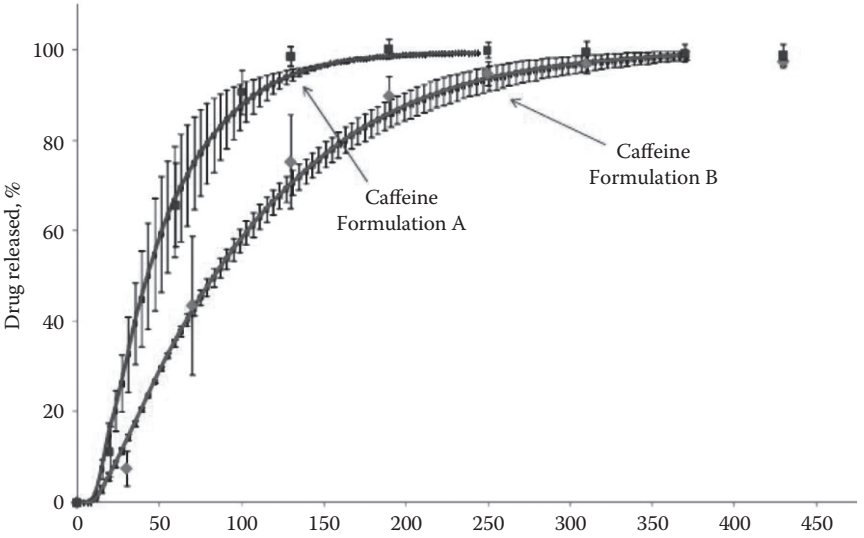

FIGURE 20.18 Dissolution profile of two different caffeine tablet formulations. The time axis represents the number of *updates*, that is, the time evolution (Figure 20.16). (From Krausbauer, E., Contribution to a science based expert system, PhD thesis, University of Basel, Faculty of Science, http://edoc.unibas.ch/diss/DissB_8879, 2009.)

of freedom of the formulation design space in clinical phase III (Leuenberger and Leuenberger 2016). As mentioned earlier the goal of the *Right, First Time* concept is to minimize the number of failures due to poor pharmaceutical processes and formulations. To a large extent this concept is realized in the automotive and aircraft industries, that is, the design and testing of the prototype *in-silico* and manufacture of fully functional vehicles according to the *Right, First Time* approach. However, in case of the pharmaceutical industry, it is not sufficient to apply a software platform such as F-CAD to design and test the drug delivery vehicles. All efforts with F-CAD at an early development stage will not prevent failures if process scale-up issues are neglected. For this purpose, a harmonization of the equipment and of the processes will lead to more important savings than the isolated application of an F-CAD platform to resolve problems of poor formulations. (Leuenberger, 2015). In other words a holistic approach is needed, where it is only possible to contribute to the knowledge on the specific formulation chosen, if all *in-silico* and laboratory experiments are kept within the same formulation design space during the full development from clinical phase I to registration of the formulation. Ideally, all data collected during the early development phases of clinical phases I and II that are part of the road map should also contribute to the knowledge. In this context the application of a fully continuous granulation line needs to be discussed in depth. Large amount of scientific work on continuous pharmaceutical granulation exists in the literature (Vervaet and Remon 2005; Swanborough, 2008; Jarvinen et al., 2012; Dhenge et al., 2013; Parikh, 2016) and there is a trend to implement such a concept in industry (Lee et al., 2015). In the early development phase, however,CS1 maint: Multiple names: authors list (link) there is not enough of the API available for developing and introducing a fully continuous granulation line. For this reason, only a semicontinuous granulation line such as the Glatt Multicell™ concept, as an example, is discussed within the concept of harmonization of the equipment during all clinical phases.

Harmonization of the processes during scale-up must be combined with an intensive use of PAT devices (Leuenberger and Leuenberger, 2016). In this context the PAT power consumption device, which was developed together with Marcel Dürrenberger of the Engineering Department at Sandoz (Novartis), was able to take into account changes in the particle size distribution and of the moisture content of the primary material in order to control the wet agglomeration process (Leuenberger,