Fluid Motion

A new process for applying computational fluid dynamics to spray drying has been introduced. Currently used in the food industry, it is now being implemented for pharmaceutical purposes

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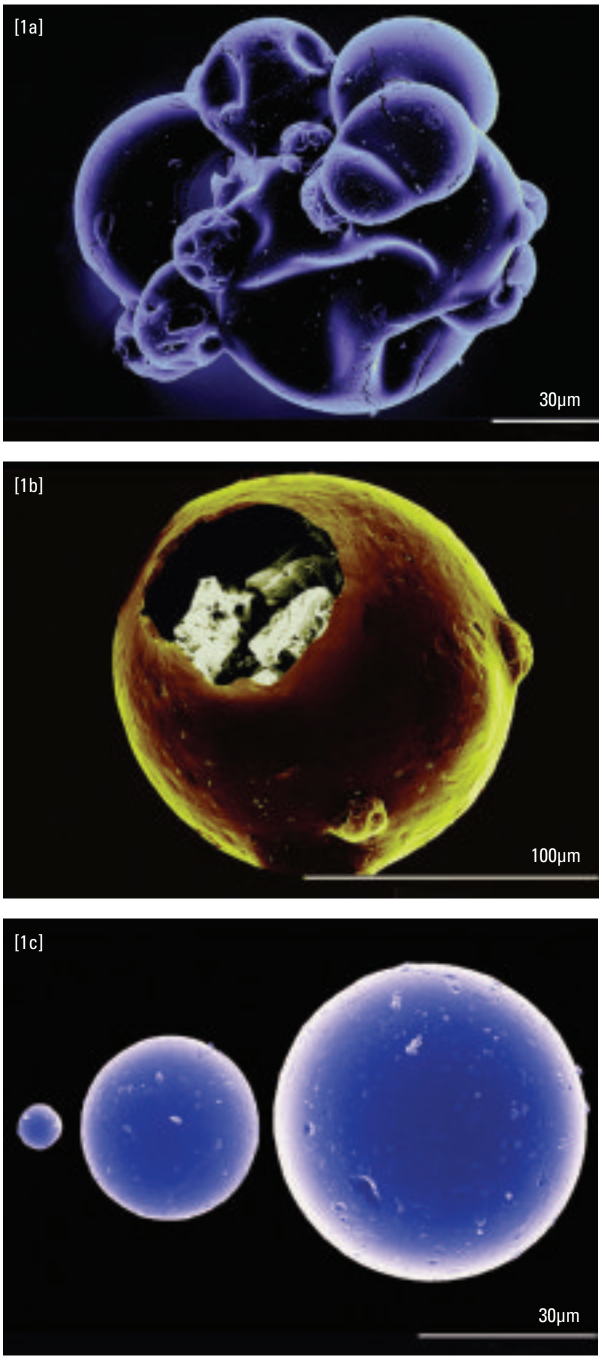


Figure 1: Examples of particles in which properties were enhanced by spray drying. From top to bottom: agglomerates/direct compressible powders; microcapsules; and particle size control from inhalation to free flowing powders

Spray drying is now considered one of the key technologies used in the pharmaceutical industry for enhancing the performance of an active pharmaceutical ingredient (API). The relatively short exposure time to elevated temperatures, the high specific area for drying and the evaporative cooling effect make spray drying very suitable for processing thermo-labile materials. One of the most successful applications of spray drying in the pharmaceutical industry is the production of amorphous solid dispersions, where the API is molecularly dispersed, typically in a polymeric matrix, for enhanced bioavailability. The expectation is to potentiate and maintain supersaturation of the amorphous and metastable API in the dissolution media, while at the same time minimising the risk of recrystallisation and providing an acceptable drug shelf life.

Another very interesting application is microencapsulation, in which the microcrystalline API (ranging from nanoparticles to microparticles) is spray dried along with an encapsulating excipient for drug protection, controlled release or taste-masking. Spray drying also shows a remarkable flexibility for inhalation powders, as it enables fine-tuning of the particle size and density, both of which need to be small for optimal aerodynamic performance, and the generation of very low levels of residual solvent in the powder. Spray drying powders for inhalation typically requires the use of special atomisation mechanisms and cyclone designs for efficient product collection. Examples of particles obtained by spray drying for the different applications, as discussed in this article, are shown in Figure 1.

Computational Fluid Dynamics

Computational fluid dynamics (CFD) modelling is well-established in academia and in all areas of industry including, increasingly, the pharmaceutical industry, which is known to have a larger inertia than the others in the adoption of new methodologies. CFD enables the determination of fluid flow, heat and mass transfer with high resolution in space and time, thereby supporting process development scientists in the optimisation of the spray drying process and enhancing the quality of the final product. As the pharmaceutical industry shares most of its unit operations and equipment with the food industry – as in the case of spray drying – the knowledge obtained

Figure 2: CFD simulation of a pharmaceutical spray dryer: 3D unsteady flow pattern with large grid resolution

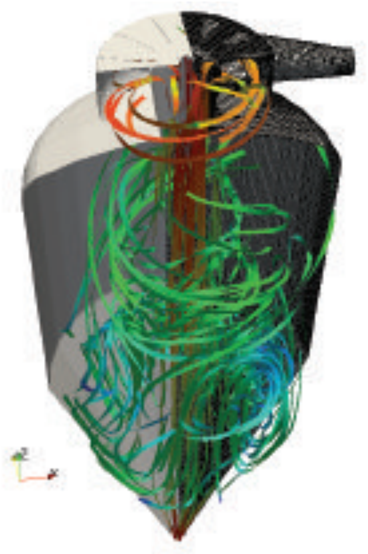
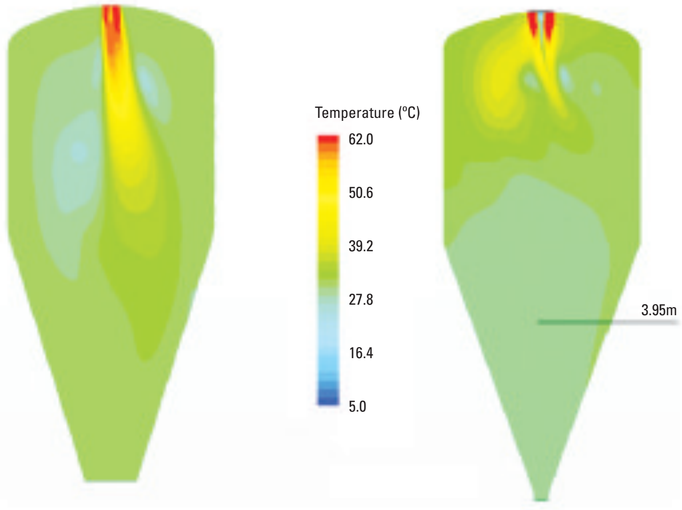


Figure 3: Temperature profiles for two different commercial scale spray dryers



from one industry can be readily applied to the other. This enables the use of a large wealth of scientific articles and technical documents on CFD derived from the food industry, where the processes are aggressively optimised due to lower profit margins and very large production volumes. A good example is the use of CFD for milk powder spray drying (1).

CFD deals with the numerical solution of the continuity and Navier-Stokes equations. An analytical solution for these equations is only available for very simple situations such as flow of fluid through a pipe, which makes the use of numerical methods mandatory for investigating industrial equipment. There are a number of commercial CFD packages available that report a good fit with the pharmaceutical industry. Among those, Fluent and CFX (Ansys), and Star CCM+ (CD-adapco) are some of the most widely used. Open-source alternatives also exist, OpenFOAM (ESI-OpenCFD) being one of the leading packages. The images shown in this paper refer to CFD simulations using OpenFOAM and Star-CCM+.

The typical procedure for a CFD simulation is as follows. First, the physical system is defined (both in terms of physical models to be used and the computational domain to be considered for simulation). The second step is to generate the computational grid, where the computational domain is divided into a given number of cells – in each cell a set of discretised equations (continuity and Navier-Stokes) are to be solved. Next, a matrix comprising the equations in all cells is solved using numerical algorithms until a converged result is attained. The final step is the post-processing of the simulation results, where the data is represented in the most appropriate graphical form.

Spray Drying

Process development for pharmaceutical spray drying typically relies on macroscopic heat and mass balance to the spray dryer, where such models are able to accurately describe the resulting temperature and solvent content profiles in the drying chamber for a given set of operating conditions. There are, however, phenomena which occur

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during droplet drying and particle formation in the drying chamber that are not captured by macroscopic modelling; these can affect the properties of the spray dried material, and ultimately the efficacy of the drug. These are usually dealt with by running a large number of design of experiments (DoE) which require large quantities of API.

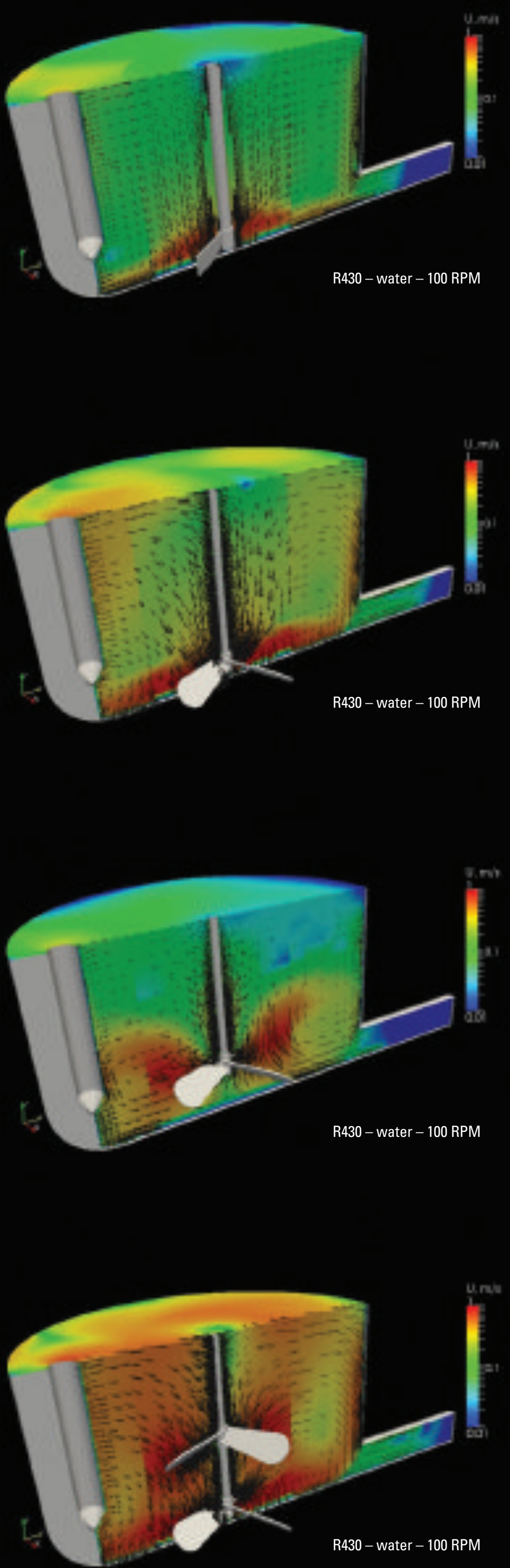
The application of CFD in spray dryers has been evolving, along with the improvement of computer power. CFD in spray drying is extremely challenging given the high number of concurrent physical phenomena:

- A highly turbulent flow of drying gas enters the drying chamber in a swirling motion
- The liquid feed solution is atomised in the nozzle into small droplets
- Heat and mass transfer needs to be accounted for when the drying gas and the small droplets come into contact
- There is phase transfer occurring from the liquid droplets to the drying gas

The flow pattern in the drying chamber is reported to be unsteady in nature, requiring three-dimensional and transient CFD simulations to be able to correctly capture the main flow features (see Figure 2) (1,2). Hence, these CFD simulations are very expensive from a computational point of view, requiring extended run times and significant computational resources.

As expected, both gas and droplet flow patterns are critical to some of the product quality attributes (such as density and particle size). Given the complexity of the spray drying process, the multi-phase systems (solid-liquid-gas) and phase transitions, CFD is the most useful in understanding and troubleshooting the dynamics inside the drying chamber. Figure 3 presents CFD results for two commercial scale spray dryers with different geometries but similar drying capacity, comparing the profiles for temperature. Despite being of the same scale, these spray dryers show a different flow profile, which can decisively affect the location of possible hot-spots in the equipment. Product accumulation in such hot-spots is important as it may impact the process in a number of ways: it may affect the quality of the final product for thermo-labile APIs; it could increase the risk of

Figure 4: CFD simulations to optimise a tank (impeller geometry, axial position and number of impellers) targeting a homogeneous suspension (spray drying microencapsulation process)



“Mixing in the feed tank during mixture/suspension preparation also needs to be adequately understood to avoid incomplete dissolution (in the case of amorphous solid dispersions), or segregation of the suspension (in the case of microencapsulation or drying of suspended solids)”

crystallisation in the case of amorphous materials; or it could cause potential combustion of the solids that remain inside the drying chamber in the case of the units that operate with air.

To address such complexity, multiple approaches have been used. In a recent paper by Ullum *et al*, a new strategy for applying CFD to spray drying is presented, where first principle relations for fluid flow are combined with an empirical model for hindered droplet drying (3). This approach enabled an improved prediction of product deposition in the walls of the drying chamber. Dobry *et al* also published a similar methodology for spray drying process development using CFD in order to determine whether wet or sticky particles are in contact with the drying chamber walls (4). Despite the recent advances in understanding of the underlying phenomena of spray drying and their modelling within a CFD framework, the numerical results should be taken with caution and experimental work is always recommended.

Tank Mixing

Mixing in the feed tank during mixture/suspension preparation also needs to be adequately understood to avoid incomplete dissolution (in the case of amorphous solid dispersions), or segregation of the suspension (in the case of microencapsulation or drying of suspended solids). In the specific case of microencapsulation the stirring dynamics are fundamental to maintaining the expected API potency values within the targets through the batch and avoiding any possible deviations.

Figure 5:
CFD predictions for the flow pattern in a cyclone

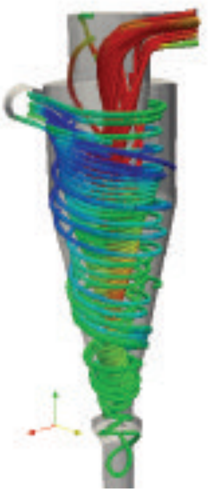


Figure 4 (see page 79), which relates to a case study from a spray drying microencapsulation process, illustrates a tank optimisation exercise (impeller geometry, axial position and number of impellers) targeting a homogeneous suspension supported by CFD. Here the benefits of using this tool are evident, as a very detailed flow pattern can be obtained which can serve to detect potentially problematic zones where high-density solid material can accumulate. There is a fine balance between homogeneously dispersing the API in the feed tank (sufficient mixing) and avoiding segregation (insufficient mixing) or foaming (over mixing). Additionally, engineering parameters can be obtained from the CFD simulations (such as the power per unit volume), where equipment revamping can be initially tested on the computer, which saves time, costs and prevents wastage of API.

Other challenging situations arise when foam-prone materials or floating solids are intended to be dissolved or dispersed (depending on the application). These particular situations require the use of more complex CFD strategies as described by Koganti *et al* and Waghmare *et al* (5,6). The particularities of the feed tanks used in the pharmaceutical industry (which have non-conventional impellers and baffle geometries) are investigated in those papers, showing that CFD is a very useful tool to minimise both the cycle time and the impact of the mixing in the quality of the product. In the particular case of solution preparation for spray drying of amorphous solid dispersions, the addition of the polymer fits the floating solids challenge perfectly. Solution preparation is often extended in time due to an inadequate mixing pattern in the tank, where the polymer is not drawn down efficiently and remains floating at the liquid surface. The additional hold time in the tank increases the risks to the final product's quality due to API chemical stability concerns.

Cyclone Separation

Understanding gas-solid separation in the cyclone is of the utmost importance since the spray dried powders can have distinct properties that affect the efficiency of product collection. The process of gas-solid separation in cyclones is well-established in the literature, where collection efficiency is highly dependent on the centrifugal forces that are applied to the solids, which make them collide with the outer wall and slide down to a container attached to the discharge chute. The flow pattern in a cyclone is characterised by a double vortex (see Figure 5), where the gas enters the cyclone in a descending spiral motion close to the outer wall, and then exits through a centered ascending vortex (7). Very small particles can be entrained in the inner vortex if centrifugal forces are not sufficiently strong. As the cyclone performance is very dependent on the flow pattern, CFD can be regarded as a very useful tool to support modifications and understand the collection efficiency for a given cyclone geometry. In a recent publication by Graham *et al,* optimisation of cyclone performance was achieved by using a combination of classical correlations and CFD, where an approximately 10 per cent increase in collection efficiency could be achieved after one single iteration (which involved a modification to the inlet of the cyclone suggested by CFD) (8). The optimisation of cyclone efficiency by CFD is crucial in the case of very small particles typical of inhalation powders.

Conclusion

The production of enhanced API formulations by pharmaceutical spray drying can surely benefit from a better process understanding provided by CFD. The recent push by the Food and Drug Administration to base pharmaceutical process development on a Quality by Design framework is perfectly aligned with the use of tools such as CFD. Hence, it is expected that the pharmaceutical industry will strive to embrace CFD as an equal partner to the experimental work, including it within the typical spray drying process development flowchart.

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