Powder Technology 191 (2009) 72–77

Contents lists available at ScienceDirect

Powder Technology

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

Influence of flaws and crystal properties on particle fracture in a jet mill

Onno de Vegt [a,*], Herman Vromans [a,b], Jaap den Toonder [c,d], Kees van der Voort Maarschalk [a,e]

[a] Department of Pharmaceutics, NV Organon, part of Schering-Plough Corporation, P.O. Box 20, 5340 BH Oss, The Netherlands
[b] Department of Pharmacy and Pharmaceutical Technology, University of Utrecht, The Netherlands
[c] Philips Research Laboratories, Eindhoven, The Netherlands
[d] Eindhoven University of Technology, Department of Mechanical Engineering, Eindhoven, The Netherlands
[e] Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 5 June 2007
Received in revised form 8 August 2008
Accepted 23 September 2008
Available online 7 October 2008

Keywords:
Flaws
Mechanical material properties
Milling
Nanoindentation
Particle rate of breakage
Particle size reduction

ABSTRACT

Jet milling is commonly used for reducing the particle size of active pharmaceutical ingredients. Unfortunately, this process is sometimes difficult to control as pre-existing flaws and mechanical properties affect the particle fracture behaviour in a mill. In this study the effect of pre-existing flaws on mechanical material properties of crystals of a model material, sodium chloride, 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. The paper shows that particles that have a small average flaw size possess the lowest constraint factor (i.e. the constraint factor is defined as the ratio of the hardness and the yield pressure and is an expression of the ductility of the material) whereas particles that have a large average flaw size have a high constraint factor and hence behave more ductile. Moreover, the study shows that the rank orders of the mechanical properties are consistent with the rank order of the experimentally determined particle rate of breakage. Materials that have a relatively low hardness show the highest particle rate of breakage. The degree of particle fracture during jet-milling tends to decrease for particles that have a smaller flaw density and behave more ductile. The paper shows that pre-existing flaws have an impact on mechanical properties and on particle fracture behaviour in a jet mill. It is concluded that the increase of the particle rate of breakage as a function of particle size is influenced by the number of flaws rather than by flaw length.

1. Introduction

In recent years and particularly in the pharmaceutical industry, product quality criteria have become more and more strict, leading to specifications like a narrower particle size distribution and hence closer control of particle size. Active pharmaceutical ingredients (APIs) used in pharmaceutical product development are rarely ready for use as crystallised drug substance. Frequently, the particle size needs to be reduced in order to meet the specific requirements. For example, the route of administration dictates the particle size distribution, like pulmonal delivery for which typically particle sizes in the range of 1–6 μm are required [1]. Milling operations in pharmaceutical industry are generally limited to two or three types of equipment e.g. jet mills, impact mills or conical cone screen mills where the main criteria of choice is the ability to obtain a certain product quality, in terms of particle size or specific surface area. Unfortunately, size reduction by milling has remained essentially an empirical science [2]. This is not due to either a lack of interest or research conducted since the number of references in the literature dealing with milling is overwhelming mainly as an effect of the needs to maximise production capacity and to minimise energy consumption in the mineral energy [5]. Moreover, fundamental particle breakage studies have attracted a great deal of attention of researchers over the last few decades [3,4]. Despite intensive use and research the detailed mechanism of jet milling is not yet entirely understood [6]. This leads to the situation that the milling conditions have to be determined for each material using pilot-scale trials. This is both material and time consuming [7]. It is believed that both particle deformation and fracture mechanisms play an important role in particle breakage and hence in milling performance. The particle fracture behaviour of a material in general depends on the mechanical properties of the material to be milled, processing conditions like stressing intensity, impact velocity, temperature, and the pre-existing imperfections and flaws in the material [8]. For instance, the fracture strength of particles of identical material and identical size differ because different flaws are present on the particle surface [8]. Zügner et al. [6] reported that elastic plastic properties of the materials to be milled are important as these determine the resistance against particle fracture as well as the formation and propagation of cracks. In the theory of milling it is common practice to evaluate the particle fracture behaviour as an entangled effect of pre-existing flaws and cracks as well as mechanical parameters. Moreover, sometimes it is assumed that particle fracture behaviour is governed largely by pre-existing flaws. Currently, to the

* Corresponding author. Tel.: +31 412 668450; fax: +31 412 662524.
E-mail address: onno.devegt@spcorp.com (O. de Vegt).

0032-5910/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.powtec.2008.09.014

Table 1
Particle size and true density of the different types of sodium chloride crystals

Type	$D(v,10\%)$ [μm]	$D(v,50\%)$ [μm]	$D(v,90\%)$ [μm]	True density [kg/m^3]
Salt 1	182	351	577	2150
Salt 2	225	391	555	2149
Salt 3	202	393	686	2149
Salt 4	201	411	625	2154

knowledge of the authors it is not clear whether either pre-existing flaws or material properties dominate particle fracture. The purpose of this paper is to investigate the effect of pre-existing flaws and mechanical properties on particle fracture in a jet mill in order to improve control of the milling process.

2. Material and methods

2.1. Material

Sodium chloride has been chosen as a model compound. The reason for this choice is that different sources and production methods give different inclusions in the form of vacuoles (that contain brine) and other lattice defects, which offers the possibility of controlled variation of defects in the material. At the same time, the particle size and shape remain largely unchanged. Therefore, sodium chloride is a suitable model compound for this study. Sodium chloride crystals are cubic in shape and were produced by evaporation of pickling brine saturated in natural rock salt. All materials used were produced by Akzo Nobel at different production areas: salt 1 from Stade (Germany), salt 2 from Hengelo (The Netherlands), an intermediate quality salt 3 Mariager (Denmark), and salt 4 from Stade which is chemically the purest salt. Table 1 shows the particle size distribution of sodium chloride and the true density of the four types of sodium chloride investigated.

2.2. Methods

2.2.1. Determination of yield strength

The yield pressure was determined as proposed by Heckel [9]. The porosity-pressure relation of the compounds was investigated using a high speed compression simulator (ESH, Brierley Hill, UK). This compression simulator enables the assessment of compaction behaviour with single tablets. A powder sample of 500 mg was compressed into a cylindrical compact with a diameter of 13 mm. Compression load and compact volume with time were recorded. The average punch speed was 3 mm/s. The compression profile was sinusoidal. It has been shown by Heckel [9] that the porosity (ε) is related to the compression pressure (P) by:

$$-\ln(\varepsilon) = K \cdot P_c + A \tag{1}$$

The symbol A is a constant which is thought to be a measure of the relative density of the powder bed after particle rearrangement [10]. The linear part of the curve has slope K and this slope is related to the yield strength (σ_c) by:

$$\sigma_c = \frac{1}{3 \cdot K} \tag{2}$$

The yield pressure of a material is approximately equal to 3 times the yield strength [11]. Hence, the reciprocal of K can be regarded as numerically equal to the mean yield pressure:

$$P_y = 3 \cdot \sigma_c = \frac{1}{K} \tag{3}$$

The true density of sodium chloride was determined with a gas pycnometer (AccyPyc 1330, Micromeritics) using nitrogen as test gas.

2.2.2. Indentation procedure

Reproducible nanoindentation measurements can be performed only on smooth and almost horizontal surfaces. The nanoindentation samples had to be processed in a special way, avoiding use of water which would dissolve the material. The crystals were embedded in epoxy (containing no water). Subsequently, the samples were dry-ground (i.e. using no lubricant) according to the DIN-norm using, consecutively silicon carbide abrasive paper with decreasing coarseness: Grit 800 (~0.5 mm), Grit 1200 (~0.1 mm), Grit 2400, and Grit 4000. After this, a polishing step of 75 s was carried out, using 0–1 μm diamond powder on a Dur-polishing cloth (Struers), using ethanol p.a. as a lubricant. As shown in Fig. 1 the procedure resulted in a polished crystal surface with a typical surface roughness (Ra) smaller than 0.5 μm.

In indentation, a sharp diamond pyramidal tip (an "indenter") is pressed into the surface of the material, while the force on the tip and the penetration depth of the indenter into the material is measured. From the resulting force–displacement curve, together with subsequent observation of the probed surface, the static mechanical properties can be determined. Load-control nanoindentation tests (Nano Indenter XP, MTS Systems Co., Oak Ridge, TN) were performed on the embedded specimens using a Berkovich diamond indenter. The tests were performed in a vibration isolation cabinet at room temperature and stable humidity to ensure that the influence from thermal drift was minimal. The loading rate was $(dP/dt)/P = 0.075\ s^{-1}$, and the maximum indentation depth was 1 μm. After reaching the maximum depth, the force was kept constant for 10 s, after which the unloading took place at $(dP/dt)/P = 0.075\ s^{-1}$.

From this protocol load-displacement curves were obtained and the Oliver and Pharr method [12] was applied to determine the elastic modulus and the hardness. Using the contact area A_c, and the contact stiffness S, which is the slope of the initial portion of the final unloading curve, assumingly representing a purely elastic effect, the

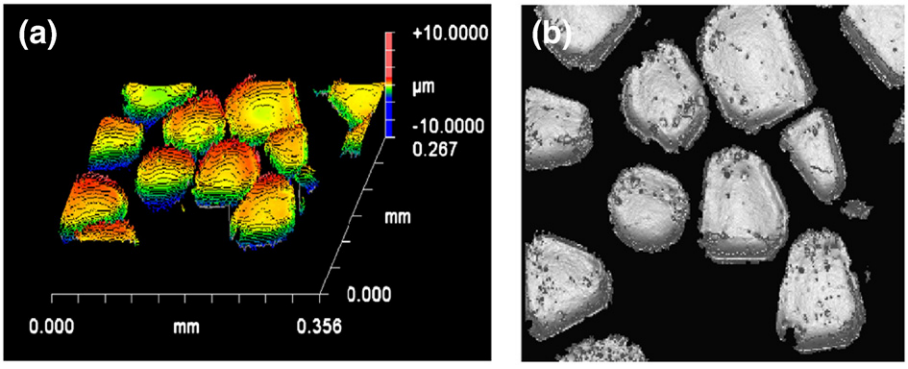

Fig. 1. Micrographs of the polished crystals for nanoindentation; (a) optical interferometry plot (Zygo); (b) white light optical micrograph.