## 4. GETTING STARTED

It is probably best to approach method development with the intention of using the developed method for stability assessment as a final application, after the method has been validated. This approach entails determining the discriminating ability of the selected method up front before investing time and money in evaluating other analytical parameters prior to assessing the stability-indicating element of the method.

Reversed-phase HPLC is the method of choice for stability-indicating and stability-specific methods, although thin-layer chromatography (TLC), gas chromatography (GC), and capillary electrophoresis (CE) are also acceptable choices. Reversed-phase HPLC coupled with ionic suppression account for probably over 85% of stability-indicating methodologies for small molecular weight pharmaceutical entities. This combination is well suited for applications in release testing, in-process as well as stability testing. Additional applications may be in cleaning validation and performance testing. Other techniques such as titration and UV spectroscopy, while commonly used for release testing, are generally considered nonspecific and thus are not considered for stability assessment.

Invariably when one is faced with finding or developing a method, one or two routes may be used depending on the nature of the chemical entity: modification or development. Modification is used when there is information or a method already exists for a similar entity. In this case, the existing method is modified or tweaked to accommodate the new entity. This may or may not be suitable; if not, development (starting from scratch) is the way to go. The goals of the separation should also be considered at this point.

### 4.1. Background Information

Knowledge of physicochemical properties of the API is invaluable to the method development process. Information on the various properties has been collected, either through a systematic program of generating the appropriate information in support of drug discovery (organic chemistry synthesis) on the one hand, or on the other, from a search of the literature or from company drug profiles, spectral libraries, or reports. Information such as dissociation constants, partition coefficients, fluorescent properties (if any), chromatographic behavior, spectrophotometric properties, oxidation-reduction potentials, formulation stability studies, and solubility studies are all very useful and can expedite the development process.

Dissociation constant and partition coefficients can be used to develop efficient liquid/liquid extraction procedures, and data on fluorescence, spectrophotometric, chromatographic, and oxidation-reduction properties can be used to determine the best means of measuring and quantifying the analyte of interest. Stability studies are performed on the drug substance, in solution and mixed with pharmaceutical excipients as part of compatibility studies. Labile functional groups are identified, and the susceptibility of the drug to hydrolysis, oxidation, thermal degradation, etc. is determined. Compatibility studies are performed to assess the stability of the API when mixed with common excipients and lubricants as well as to determine any interaction between the drug and the (inactive) raw materials. Solubilities should