the sodium chloride particles in a liquid with the same refractive index as sodium chloride has. This makes the flaws and cracks better visible. Microphotographs were made and flaws were counted manually. This study shows that the flaw density has an impact on the fracture behaviour of particles. The degree of fracture tends to increase with increasing flaw density. This chapter also shows however, that the mechanical properties of the material as well as the starting particle size dominate the significance of the impact of flaws on fracture behaviour.

Often it is assumed that particle morphology influences particle fracture behaviour. In order to investigate this assumption chapter 5 evaluates particle morphology and hardness of (pharmaceutically important) crystals. The purpose of this study was to predict the hardness

of crystals based on crystal morphology. Unfortunately, anisotropy occurs during determination of the hardness. Anisotropy is the phenomenon that directional differences occur in the physical properties of a material. Literature reveals very clearly that anisotropy in hardness is determined by crystal structure and the primary slip system. The slip system of a crystal was quantified on the basis of crystal structure, cohesive energy density and the hardness which was calculated from the mean yield pressure as obtained by compression tests. Furthermore, the aspect ratios of the compounds were determined. Based on theoretical considerations and experimental validation an inverse correlation between crystal's morphology (represented by the aspect ratio) and the slip system of crystals has been established. The hardness was predicted of four other compounds based on the correlation established in this chapter. Subsequently, the predicted hardness was compared with the experimentally determined hardnesses as reported in literature. Consequently, the hardness of crystals can be predicted using the crystal's morphology and structure.

It is common practice to evaluate the particle fracture behaviour as an entangled effect of pre-existing flaws and cracks as well as mechanical material parameters. Moreover, sometimes it is assumed that particle fracture behaviour is governed largely by pre-existing flaws. Up to now, it was not clear whether either pre-existing flaws or mechanical material properties dominate particle fracture. The purpose of chapter 6 was to investigate the effect of pre-existing flaws on mechanical material parameters. Secondly, the aim was to correlate these properties with particle fracture in a jet mill in order to improve control of the milling process. In this study the effect of pre-existing flaws on mechanical material properties of crystals of a model material, sodium chloride (like in chapter 4), from different sources have been investigated using optical microscopy, nanoindentation, and powder compaction. Subsequently, these properties have been correlated with particle fracture in a jet mill.

Chapter 6 shows that particles that have a small average flaw size or high flaw density possess

a relatively small constraint factor and hence behave more brittle whereas particles that have a high average flaw size have a high constraint factor and hence behave more ductile. On the basis of an existing model the conclusion is that flaw density plays a more significant role than the average flaw size. Chapter 6 shows that the rank orders of the mechanical material properties where consistent with the rank order of the experimentally determined particle rate of breakage. Materials that have a relatively low hardness show the largest particle rate of breakage. The degree of fracture tends to decrease for particles that have a smaller flaw density and hence behave more ductile. It is concluded that crystal's flaw size and density of flaws has an impact on the mechanical material properties and subsequently, on fracture behaviour of particles in a jet mill. Therefore, unit-operations like crystallization which has an impact on impurities and flaws in crystals, influences also the fracture behaviour of particles in a jet mill.