International Journal of Pharmaceutics 407 (2011) 12–20

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Computational and experimental investigation of needle-shaped crystal breakage

Zdeněk Grof[a], Carl M. Schoellhammer[b], Pavol Rajniak[b], František Štěpánek[a,*]

[a] Department of Chemical Engineering, Institute of Chemical Technology, Technická 5 166 28 Prague, Czech Republic
[b] Merck & Co., Inc., West Point, PA, USA

ARTICLE INFO

Article history:
Received 14 June 2010
Accepted 29 December 2010
Available online 11 January 2011

Keywords:
DEM
Population balance modeling
Fragmentation
Daughter length distribution
Breakage kernel

ABSTRACT

Needle-shaped crystals are a common occurrence in many pharmaceutical and fine chemicals processes. Even if the particle size distribution (PSD) obtained in a crystallization step can be controlled by the crystal growth kinetics and hydrodynamic conditions, further fluid–solid separation steps such as filtration, filter washing, drying, and subsequent solids handling can often lead to uncontrolled changes in the PSD due to breakage. In this contribution we present a combined computational and experimental methodology for determining the breakage kernel and the daughter distribution functions of needle-shaped crystals, and for population balance modeling of their breakage. A discrete element model (DEM) of needle-shaped particle breakage was first used in order to find out the appropriate types of the breakage kernel and the daughter distribution functions. A population balance model of breakage was then formulated and used in conjunction with experimental data in order to determine the material-specific parameters appearing in the breakage functions. Quantitative agreement between simulation and experiment has been obtained.

1. Introduction

Needle-shaped crystals (crystals with a large aspect ratio) are commonly encountered in pharmaceutical processes. While the particle size distribution (PSD) can nowadays be controlled relatively precisely in the crystallization step by adjusting the supersaturation, seeding, and hydrodynamic conditions in the crystallizer (Yu et al., 2007), further downstream fluid-solid separation steps such as filtration, filter washing, drying, and subsequent solids handling can often lead to uncontrolled changes in the PSD due to attrition and breakage (Müller et al., 2006; Kalman, 2000). The effect of breakage on the particle size distribution can be described by population balances (Hill and Ng, 1997; Kostoglou, 2007). For population balance models of breakage to be effective, two material- and stress-field specific functions need to be known: the breakage kernel (selection function) and the daughter distribution function (breakage function) (Austin, 1971; Kelly and Spottiswood, 1990). The breakage kernel determines the breakage rate of particles from each size fraction, while the daughter distribution function describes the size distribution of daughter particles (fragments) that are formed once a particle of a given size does break.

Although methodologies for experimental determination of the breakage kernel and daughter distribution functions are known (Gupta et al., 1981), they either require a relatively large number of experiments or the solution of an inverse problem (Sathyagal et al., 1995). An alternative approach is based on trying to determine the functions theoretically (Hill, 2004) or computationally by detailed mechanistic modeling of the breakage of single particles (Khanal et al., 2005) or particle ensembles (Bobet et al., 2009; Ketterhagen et al., 2008). Grof et al. (2007) recently demonstrated the feasibility of detailed numerical simulation of the breakage of needle-shaped particles within a random packed bed subjected to uni-directional compaction, using the discrete element method (DEM). Elongated particles with a chosen aspect ratio have been created by linking individual spherical discrete elements by rigid bonds, characterized by a given bending stiffness and ultimate bending strength. A randomly packed bed of these elongated particles has been formed and gradually compressed between two infinite parallel solid planes. The particle size distribution as a function of the compaction ratio has been studied while systematically varying the individual particle strength, the initial particle length, and its distribution.

The aim of the present work is to develop and validate a novel methodology for the determination of the breakage kernel and daughter distribution functions, based on the combination of computational and experimental techniques. The methodology consists of four parts: *(i)* the DEM simulation of needle-shaped particle breakage under uni-axial compaction as described in (Grof et al., 2007); *(ii)* post-processing of the DEM simulation outputs using population balance models and explicit evaluation of the appropriate types of the breakage functions; *(iii)* experimental study of the breakage of real needle-shaped crystals under uni-axial

* Corresponding author. Tel.: +420 220 443 236; fax: +420 220 444 320.
E-mail address: Frantisek.Stepanek@vscht.cz (F. Štěpánek).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.12.031

Nomenclature

a	compression parameter (dimensionless)
A	die cross-section area (m^2)
C	span of Gaussian function (dimensionless)
E	specific energy input (J/kg)
F	compaction force (N)
$f(y)$	compression function ($m\,s^{-2}$)
$g(F)$	alternative form of compression function (m/kg)
h	bed height (m)
$k(L_i)$	breakage kernel (kg/J)
k_0	breakage constant (dimensionless)
L_i	length of a crystal from the ith size class (m)
L_0	characteristic length (m)
m	sample mass (kg)
N	number of size classes (dimensionless)
n_i	number concentration of crystals from the ith size class (kg^{-1})
P	compaction pressure (Pa)
r_i	breakage rate (J^{-1})
$S_m(L_i)$	breakage probability (dimensionless)
U	objective function (kg^{-2})
y	relative piston position (dimensionless)
z	piston travel distance (m)

Greek letters

$\beta(i,j)$	daughter distribution function (dimensionless)
$\beta'(x)$	transformed (universal) daughter distribution function (dimensionless)
γ	breakage exponent (dimensionless)

compaction; *(iv)* fitting of the population balance models to the experimental data and evaluation of the material-specific parameters in the breakage functions.

2. Population balance model

When applying the rigorous population balance model (Vanni, 2000) to needle-shaped crystals we assume that the crystals are linear aggregates of primary particles (or "monomers") of equal size. Such a description is consistent with the multi-element particle model (Favier et al., 1999; Grof et al., 2007) used for the representation of elongated (needle-shaped) particles or crystals. This assumption makes it possible to correlate the length L_i of a crystal with the number of primary particles i that form it as:

$$L_i \approx i. \tag{1}$$

The particle size distribution is then a discrete function, whose values n_i, $i = 1, \ldots, N$ are the number concentrations of the particles consisting of i monomers and N is the number of size classes.

Theoretical treatments of Weichert (1992), Fuerstenau et al. (1996, 2004), lead to expressing the population balance equations for the breakage under uni-axial compression in terms of the specific energy expended rather than in grinding time as follows

$$\frac{dn_i}{dE} = -r_i + \sum_{j=i+1}^{N} \beta_{ij} r_j. \tag{2}$$

The first term on the right side of Eq. (2) is the rate of death of particles i to generate smaller fragments, while the second one is the birth of particles i due to rupture of larger particles.

The specific energy input E can be equated with the work of compression per unit feed mass (Fuerstenau et al., 1996)

$$E \approx \frac{APz}{m} = \frac{Fz}{m}, \tag{3}$$

where A is the die cross-sectional area, P is the compaction pressure, F is the compaction force, m is the sample mass which is proportional to the initial bed height

$$m \approx h_0 \tag{4}$$

and z is the piston travel distance which may be expressed in terms of h_0 and h, the initial and instantaneous bed heights

$$z = h_0 - h. \tag{5}$$

Kawakita and Lüdde (1971) listed 15 equations of compaction that relate pressure with volume (or bed height). For example the Kawakita piston compression equation has the form

$$\frac{z}{m} \approx y = \frac{h_0 - h}{h_0} = \frac{abP}{1 + bP} = \frac{acF}{1 + cF} \tag{6}$$

or

$$P = \frac{y}{b(a - y)}, \tag{7}$$

where y is the degree of volume reduction (or relative piston position) and a and b are parameters characterizing the powder. The parameter a is equal to the initial porosity in the case of piston compression. By combining relations (3)–(7) and lumping all proportionality constants, the specific energy may be expressed as

$$E \approx Py \approx \frac{y^2}{a - y} \tag{8}$$

and consequently

$$dE \approx \frac{2ay - y^2}{(a - y)^2} dy = f(y)\,dy. \tag{9}$$

Breakup is usually a first order process with respect to particle concentration, since it generally depends on the local stress field acting on the particles. It is convenient to express the death rate as

$$r_i = k(L_i) n_i, \tag{10}$$

where $k(L_i)$ is the breakage kernel. There is a strong dependence of the breakage kernel on particle size, L_i. Different breakage kernels are summarized in (Vanni, 2000; Rajniak et al., 2008).

Finally, introducing (9) and (10) into the rigorous population balances (2) and lumping different proportionality factors together we get the population balance equations in terms of the relative piston position y

$$\frac{dn_i}{dy} = -f(y)k(L_i)n_i + \sum_{j=i+1}^{N} \beta_{ij} f(y) k(L_j) n_j \tag{11}$$

with $f(y)$ defined by Eq. (9).

There exist many different fragment (daughter) distribution functions β_{ij} defining the number of daughter fragments in class i produced upon breakup of a mother particle j (Vanni, 2000; Rajniak et al., 2008). Here we have considered only the formation of two fragments during every breakage event, i.e. corresponding binary breakage distribution functions are normalized with respect to condition (12)

$$\sum_{i=1}^{j-1} \beta_{ij} = 2. \tag{12}$$