FROM POWDERS TO TABLETS

The Pharmaceutical Physics group at Uppsala University uses modelling and simulation to solve industrial and scientific problems for powder compaction

IT has been claimed that the manufacturing techniques used by the pharmaceutical industry lag far behind those of potato chip and laundry soap makers. Irrespective of the veracity of this statement, it is nowadays widely recognised that the development of pharmaceutical process technology has been limited, being largely based on empirical relationships rather than a fundamental process understanding. There is a need for measures that can be used to guarantee a consistent high quality of the final product. The concepts Quality by Design (QbD) and Process Analytical Technology (PAT) are much discussed.

Pharmaceutical Physics tries to address these issues in two different ways: first, through the development of new measurement techniques, often based on an analysis of optical or acoustic waves, that would result in improved ways to monitor manufacturing processes; and second, through modelling and simulation of pharmaceutical systems, to obtain tools to control manufacturing processes and predict their outcomes.

The work done in the Pharmaceutical Physics group at Uppsala University centres on questions related to handing and processing of powders and granular materials. Such questions are highly relevant to pharmaceutics, since both the active pharmaceutical ingredient and various excipient materials are typically handled and processed in powdered form during manufacturing tablets and related widely used dosage forms.

Bottom-up strategy

We currently focus on the behaviour of powders and granular materials when subjected to high pressures such as during manufacturing of tablets by confined compression. A bottom-up strategy is used, where the behaviours of the powder and final product are inferred from those of the constituent particles. Specifically, this is done in three consecutive steps.

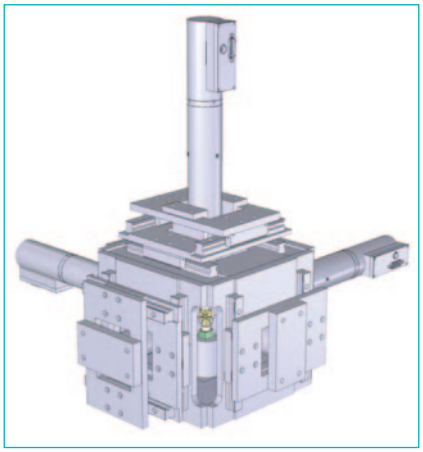

Fig. 1 Test equipment, currently under construction, for individual particles

First, we are developing equipment that enables the mechanical response of individual particles to be studied under complex loading conditions. The particle is confined in a rectangular box whose side lengths can be varied independently of each other. As illustrated in Fig. 1, three motors mounted perpendicularly to one another allow the particle to be compressed along all spatial directions.

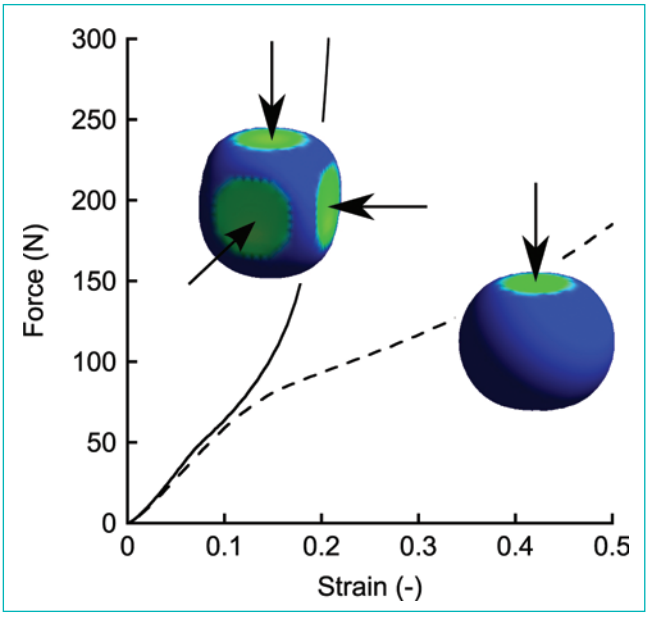

Fig. 2 Force-displacement curves for single particles obtained from FEM simulations

Force sensors enable the resulting forces to be sampled. The intention is to mimic the conditions prevailing during tableting, where each particle deforms under the influence of a relatively large number of neighbouring particles and the deformation is confined because the neighbours occupy most of the surrounding space.

Second, based on the experimental results in conjunction with detailed simulations of the single particle behaviour, new models for the interaction between particles are formulated. The challenge is to incorporate the dependence between contacts that arises when a particle is simultaneously deformed by contacts with multiple neighbours. They must also account for the fact that deformation occurs during spatial confinement. As shown in Fig. 2, which displays results from simulations, these factors considerably influence the force – displacement curves.

Third, the developed contact models are implemented in computational software and simulations are performed to translate the knowledge on the particle scale to the behaviour of the powder when compressed to tablets, typically by a mobile upper punch as shown in Fig. 3.

Although the basic methodology for simulations of a large number of interacting particles is well developed (generally, the so-called 'soft particle' DEM is used), simulation of confined

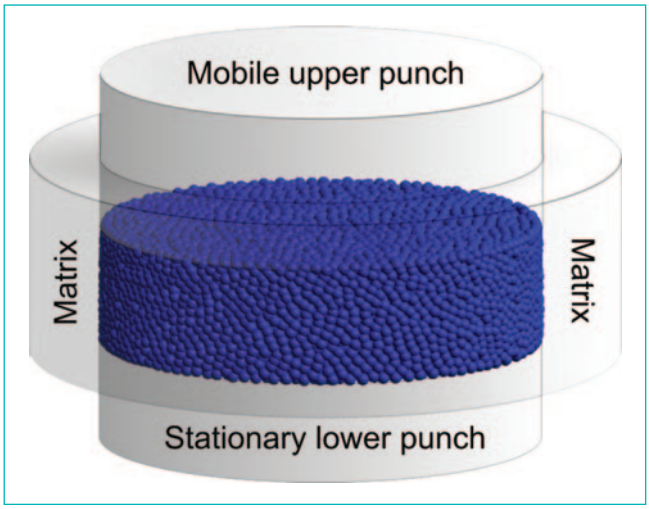

Fig. 3 Illustration of simulations of confined compression using the soft-particle DEM

compression poses some challenges that can be traced back to the modes of particle deformation. Specifically, contacts can no longer be considered independent and measures need to be taken to determine the degree of confinement. The most promising approach is to use a geometrical construction attributed to Voronoi in order to determine the space in which deformation can occur for each single particle.

Superior representation

We also perform simulations using more advanced methods that enable a superior representation of particle deformation, but also result in a significantly higher computational cost. An example is shown in Fig. 4, where compression of 1,000 millimetre-sized plastically deforming granules has been simulated using the combined FEM/DEM. Such simulations are highly valuable in the detailed study of systems comprising a few particles, but are unpractical for large-scale simulations due to its prohibitive computational cost.

Our methodology allows us to investigate the compression process in depth, so that the key factors that control the evolution in tablet structure and tablet strength can be identified. We are also in a position where we can address fundamental scientific questions related to the behaviour of granular materials under confined conditions. Examples include the mechanical response of single particles experiencing complex loadings and the importance of stages in the compression process as well as force distributions and jamming (see below).

Although our work is motivated by the challenges faced by the pharmaceutical industry, the interest in powder compaction is by no means limited to pharmaceutics. On the contrary, powder metallurgy revolves around powder compaction, which allows various parts for the automotive, aerospace and other industries to be manufactured from metals in powdered form. Powder compaction by dry pressing is the preferred and most widely used method to make ceramic parts such as cutting tools. Many chemical engineering and food science products are manufactured by powder compaction.

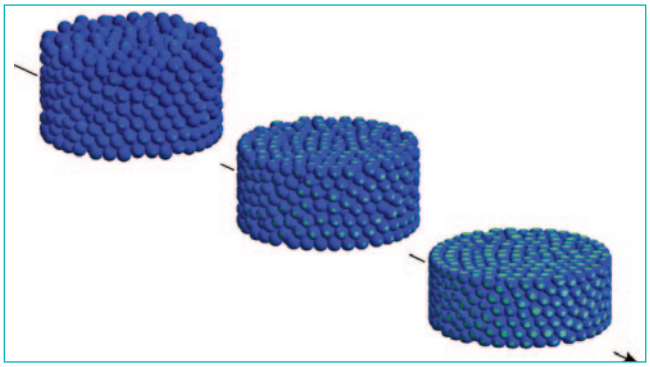

Fig. 4 Example of simulation results obtained using the advanced but costly combined FEM/DEM. The particle surfaces are coloured based on their level of stress

Constrained state

Granular materials and their behaviour under confined conditions have also attracted a considerable basic scientific interest. For example, experiments and simulations have been performed to determine how an applied force is distributed between the particles in a powder. Contrary to more homogenous materials, force is transmitted along certain load-bearing structures referred to as force chains, whereas a relatively large number of particles act as spectators.

When the bulk volume of a powder is reduced, each single particle eventually enters a constrained state, since its motion is precluded by neighbouring particles. This jamming transition has been much investigated and discussed. It represents a transition from a fluid-like to a solid-like state that is seen not only for granular materials but also for colloids and macromolecular systems and can unify concepts such as the glass transition, gelation and aggregation.

Transcending pharmaceutics

Pharmaceutical Physics is a multifaceted subject. The work performed in the Pharmaceutical Physics group at Uppsala University emanates from central pharmaceutical issues but transcends pharmaceutics. Our ambition is to deliver findings that not can only be translated into more efficient pharmaceutical development and manufacturing, but also are of considerable intrinsic scientific interest in their own right.

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