TABLE 20.9
Harmonization of the Processes "Wet Agglomeration" and "High Speed Tableting" Thanks to an Intelligent PAT Power Consumption Device That Is Similar to the One Offered by MCC

Type of Mode	% Yield (w/w) 90–710 µm	% Undersize (w/w) < 710 µm	% Undersize (w/w) < 90 µm
Classical mode N = 20 batches (no PAT device)	81.03 ± 2.42	88.30 ± 2.05	6.80 ± 0.51
Automatic control. (with PAT device)	91.45 ± 0.36	96.80 ± 0.31	5.40 ± 0.35

Source: Leuenberger, H., *Pharm. Acta Helv.*, 37, 72–82, 1982a.

1982a). Such a device can take into account the specific properties of the primary material to be processed as an internal reference. Harmonization of the wet agglomeration with the tableting process means that the settings of the high-speed tableting machines can be kept constant from batch to batch. This is possible because the batchtobatch variability of the granule size distribution has been kept at a minimum (Table 20.9). Without the PAT power consumption device, the machine settings have to be adapted from batch to batch in order to get the same properties of the resulting tablets such as hardness and disintegration time.

The harmonization of subsequent processes such as *wet agglomeration process* and *tableting* is as important as the harmonization of the equipment between the development and the production department, which was described in the section on the *API–excipient technological screening program*.

Scale-up in the 4th Dimension and the Glatt Multicell™

In classical scale-up the dimensions of the equipment *x, y, z* are changed and the process time is kept constant. However, in case of the scale-up in the 4th dimension, the size of the equipment is kept constant and the process is repeated in time, thus the time becomes the 4th dimension. The Glatt Multicell™ illustrates the scale-up in the 4th dimension. The optimal harmonization of processes between early development and manufacturing starts with the installation of the same equipment in both departments. Using the Glatt Multicell™ in the production department only without a counterpart in the research and development (R&D) department is completely incorrect as the formulation of the R&D department using different equipment needs to be adapted to the Glatt Multicell™, which was demonstrated by Roche (Basel) and Pfizer (Freiburg, Germany) when H. Leuenberger was consulting the Glatt Group. Only this semi-continuous process offers a real solution to scale-up problems since it uses the same equipment for small- and large-scale production (Leuenberger, 2001; Betz et al., 2003, Werani et al., 2004). The Glatt Multicell™ equipment was developed from the results of the Ph.D. theses of Schade, 1992 and Dörr, 1996 at the University of Basel, Switzerland, and needs to be integrated into the workflow of the R&D and production departments using the same equipment. The quasi-continuous production line entails manufacturing of mini batches in a specially designed high-shear mixer/granulator patented by Glatt AG Pratteln (inventor H. Leuenberger) which is connected to a continuous multi-cell-fluidized bed dryer. A specified amount of powder of the formulation is added to the high-shear mixer and thoroughly mixed. Subsequently, this amount of powder is granulated by continuously adding granulating liquid up to a fixed amount based on the results of a power consumption measurement. The wet granules are then discharged through a screen into the first cell of the fluidized bed dryer unit to avoid any formation of lumps. Thus, the quasi-continuous production of granules can be described as a train of mini-batches passing like parcels through the "dry mixing," "granulation," and "drying" compartments. The multi-cell dryer consists usually of three cells which are designed for different