As described above, QbD plays a key role not only in early product development, but also significantly influences scale-up of the manufacturing process, to the pilot scale and at later stages to the commercial scale. For generic products, use of DOE to gain a better understanding of the product and process is established at the small scale and verified at the commercial scale [21]. For this approach to be successful, a clear identification of scale-dependent and scale-independent process variables along with evidence of prior knowledge with similar unit operations should be demonstrated by the ANDA sponsor [22].

Design of Experiments (DOEs)

In the new QbD paradigm, significant emphasis is placed on the use of DOEs to gain a better understanding of the product attributes and process parameters and how they impact the finished product CQAs. Development of a pharmaceutical product is essentially a technique wherein the physicochemical properties of the active ingredient, excipients, and the manufacturing process are manipulated to achieve desired quality in the finished dosage form. The traditional method of varying "One-Factor-at-a-Time" approach is less dependable and more time consuming and often provides an apparently (or marginally) acceptable formulation and process rather than characterizing the desired ranges and multivariate interactions of interest. In today's competitive market, statistically designed experiments in product and process development are becoming increasingly necessary because they are quick and cost-effective. Analysis of data from statistically designed multivariate experiments enables one to generate a mathematical model and contour plots that elucidate formulation and process parameters affecting the product quality attributes. Various software packages [23–25] are available for designing experiments, developing mathematical model, and generating response surfaces. However, the success of statistical design depends on the careful selection of factors, the use of meaningful ranges of these factors, and a specific experimental design to be utilized in the study. Optimization requires statistical skill in addition to an understanding of the CMAs of drug substance and excipients involved and their impact on the process. Identification of CMAs and CPPs from risk assessment tools and an understanding of the expected relationship between them and their impact on CQAs are crucial to the success of this approach. A brief description of experimental designs applicable in product and process characterization is given here. A sample of CPPs and the CQAs impacted in a typical tableting operation is summarized in Table 5.2. For understanding the effect of multiple process variables on product quality, factorial designs are widely chosen. The independent variables in experimental design must be carefully selected, because increasing the number of variables results in a large increase in the potential number of experiments. However, the number of experiments can be minimized by carefully modifying the design and levels of factors to be studied. Accordingly, one may choose to use full factorial, fractional factorial, orthogonal composite, nonorthogonal symmetrical composite, central composite, or noncentral composite design. The composite design is made by adding extra points (star points) to the two-level factorial or fractional factorial design. If n is the number of factors to be studied, the additional points required for the composite design is $2n + 1$, one at the center