19.3.3. Infrared Spectroscopy (IR)

Infrared is used for identification of compounds. Currently in USP 23 there is a scarcity of monographs describing the use of IR for quantitation of analytes. For example, IR quantitation is used for the analysis of simethicon bulk drug active, tablets, oral suspensions, and capsules. As such, validation parameters required may be limited to interference studies. This interference may be due to the compound itself. For example, in an infrared spectrophotometric identification test, polymorphism may produce interference. Therefore, for compounds that exhibit polymorphism, it is critical that test samples and the reference standard have similar crystalline form. It then becomes obvious that for the infrared identification test, one should demonstrate that the method is insensitive to any polymorphic form of the material, or that the polymorphic effects have been taken into account. It is pointed out that unlike the chromatographic procedure, there are no official guidelines available on the validation of an infrared technique at present. An article by Ciurczak, "Validation of Spectroscopic Methods in Pharmaceutical Analyses," gives an overview of this subject (50).

19.3.4. Titration

USP 23 has several monographs that stipulate using titrimetry for release of bulk actives. These procedures are nonspecific and may not give accurate results in the presence of reactive impurities or degradation products. Therefore, for validation of these procedures an innovative approach will be required. The parameters to validate a titrimetric method include linearity, accuracy, blank determination, and insensitivity of the method to the amount of indicator used.

For linearity studies, different weights of the compound should be titrated, and the actual and theoretical results should agree. Alternatively, the titration could be done using a narrow range of compound weight, and then it should be stated in the method that the weight of the sample must be within this range. The accuracy should be studied by showing that the volumes of titrant for replicate titrations are very close to each other. In other words, small differences in volume of titrant required to reach an end or equivalence point does not introduce any significant error into the results.

As stated earlier, titrimetric procedures are nonspecific and cannot be used for simultaneous assay of active and impurities. In this case, impurities should be monitored by another independent validated procedure. For bulk active assay, comparison of results obtained by an alternate validated method and those obtained by the titrimetric procedure will demonstrate the validity of the titrimetric method.

19.4. General Considerations

The accuracies of chromatographic methods rely heavily on the purity of reference standards. Therefore a well characterized and highly pure standard is important. The FDA recognizes two categories of reference standards, i.e., compendial and noncompendial. The USP is the source of compendial standards. As these standards are well characterized, no further characterization is required. Noncompendial standards are also of high purity and can be obtained by reasonable effort and should be