19.2. Physicochemical Characterization Method (Dissolution)

USP 23 General Chapter <1225> designates dissolution testing under Category III. The validation parameters recommended in the Compendia are precision and ruggedness studies. Other studies are left to the discretion of the end user. It is common industry practice to verify a USP dissolution method by performing studies such as linearity of standard solutions, placebo interference, capsule shell interference (if a capsule) and reproducibility of response at specified times(s) for release. However, for an in-house developed dissolution method, proper validation studies are required. These studies would include specificity (interference from placebo), precision, linearity, system suitability, filter adsorption, and sample and standard stability. For automated dissolution systems, in addition to filter adsorption, there should be evidence of nonadsorption to active tubing used for delivery throughout the system and carryover effects.

It is difficult to perform recovery studies for dissolution, as spiking of placebo in vessels is not practical. Placebo excipients have a tendency to float on top of the dissolution medium. In addition, it is difficult to make single tablets unless a hand-held press is used. Hand filled capsules lack uniformity, and the procedure is tedious. In another approach, placebo along with label claim amount of active are placed in a 900 mL volumetric flask. The flask is filled to volume with dissolution medium and a magnetic stir bar is used to stir this mixture on a magnetic plate for the specified time period. Calculations of recovery are done against an external standard prepared in the dissolution medium. Acceptance criteria for precision, specificity, system suitability, and linearity are similar to assay validation.

19.3. Nonchromatographic Methods

There are a variety of guidelines available for the validation of the chromatographic procedures, but comparatively little information is available on validation of nonchromatographic methods. In general, it is assumed that USP General Chapter <1225> on analytical validation is only applicable to chromatographic methods. This assumption is incorrect, as USP General Chapter <1225> does not state that the validation parameters given in this chapter cannot be used for nonchromatographic techniques. By careful selection of parameters, a validation protocol can be designed for validation of nonchromatographic methods. Brittain has discussed validation issues and data elements required for validation of nonchromatographic methods (49).

19.3.1. UV Spectrophotometry

For UV spectrophotometric methods for assay, one needs to study parameters such as precision, accuracy, specificity, and linearity (49). For precision, a sufficient number of individual sample preparations should be assayed to permit the calculation of a statistically valid relative standard deviation. Accuracy can be determined by spiking a mixture of excipients (placebo) with known amounts of drug active at different concentration levels. Spike levels are, in general, similar to the linearity range. Spiked samples are prepared by following the "sample preparation" procedure and assayed against an external standard at the target level concentration. The accuracy is calculated from the test results as the percentage