and the ability of the integrated continuous process in managing such issues. Finally, demonstration of quality maintenance from start to finish throughout the manufacturing process poses its own challenges.

Many organizations and scientists have engaged in developing continuous processing systems that integrate several unit operations to minimize the scale impact (Gamlen and Eardly, 1986; Lindberg et al., 1987; Lindberg, 1988; Bonde, 1998; Dorr and Leuenberger, 1998; Silke et al., 1999; Pathak et al., 2000; Keleb et al., 2001; Leuenberger, 2001; Ghebre-Sellassie et al., 2002). Such systems offer distinct advantages in minimizing scale impact and allow for flexibility in running the process, on the basis of realistic commercial demand. Consistent with *lean manufacturing* principles, this can be considered a *pull system* of batch processing rather than a *build-to-stock* approach, as batch size can be customized to market needs. The following are a few examples of concepts that have been implemented to facilitate the manufacture of pharmaceutical products in a continuous fashion.

Glatt Multicell™ Unit

In 1994, Glatt developed the concept of a semicontinuous wet granulation production line. The concept leveraged the knowledge developed in producing granulation in the 5–9 kg scale range in the research environment and provided the capability to sequentially dry the minibatches in continuous manner in a series of fluidized bed dryers. The prototype consisted of HS granulation, screening, and drying in sequential steps. The drying is accomplished in a temperature gradient with the first dryer operating at higher temperature (~60°C) and the third at ambient temperature and humidity conditions. The miniature batches are processed one at a time and transferred to the dryers for further processing. If required, additional dryers can be added to the system.

The HS granulator design allows for high-pressure spraying and a dosing system that provides the capability to induce high energy into the granulator in comparison to the conventional granulators. The design allows for continuous cleaning of the granulator walls and is capable of self-discharging. In this system, the batch quantity of the material is introduced into the granulator, mixed, and granulated. The granulated material is then wet milled before discharge into the three sequential dryers. The dryers operate on the typical fluid-bed principle, and the drying is accomplished in sequential steps to achieve the desired moisture level.

The advantage of this system is that the optimized research-scale batch is leveraged for manufacturing a series of minibatches to meet commercial production requirements. This aspect of the system allows for minimizing the waste associated with costly scale-up studies required before regulatory filing. The granulation is fairly reproducible, provides better control observed on a smaller scale, and is a self-cleaning system. The drying is accomplished in a gentle manner to accommodate temperature-sensitive drugs.

Along with these advantages, this semicontinuous wet granulation production system poses certain challenges as well. This system may not accommodate material with diverse physical properties (e.g., densities). In addition, the granulation and the sequential drying steps timing need to be fairly synchronized to achieve a turnkey, automated, continuous operation without any slack. Of course, equipment breakdown in any system component may jeopardize batch material quality in various stages of processing.

Twin-Screw Granulation

Twin-Screw Wet Granulation

The twin-screw extrusion (TSE) technology is utilized extensively in the plastics and food industries to complement continuous manufacturing of products. Ghebre-Sellassie et al. (2002) and Keleb et al. (2001) have cited the application of this technology in the continuous production of pharmaceutical products. Commercially available TSE provide the great flexibility required for effective continuous mode of operation. The schematic of such a system is shown in Figure 23.6.