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Pharmaceutical Industry

Necessity to apply CFD-DEM two way coupling to the Pharmaceutical development process

EXCELERATE

R&D - Scale-up - Operations

Currently, the pharmaceutical industry faces a number of regulative and economic challenges that are related to processing development. From a regulatory perspective, the development of the manufacturing process should be based on systematic process understanding and process control to ensure the quality of the drug product in accordance with the quality by design (QbD) approach.
In addition, the development of the manufacturing process may require considerable time and resources from an economic perspective. These challenges may result from the lack of cost-effective and reliable modeling tools of unit operation development in the pharmaceutical industry.

In general, the modeling tools for the manufacturing process are- empirical model and mechanistic models. The empirical models include multivariate analysis (MVA), artificial neural network (ANN) and design of experiments (DoE), based on empirical, semi empirical or statistical methods. The mechanistic models include in silico tools, such as computational fluid dynamics (CFD), finite-element method (FEM) and discrete element method (DEM). These mechanistic models generally perform the process simulation; they capture the underlying physical phenomena through fundamental first principles such as mass, momentum and energy.

The mechanistic models have been applied widely for the prediction of the effect of process parameters and to present insights into unit operations in the pharmaceutical industry. CFD—a popular and powerful modeling tool that provides insights into mathematical physics and numerical methods for fluid flow, numerically solves mass, momentum and energy balance. The model is suitable for systems consisting of fluids. Among the mechanistic models, one of the more commonly used is DEM that simulates the velocity, position and motion of individual particles. DEM can provide information, such as trajectory or forces acting on individual particles, which is difficult to obtain experimentally; moreover, it can address the size distribution of individual particles. In addition, DEM can be used in combination with modeling tools such as CFD for simulation of many processes, which involves fluid as well as particles.

The application of CFD- DEM two way coupling in these manufacturing processes is described in detail in the following section.

Wet Granulation

It is a preferred process as it improves the flow ability of fine powders and reduces the possibility of dust generation. In addition, the granulation process can prevent segregation that may occur in the subsequent processes and therefore, improves the content uniformity of the final solid dosage forms.

Using CFD-DEM simulation,

- It analyses various input parameters and provides the better insight on the outcome of the system.
- It helps in Batch cycle time reduction and Utility cost cutting.
- Describe and resolve the issues at the grain scale, kiln scale as well as the plant scale.

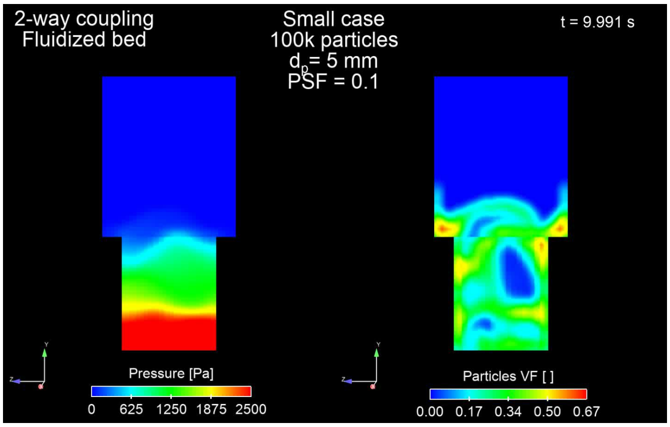
Sr No	Equipment	Contact model	Predicted model based on the process simulation
1	High Shear Granulator	LSD	• Liquid drop penetration into a particle bed • Droplet impingement on a dynamic particle bed • Droplet in vertical direction
2	Fluidised Bed Granulator	Hertz-mindlin model	• Mean particle residence time • Recirculation time • Total particle passes • Mean solid volume fraction • Mean crossing length • Mean particle velocity and particle wetting • Time averaged gas velocity • Particle collision velocity • Density distribution and angular velocity
		Hertz-mindlin no slip model	• Particle position and velocity distribution • Residence time distribution • Solid volume fraction • Particle collision and collision velocity • mean contact time.

Fluidized Bed Coater

For the tablet, the active coating should be managed as it is directly related to the content uniformity. However, it is not easy. The CFD-DEM coupling can be used to investigate the effect of process parameters on coating uniformity, as well as to achieve a detailed mechanical understanding of the coating process. In this study, CFD was applied to simulate fluidization air and DEM was used to simulate the particles involved in the coating process.

With CFD- DEM simulation,

- Tablet coating variability can be predicted through the developed CFD- DEM model.
- Can determine particle cycle and residence time distribution in a fluidized bed coater.
- It enables the strategies for cycle time reduction, throughput increase and energy optimization by studying coating score distribution, air flow velocity, spray pattern, bed position, contact time distribution and coating thickness.
- It helps to understand principles of the tablet coating process by analyzing various critical process parameters and critical parameter matrix.
- It provides the optimal process conditions in regard to the heat and mass transfer.



Milling:

Milling is a manufacturing process often applied in the pharmaceutical industry to improve the solubility of poorly soluble drugs. Through the milling process; mechanical energy is applied to break down the coarse particles into fine particles such as 2 µm until 500 nm.

With CFD- DEM simulation:

Lab-scale milling processes allow comparatively rigid control but control of milling when scaled up presents a significant challenge. Therefore, it is necessary to develop a model that can predict the progress of milling in various milling equipment

Sr No	Equipment	Contact model	Predicted model based on the process simulation
1	Fluid Energy Mill (Jet mill)	Hertz-mindlin model	• PSD • Particle of air flow pattern, • Particle velocity distribution, • Number of particle in each zone • Particle collision frequency and velocity.
2	Stirred Media Mill	Hertz-mindlin	• Fluid velocity • Bead and fluid behavior in stirred media mill • Bead velocity • Average size of aggregated particle • Fluid shear power distribution

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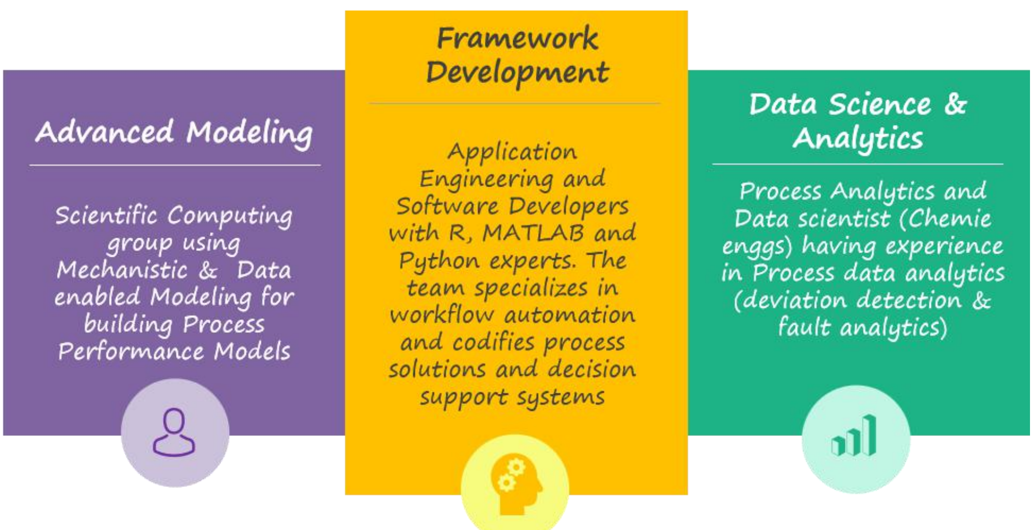

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