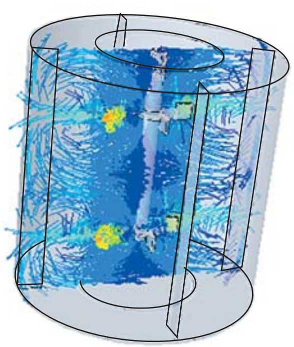
The Role of Computational Fluid Dynamics in the Pharmaceutical Industry

H.S. Pordal,* C.J. Matice, and T.J. Fry



Computational fluid dynamics can be a viable tool to analyze and troubleshoot various process equipment used in the pharmaceutical industry. Because typical unit operations process large amounts of fluid, even small improvements in efficiency and performance may increase revenue and decrease costs.

H.S. Pordal, PhD, is a staff consultant, C.J. Matice, PhD, is the principal and team leader, and T.J. Fry, PhD, is a senior associate at SES Process Technology Group, 5380 Courseview Dr., Mason, OH 45040, tel. 513.336.6701, www.processinnovation.com.

*To whom all correspondence should be addressed.

The pharmaceutical industry faces new challenges associated with increased market globalization, demands for cleaner environments, higher customer expectations, the push for increased profitability, tighter FDA regulations, and the ever-increasing demand to reduce time to market. The industry is under pressure to reduce waste and improve process efficiency. The traditional approach of taking a product from laboratory scale to pilot plants and then to production is no longer attractive. Process and product development often are initiated simultaneously, and as a result, rapid prototyping and analysis are required. To meet these challenges, the industry must implement innovation at all phases of product development.

Technology Vision 2020 (1), a document that highlights the plans for the chemical process industries for the next 20 years, has identified three enabling technologies. Computational fluid dynamics (CFD) is one such technology that is expected to lead chemical process companies into the future. CFD methods are applied widely in various industries to examine fluid flow and heat-transfer behavior. For example, in the aerospace industry, CFD routinely is applied for aerodynamic calculations of lift and drag. In the automotive and heavy-equipment industries, CFD is used to calculate external drag, climate control, and underhood cooling. The heating and ventilation industry, power generation industry, and chemical process industries, including the pharmaceutical industry, now are beginning to apply CFD methods to gain insight into their various processes.

The integration of CFD methods can lead to shortened product-process development cycles, optimization of existing processes, reduced energy requirements, efficient design of new products and processes, and reduced time to market. Unit operations in the pharmaceutical industry typically handle large amounts of fluid. As a result, small increments in efficiency may generate large increments in product cost savings. Thus, research and development staffs as well as plant and production managers should understand the benefits of CFD so that it can be integrated into the development process.

CFD can be a viable tool for analyzing process equipment. Mixing, separation, drying, fluid transport, and heat generation operations are some of the processes that can benefit from CFD analysis. The flow fields associated with these processes are very complex. Conventional methods of analysis often are not adequate, and experimental measurement is not always possible. Although measurement probes provide point data, very often full-field data or data at multiple locations are required to fully diagnose a problem. Troubleshooting as well as improvements in efficiency and performance typically are achieved by trial and error on the basis of past experience. Process monitoring very often is used to identify the onset of critical conditions; however, it does not identify the underlying cause of the problem. Process-equipment failure causes undesirable downtime and loss of revenue. Hence, improved troubleshooting techniques are required so that downtime can be minimized. Unlike experimental methods, CFD provides full-field data. Pres-

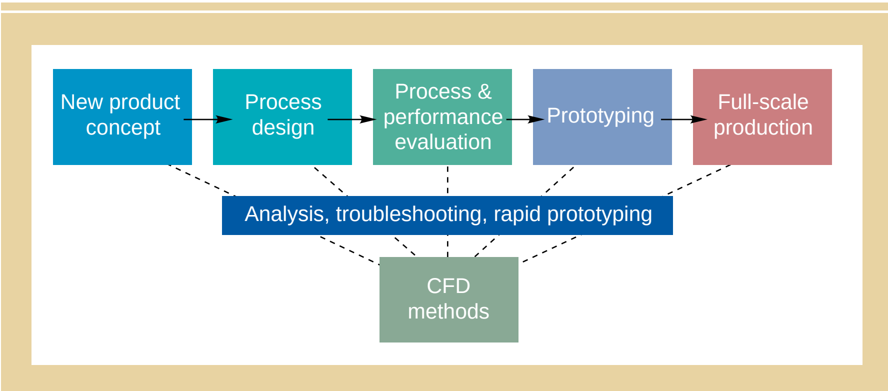


Figure 1: The role of CFD methods.

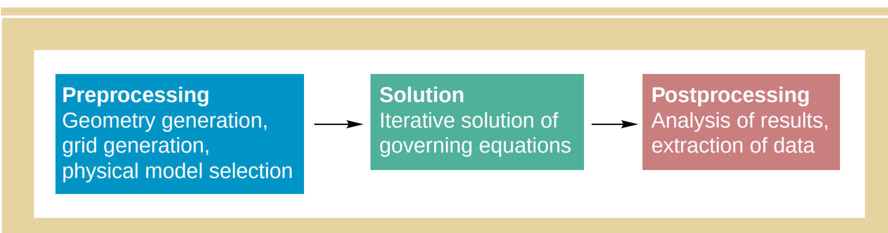


Figure 2: Steps in performing a CFD analysis.

sure, velocity, density, temperature, and other parameters of interest can be obtained at each point in the simulated flow domain. Thus CFD can be implemented in analysis, design, and rapid prototyping at various stages (see Figure 1).

Overview of CFD methods

CFD methods are based on the first principles of mass, momentum, and energy conservation, which are described by the following equations:

mass:

$$\frac{\partial \rho}{\partial t} + \frac{\partial \rho u_j}{\partial x_j} = \mathrm{Sm} \quad [1]$$

momentum:

$$\frac{\partial \rho u_i}{\partial t} + \frac{\partial \rho u_i u_j}{\partial x_j} + \frac{\partial P}{\partial x_i} = \frac{\partial \tau_{ij}}{\partial x_j} + \mathrm{Sf}_i \quad [2]$$

energy:

$$\frac{\partial \rho H}{\partial t} + \frac{\partial \rho u_j H}{\partial x_j} + \frac{\partial q_j}{\partial x_j} = \frac{\partial u_i \tau_{ij}}{\partial t} + \frac{\partial \rho}{\partial t} + \mathrm{Sh} \quad [3]$$

In these equations, ρ is fluid density, t is time, x is coordinate, u is velocity, P is fluid pressure, H is fluid enthalpy, τ is shear stress, and $i, j, k = 1, 2, 3$ represents the three coordinate directions. Sm is mass source caused by reactions or other mass-transfer mechanisms. Sf represents momentum source caused by mass transfer and body forces such as gravitational force. Sh is energy source caused by mass transfer, phase change, and energy generation by other mechanisms.

CFD involves solving conservation equations for mass, momentum, and energy at thousands of locations within the flow domain. These locations are created by generating a mesh. The equations are applied at various mesh locations using discretization techniques. Patankar and Anderson et al. have described these methods in detail (4,5). The computed solution provides flow variables such as velocity, pressure, temperature, density, concentration, and so forth at thousands of locations within the domain.

Several CFD software packages include CFD solvers that are wrapped in a user-friendly graphical interface. These general-purpose CFD software packages can be applied to simulate fluid flow, heat transfer, chemical species transport, and reactions for a wide variety of applications. The look, feel, performance, and accuracy may differ between one CFD software package and another; however, the basic principles and steps involved in performing a CFD analysis are the same.

CFD analysis can be categorized into three main steps: preprocessing, solution, and postprocessing. Figure 2 shows the main steps of performing a CFD analysis.

Preprocessing. Preprocessing involves identifying the flow region of interest, geometrically representing the region, defining a suitable mesh, and then applying the principles of flow physics. The proper selection of the region of interest and appropriate simplifications are key for conducting a successful calculation. Once the region is defined, a computer model of the geometry is created. Most commercial CFD packages provide a computer-aided design–like geometry generation engine.

The next step is mesh definition. The governing equations are solved at discrete locations in the flow domain. These locations depend on the resolution of the mesh. The accuracy of a CFD calculation and the computer time required for a solution also depend on mesh resolution. User experience and skill play a crucial role in the choice of a suitable mesh. Appropriate boundary conditions are applied to define regions of inflow, outflow, walls, and other important features. Physical models within the software are activated to simulate flow physics pertaining to the application. For example, a turbulence model is activated to simulate turbulent flow. Selection of appropriate physical models and their applicability to the flow physics is critical to the overall accuracy of a CFD solution.

Solution. Once the problem definition is completed, it is submitted to the solver for the computation of a solution. This is the solution step. The governing equations are coupled and nonlinear in nature. Therefore, a guess-and-correct, iterative strategy is adopted to compute the solution. Although the solution method is automated, user intervention frequently is required to obtain a stable converged solution.

Postprocessing. CFD results are analyzed in the postprocessing step. A CFD solution provides full-field data; flow variables at thousands or even hundreds of thousands of locations are available. A representation of the flow field is created by plotting flow variables in space on a plane, in a line, or in a three-dimensional region of interest. The spatial plots provide the analyst with a look inside the unit, which otherwise is unavailable experimentally. However, the real value of CFD simulation often is found in its ability to provide accurate predictions of integrated quantities such as heat-transfer rates, mass-transfer rates, and forces imposed on the inside of vessels. Work by Patankar and Anderson et al. provide numerical details of mesh generation, discretization, and CFD solver techniques (4,5).

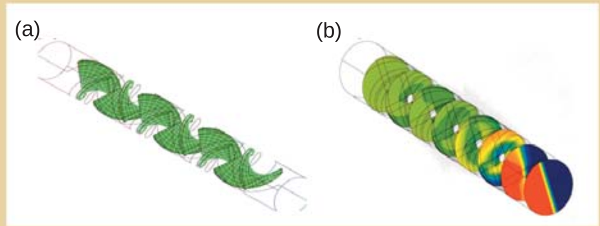


Figure 3: (a) Kinecs mixer, blade orientation; (b) mass fraction contours.

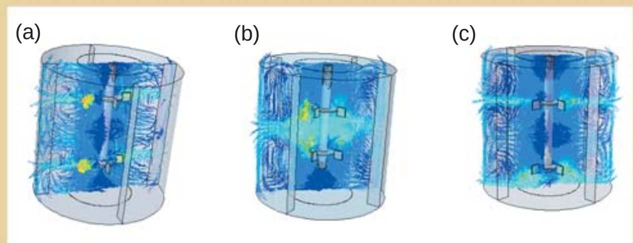


Figure 4: (a) stirred tank, radially pumping impellers; (b) stirred tank, closely placed impellers; (c) stirred tank, impellers too far apart.

CFD for the pharmaceutical industry

The application of CFD to a few key unit operations and processes in the pharmaceutical industry is described in the following paragraphs.

CFD for mixing. Mixing processes lie at the heart of the pharmaceutical industry. A wide variety of mixing equipment such as static mixers, stirred tanks, homogenizers, and emulsifiers is used. Mixing processes can involve the blending of two streams of the same fluid but at different temperatures (thermal mixing), or it can involve the mixing of two or more different fluids with or without chemical reactions. The degree of mixing required and the equipment applied depends on the application.

Static mixers for fluid–fluid mixing commonly are used for pastes and high-viscosity fluids. These mixers operate on the principle of slicing and mixing layers of fluid. CFD methods can be applied to examine the performance of static mixers and to predict the degree of mixing achieved, thus indicating whether more mixing elements are required. Figure 3a shows surface mesh and blade orientation for a Kinecs mixer. Figure 3b depicts the mass fraction concentration of the two species being mixed. The degree of mixing is shown as the color proceeds from distinct inlet streams (red and blue) to the fully mixed outlet stream (green). A CFD solution can be used to derive the pressure drop, hence the power required.

Stirred tank reactors are the most commonly used equipment in the pharmaceutical industry. The primary function of these vessels is to provide adequate stirring and mixing. The mixing characteristics can influence product quality and the efficiency of the process to a great degree.

Stirred vessels are available in various shapes and sizes and are equipped with many types of impellers. Very often, one vessel is required to perform various duties, and it is essential for engineers to ensure that adequate shaft power is available to perform the mixing process. More important, one must ensure efficient operation of the vessel for a particular duty. This task very often is accomplished by placing the impellers in the vessel at various locations. Heuristic approaches based on trial-and-error methods lead to product delays. Empirical correlations for estimating vessel performance exist; however, these correlations are unable to predict the performance accurately and very often are based on the assumption of the linear superposition of data.

In the following example, CFD methods were used to analyze the flow field and vessel flow characteristics as well as to describe the influence of impeller location on the flow field. The example involves single-phase flow in a flat-bottom, baffled tank with dual four-bladed Rushton impellers (Rushton impellers typically are used to generate radial flow). Figure 4a shows properly placed impellers in the vessel. The radial flow field generated by the impellers leads to the formation of four toroidal recirculation regions. The impellers in this case operate with little if any interaction between them. If the impellers are placed closer to each other, a converging flow pattern is generated (see Figure 4b). The upper impeller pumps downward, and the lower impeller pumps upward. However, if the impellers are placed farther apart, a diverging flow pattern is generated (see Figure 4c). In this case, the lower impeller pumps downward, and the upper impeller continues to pump radially outward. Changes in impeller position lead to a drastic change in the flow pattern, which has a strong effect on vessel performance, mixing characteristics, and hence product quality and efficiency. Impeller–impeller interaction is a strong nonlinear effect and cannot be predicted by simple empirical correlations. CFD is a viable method to analyze and optimize stirred tank performance. Impeller performance and flow-field characteristics can be successfully predicted using CFD.

CFD also can be applied to predict shear stress distribution within a stirred vessel. This evaluation is important for dissolution, emulsification, and dispersion applications. Shear stress distribution also is important during the processing of biochemical products, when excessive shear may lead to damage of biocells and loss of product efficacy.

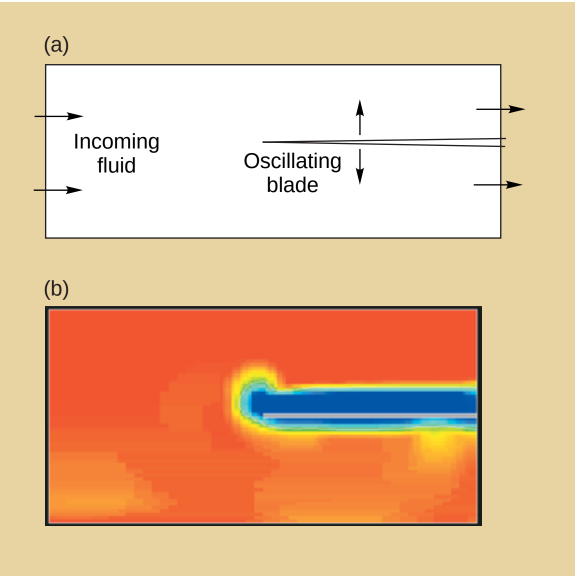


Figure 5: (a) ultrasonic emulsifier configuration; (b) cavitation bubbles around an ultrasonically vibrating blade.

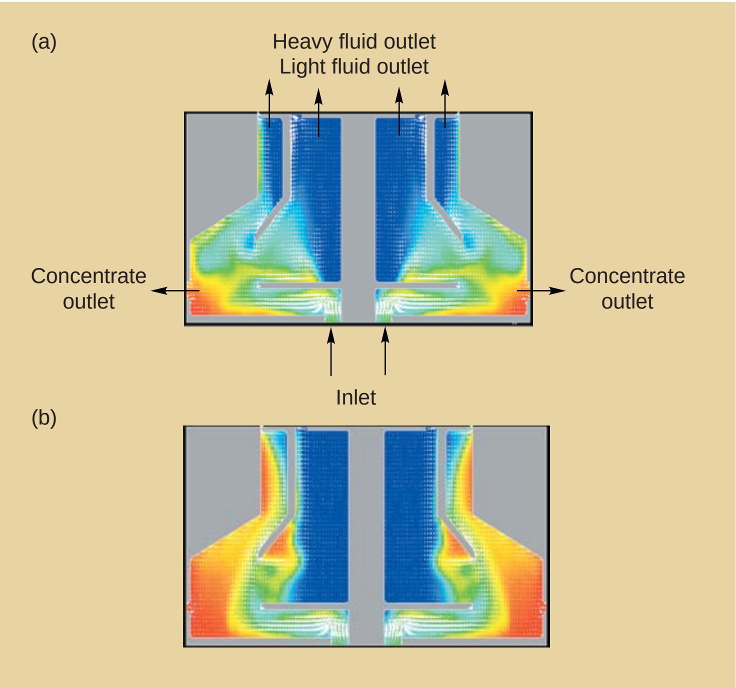


Figure 6: (a) centrifuge configuration (original design); (b) centrifuge configuration (modified design).

Emulsification involves the dispersion of one liquid into another as small droplets. This process is achieved by the action of high, local shear. High-speed dispersing units, valve homogenizers, and ultrasonic emulsifiers commonly are used for such tasks. The power required for ultrasonic emulsification is less than that used for valve homogenizers. As a result, ultrasonic homogenizers are preferred over other emulsifiers. In ultrasonic homogenizers, high-pressure (150 bar) fluid is pumped through an orifice to produce a high-velocity stream over a vibrating blade. High-frequency vibrations of the blade create cavitation, which produces high-quality emulsions and dispersions. Parameters such as fluid viscosity, temperature, and the amount of dissolved gas affect cavitation intensity. Cavitation intensity also is related to ultrasonic power and ultrasonic frequency. However, uncontrolled cavitation can be harmful because it can lead to the pitting and erosion of material. Manufacturers can improve the performance of ultrasonic emulsifiers by increasing their understanding of the formation, size, density, speed of collapse, and intensity of implosion of cavitation bubbles. Regions of cavitation bubbles can be identified by studying the flow field around ultrasonic actuators. CFD methods can be applied to simulate fluid flow and obtain a detailed understanding of the flow physics. The influence of actuator frequency and amplitude on cavitation bubble region formation as well as the transport of cavitation bubble regions can be studied using CFD techniques. Figure 5a shows an ultrasonic emulsifier configuration analyzed using CFD. Figure 5b depicts the distribution of volume fraction of liquid around an ultrasonic oscillating blade (red regions correspond to liquid regions, and blue regions correspond to vapor regions where cavitation bubbles reside).

CFD for solids handling. Nearly 60–80% of pharmaceutical products are in the form of solids. The handling and transport of solid particles pose several challenges. For example, pneumatic transport of particles is very common. At times, particles impact the walls of the transport equipment, thus increasing the risk of erosion. CFD techniques can be applied to analyze such flows and minimize or eliminate the risk of erosion. CFD also can be applied to analyze the unsteady and chaotic flow behavior in fluidized beds. Simulation of such a flow field requires unsteady flow calculations and small time increments. As a result, performing calculations can take an extensive amount of time. Simulations of gas–solid flows in complex three-dimensional reactors can take months of computational time and are not practically feasible. However, with the use of fast computers and parallel processing capabilities, one can simulate the gas–solid flows in complex reactors.

CFD for separation. Crystallization, precipitation, and centrifuge separation are very common pharmaceutical processes. Industrial centrifuges typically are used for separating solids from liquids and in performing liquid–liquid separations. In general, centrifuges are used for thickening, separating, and during posttreatment. Modern centrifuge separators function at low operating costs as a result of design improvements and the development of new models.

In the following example, design modifications to a centrifuge were examined using CFD. The original design (shown in Figure 6a) resulted in a slugging of material. As part of the design-change investigations, the concentrate outlet port (side port) was closed. This caused high-density liquid to exit the low-density port (an undesirable situation). Next, the side port opening was reduced. This modification minimized slugging, which led to a near-steady flow. Figure 6b shows the modified design and fluid-density distribution (red denotes regions of high density, and blue represents low-density fluid).

CFD techniques are used for analyzing

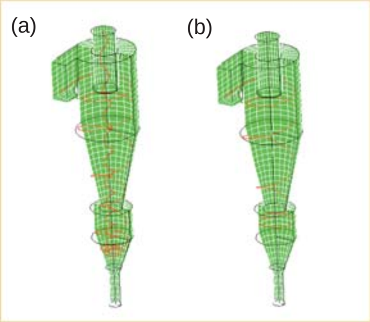


Figure 7: (a) cyclone, pathline of 1-μm particle; (b) cyclone, pathline of 10-μm particle.

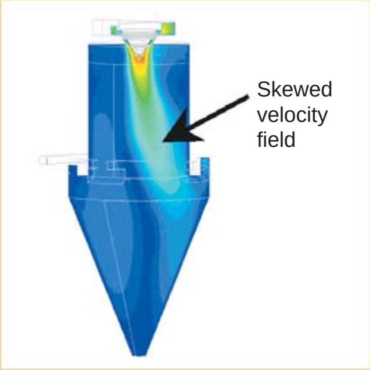


Figure 8: Spray dryer, velocity field.

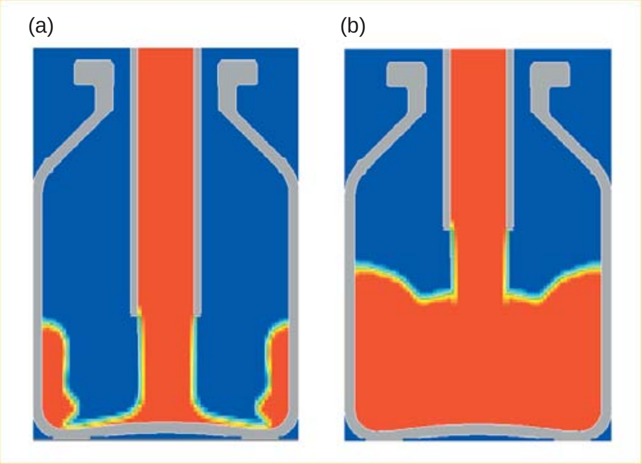


Figure 9: (a) filling process, liquid surface location, strong splash; (b) filling process, liquid surface location, no splash.

separation devices such as cyclones and scrubbers. The following example incorporates CFD methods to optimize and predict performance of an existing cyclone design. CFD solutions depict particle paths for various particle sizes (see Figure 7). In this example, CFD techniques were used to perform what-if analysis for optimization of the design. The performance computed with CFD closely matched that observed in physical testing wherein 90% of 10-μm particles were removed, but only 10% of 1-μm particles were separated from the air stream.

CFD for dryers. Drying equipment usually is large and expensive. As a result, a dryer's efficiency influences production and operation cost.

As an example of how CFD can be beneficial in drying applications, we used CFD to analyze the performance of an industrial spray dryer before making major structural changes to the dryer. This strategy minimizes the risk of lost profit during changeover, especially if the improvement does not materialize. CFD was applied to examine configuration changes, thus minimizing risk and avoiding unnecessary downtime during testing. Figure 8 shows the velocity distribution (skewed flow). This flow is a result of uneven pressure distribution in the air-dispersing head. CFD models were applied to determine optimum equipment configuration and process settings. CFD results provided the necessary confidence that the proposed modifications would work so capital equipment would be ordered and field-testing could be scheduled.

CFD for packaging. Liquid pharmaceutical products primarily are supplied in bottles, and decreasing filling time can shorten time-to-market and increase productivity. To save time, filling equipment can be adapted to package various products, but splashing, spillover, and frothing are some of the problems associated with such filling lines. CFD can be applied to conduct virtual experiments before changes are made to the filling lines or to the package geometry. This method allows a wide range of conditions to be tested and leads to an optimized filling process. Figure 9 depicts the filling of a container. The figures shown are typical of solution results that are used to optimize filling processes to increase throughput and reduce foaming.

CFD for energy generation and energy-transfer devices. Heat-transfer equipment such as heat exchangers is used throughout a chemical processing plant. Failure of this type of equipment can lead to downtime and a significant loss of revenue. Hence, this equipment must perform as reliably as possible. Inefficiencies associated with heat-transfer equipment directly affect production cost. Small increments in efficiency can significantly reduce operating cost and increase revenues. CFD techniques can be applied to analyze thermal and flow fields within such devices.

Various types of process heaters are used for endothermic reactions. The two major types of heaters are direct-fired and indirect-fired heaters. High process temperatures are achieved by the direct transfer of heat from the products of fuel combustion. Heat is released by combustion and is transferred to fluids inside tubes arranged along the walls and roof of the combustion chamber. Tubes containing the process fluid are subject to combustion-process gases and high temperatures. If heating is not uniform, then hotspots may occur and lead to failure; on the other hand, inadequate heating can lead to lower process-fluid temperatures and inefficiencies. Through the use and design guidance of CFD simulations, manufacturers can reduce the formation of pollutants such as NOx.

CFD modeling methods also can be applied to gain insight into flame characteristics. Maintaining flame stability and burner efficiency is very critical to the proper functioning of a process heater, power plant, or furnace. Flame length, shape, and size can influence the process.

If the flame is too long, then it can impinge on critical regions of the apparatus and cause thermal damage. If the flame is too short, then it may wear out the burner tip. Replacing the burner or associated apparatus results in downtime and loss of product revenue.

Conclusion

The integration of CFD methods can shorten product-process development cycles, optimize existing processes, reduce energy requirements, and lead to the efficient design of new products and processes. Unit operations in the pharmaceutical industry handle large amounts of fluid. As a result, small increments in efficiency, such as those created by implementing CFD solutions, can lead to significant product cost savings. Key processes in the pharmaceutical industry can be improved with CFD techniques. The aerospace and automobile industries already have integrated CFD methods into their design process. The chemical process and the pharmaceutical industries now are beginning to integrate this technology. The full potential for process improvements using CFD solutions is yet to be realized.

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