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Single crystal fragmentation: Visualizing breakage model performance for pharmaceutical processes

Rory Tyrrell*, Patrick Frawley

Synthesis and Solid State Pharmaceutical Centre (SSPC), Bernal Institute, University of Limerick, Ireland

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ABSTRACT

The development of accurate crystal breakage kinetics is paramount to extending the capability of optimization and modelling methods within the pharmaceutical drug-product sector. However, there exists little experimental data on the performance on typical breakage models when applied to small-scale pharmaceutical crystals. Therefore, experimental investigations of crystal impacts on a steel target were carried out across a range of crystal sizes and impact velocities in order to determine critical breakage parameters for a given model. Direct observation of each impact was captured via a high-speed Shadowgraphy imaging technique, capable of 1 μm crystal size resolution and up to a 125,000 frames-*per*-second capture rate. Crystals of Darunavir Ethanolate between a nominal 100 → 500 μm size range were subject to impact velocities of 1 → 10 m/s normal to the target surface. Furthermore, upon collision crystals were classified into one of three breakage modes: intact (Mode I), chipped (Mode II), or split/disintegrated (Mode III). The resulting data was then combined with a post-processing methodology utilizing a bi-variate histogram function and Kernel Density Estimation (KDE). This in turn enabled the extraction of experimentally observed crystal failure velocities, breakage modes, and selection functions detailing how crystal breakage varies with both crystal size and impact velocity. This data was then used to evaluate the performance of current literature in describing crystal breakage within pharmaceutical applications. Furthermore, the methodology implemented in this work can be applied to a range of particulate systems, yielding a flexible tool for pharmaceutical modelling capabilities.

1. Introduction

The production and development of solid-form pharmaceutical drug products is invariably burdened by the issue of unwanted or uncontrollable crystal breakage. Active Pharmaceutical Ingredients (APIs) must not only satisfy purity standards, but also crystal shape and size specifications, with the final Particle Size Distribution (PSD) of the product staying within acceptable measures. These are often stated as various characteristic size limits such as the Sauter Mean Diameter ($D_{3,2}$), or De Brouckere/Volume Mean Diameter ($D_{4,3}$). Additionally, percentile limits such as D_{10}, D_{50}, and D_{90} may be imposed in order to limit the population in the 10th, 50th, and 90th percentiles of a distribution, respectively. In cases of large-scale crystal breakage any or all of these measures may be violated as, while breakage inherently conserves mass, it redistributes crystal mass about lower size classes throughout the process.

Production of a desired API typically requires crystallization, isolation, and drying steps. Each of these processes may then bring with it a set of harsh mechanically abrasive environments. The resulting time-evolution of the PSD will therefore depend on not only accurate kinetics for mechanisms such as growth and nucleation, but also on reliable kinetics for crystal breakage. Moreover, as breakage itself essentially forms new crystal nuclei as fragmentation occurs this process may serve to compound crystal nucleation growth kinetics ([1–3]), increasing unpredictability in the system. Furthermore, as modelling methods such as Population balances [4] are often used to predict process outcomes given changes in operating conditions or for optimization exercises it becomes clear now that developing reliable breakage kinetics is paramount for accurate process control and optimization.

Typically, modelling methods for crystal breakage include various types of functional forms for breakage kinetics, as reported by multiple authors [5–7]. Formally these functions describe selection and distribution functions that govern the number of particles that may break and their subsequent fragmentation distributions. There exists a number of methods for the determination of these functions and their parameters. Optimization/minimization techniques, such as those employed in [8,9], are a very robust method for extraction of process kinetics and model validation. However, they require advance knowledge

* Corresponding author.
E-mail addresses: Rory.Tyrrell@ul.ie (R. Tyrrell), Patrick.Frawley@ul.ie (P. Frawley).

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of the system and rarely serve to explain mechanisms mechanistically as high-dimensional parametrization may not always provide a realistic interpretation of the mechanisms at work. Recent studies utilizing a combination of numerical and experimental methods to determine the breakage characteristics of Silicon Carbide (SiC) particles have been carried out in [10,11]. While a powerful method, pharmaceutical materials have yet to be investigated to such an extent. Repeated impacts of pharmaceutical crystals have been studied in [12,13], yielding information about how crystal mass progresses during fragmentation, however the failure probabilities of these crystals was not reported. Investigations of crystal velocity profiles approaching a target wall have been carried out in [14]. However the study was concerned primarily with the boundary layer effects near the target plane in a liquid-based system, and did not yield any detailed data on any observed fragmentation. Further numerical and experimental studies determining the expected impact velocities and frequencies of crystals in a stirred vessel [15,16] have provided valuable information on the environment crystals often encounter during crystallization processes. Empirical size-velocity relationships for breakage selection functions and fragmentation distributions of pharmaceutical powders are reported in [17,18], and provide useful data on the observed breakage probabilities for range of crystal materials. Experimental breakage rate parameters have been extracted successfully in [19], however these kinetics tell us little about the fundamental mechanism of breakage occurring. Simplified binary breakage mechanisms used to model crystallization of high and low-aspect ratio crystals have also been proposed [20,21]. However, this two-body equal-volume method is typically not accurate for the vast majority of realistic breakage and fragmentation in pharmaceutical processes. [22,23] proposed a theoretical model of chipping for crystalline particles, illustrating underlying mechanisms that may be incorporated into the construction of mechanistic section functions. Furthermore, [24] describes a model for the prediction of breakage selection functions of limestone, glass spheres, and various polymers. It was shown that if the material properties are known it may be possible to theoretically determine any failure probability from fundamental material properties. However, it remains to be investigated how well this theory can be applied to pharmaceutical materials as the scale of these particles introduces significant variability in breakage characteristics, as will be demonstrated here.

Presented here is a methodology that allows for the determination of robust mechanistic breakage selection functions for pharmaceutical products, with insight into the prevailing forms of fragment distributions. Shadowgraphy imaging was used to image individual crystals with a post-processing methodology developed in the Python programming language, enabling visualization and extraction of crystal breakage probabilities and modal distributions. Using Python's built-in bi-variate histogram functionality it was possible to discern what population of crystals may break across gives size ranges and impact velocities. Furthermore, a Kernel Density Estimation (KDE) is performed on the data in order to generate a smooth, continuous function of breakage; enabling the extraction of selection functions across any desired sizes and velocities. Further to this, a crystal nano-indentation study was performed in order to determine the crystal Young's Modulus (E_c), hereto previously unknown for this compound and integral in theoretical fragmentation equations. Using this data the observed selection functions can be compared against a breakage model described in [25] in order to determine its effectiveness in pharmaceutical process modelling. This model is fundamentally parametrized by a size-velocity relationship based on the widely implemented Weibull statistics Additionally, insight into the modes of fragmentation crystals undergo as their size and impact velocities vary is enabled by establishing 3 characteristic breakage modes. This allows us to simultaneously visualize the progression of the numbers of broken crystals in a population and also *how* crystal fragments are generated upon failure.

2. Theoretical description

In order to design a set of experiments that will provide useful insight into crystal breakage an investigation into existing breakage theory must be covered. By studying theoretical foundations for predicting the comminution of particulate populations, experimental investigations may be informed as to which breakage factors may yield the most useful data. For crystal breakage there exists at least two major factors for investigation: the *amount* of breakage occurring (distributions), and *form* of the breakage mechanism (modes). Before dealing with the former, it is important to first describe what is meant when referring to different breakage types or “modes”.

2.1. Breakage modes

It is important to define breakage *modes* which are representative of the observed types of crystal breakage. For this work, three distinct breakage modes were considered: intact, chipping, and splitting/disintegration. By dividing breakage into classifications it is possible to infer something about not only the numbers of particles being broken but also the distribution of breakage modes across a range of crystal sizes and velocities. Outlined in Fig. 1 are the three modes of macroscopic breakage used. Mode I represents an intact or undamaged crystal after impact, with Modes II and III indicating progressive failure towards complete disintegration of the parent crystal after impact. While the probability of fragmentation can be determined without the description of these last two modes, as breakage is a somewhat binary choice insofar as a crystal is seen to fragment or it is not, they do provide a useful description of possible fragmentation distributions.

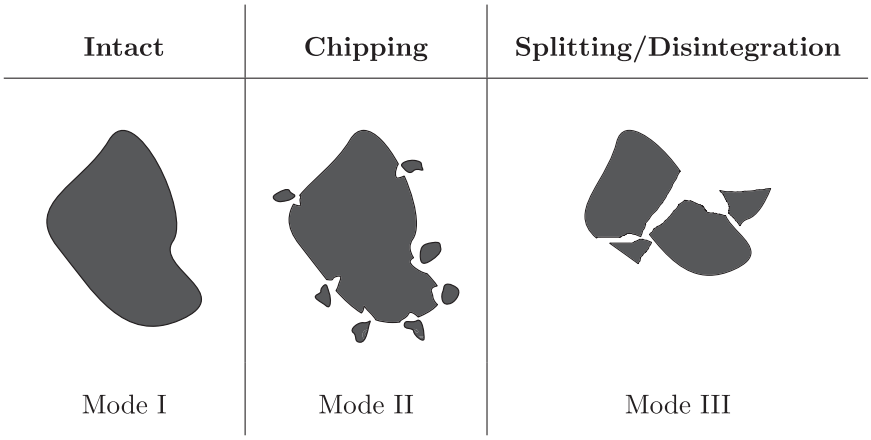

Fig. 1. Description of the three crystal states: intact, chipped, split/disintegrated.