F-CAD is using a 3D-CA approach: With each iteration step, the amount of API dissolved of the API sites is calculated and plotted in a cumulative way to show the API dissolution profile. In the case of a calculation in 1D, a linear function is expected (compare Figure 20.16). In this context the resolution, respectively the overall precision of the model, depends on the number of iterations performed to dissolve 100% of the API, which is taken care of by the parameter c_1 of F-CAD technology in 3D. It is also evident that the resolution depends on the mesh size of the grid. Thus, in 3D the tablet volume needs to be subdivided as much as possible into unit cubes that represent fine particles, a cluster of unit cubes representing coarse particles or dense granules, or void unit cubes representing pores. For this purpose, F-CAD uses the tablet designer module to define first the shape and volume of the tablet, and subsequently to subdivide this volume into a high number of unit cubes with the discretizer module. The higher the number of unit cubes, the higher will be the precision. Thus, a reasonable number of unit cells is in the range of at least 1 million. Another important point is the definition of the environment of a unit cube in 2D (Figure 20.17) respectively in 3D.

F-CAD is using the Moore neighborhood in 3D, which means that the central unit cell C is surrounded by 26 unit cubes as its nearest neighbors. It makes sense to prefer the Moore neighborhood to describe the dissolution process as, in practice, the dissolution starts at the edges of a particle. Figure 20.18 shows the dissolution profile of two caffeine tablet formulations.

The *in-silico* calculation shows (in case of dissolution profile of Formulation B in Figure 20.18) smaller error bars than the experimentally determined error points (Leuenberger et al., 2009). The error bars of the *in-silico* calculations are related to the fact that the caffeine particles are arranged at random within the tablet volume, as it is not possible to distribute the API particles each time in such a way that the particles assume the same location. Thus, if more API particles are located closer to the surface, the API is dissolved faster.

In summary, the rigorous interpretation of the formulation design space (Figure 20.2), the rigorous interpretation of the concept of *Right, First Time*, and the use of percolation theory for process development is most important. To implement the concept of *Right, First Time* in a rigorous way, the pharmaceutical industry needs to adapt the workflow approach of the automotive and aircraft industries for developing and testing first the drug delivery vehicle *in silico*. Applying the first principle approach to obtain a product and process knowledge can help reach the apex of the pyramid of knowledge illustrated in Figure 20.1.

Process Scale—Up in the Pharmaceutical Industry—Harmonization of Equipment

Process scale-up needs to follow the guidelines of ICH Q8 R (2) and should be treated on the same level of sophistication of the knowledge pyramid (Figure 20.1b). Although this statement speaks for itself, it is difficult to realize in practice. Special attention is needed when a simple service dosage form is used during clinical phase I and II with a specified composition since this limits the degree

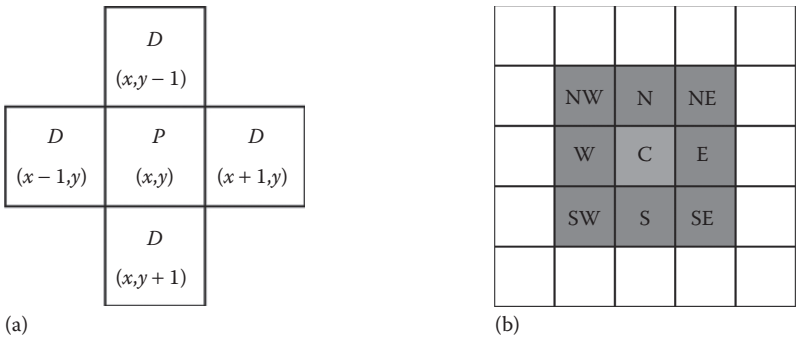

FIGURE 20.17 (a) von Neumann neighborhood of cell P. (b) Moore neighborhood of cell C in the center.