air temperatures, that is, in the first cell the granules are dried at a high temperature, for example, 60°C, and in the last cell ambient air temperature and humidity is used to achieve equilibrium conditions. Thus, a batch defined for quality control purposes consists of a fixed number of mini-batches, and a tight in-process control of the mixing/granulation and drying step that provides an excellent batch record of the quasi-continuous production of granules, as well as an excellent opportunity for a continuous validation of the process and the equipment.

Constant values of the process parameters are important aspects of quasi-continuous granulation. It is well known that certain formulations show an excellent compression profile for small batches but do not keep this property using a larger batch size. To check the compression/hardness profile of a granule batch, different subunits (S) of mini-batches were selected from two formulations and compressed into tablets using different compression forces (Figures 20.19 and 20.20). It shows that in principle the quality of the small batch is not changed by the repetitive procedure.

The above concept preceded the new MODCOS line of the Glatt Group, which is a fully continuous process. However, such a fully continuous process has the disadvantage, that this technique is not suitable for the production of small batches for early clinical trials of Clinical Phase I and Clinical Phase II due to the limited amount of API and its high costs at this early stage.

Q8—Identifying Critical Material Attributes and Process Parameters

The ICH Q8 guidelines emphasis on the importance of identifying critical material and process parameters regarding product quality and the PAT initiative focus on critical process control (Figure 20.1) are illustrated with examples in the following case studies.

Critical Material Attributes—Case Study (Carbamazepine)

APIs are routinely assayed at the time of purchase for presence and level of degradation products. However, for many drug substances it is necessary to determine critical properties which may vary as a result of differences in the manufacturing techniques and which, if not monitored, can lead

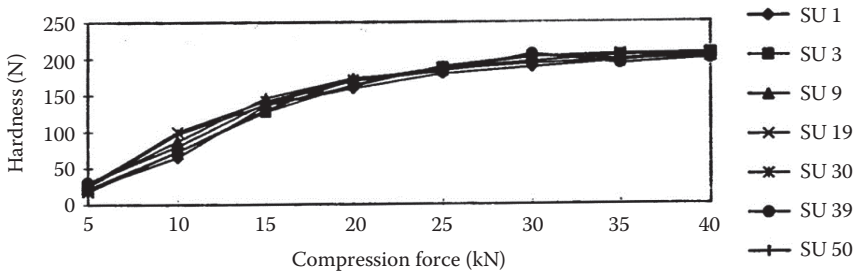

FIGURE 20.19 Compression force/hardness profile (Formulation 1). (From Betz, G. et al., *Pharma. Dev. Technol.*, 8, 289–297, 2003.)

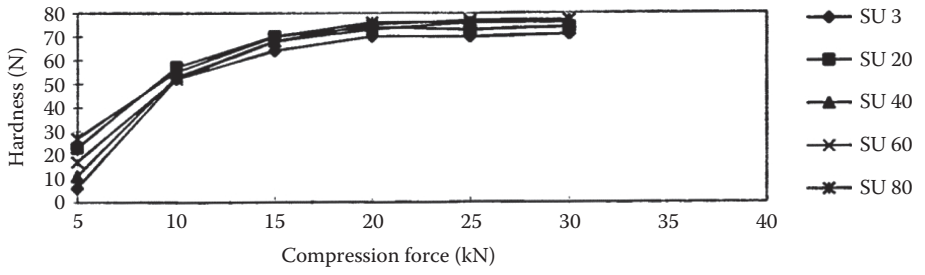

FIGURE 20.20 Compression force/hardness profile (Formulation 2). (From Betz, G. et al., *Pharma. Dev. Technol.*, 8, 289–297, 2003.)