7. ROLE OF FORCED DEGRADATION

7.1. Regulatory Basis

The 1987 edition of the FDA stability guidance document (1) stipulates that the API be subjected to a number of forced degradation conditions to include acidic, basic, and oxidative conditions. Workers in the field have also included temperature and light (photostability). The current draft stability guide (11), while not yet official, specifically includes photostability and temperature cycling requirements; no mention of acidic, basic, or oxidative conditions were made, however. The current ICH guidances (Q2A and Q2B) also do not specify how degradation studies are to be conducted; this was left to the discretion of the responsible companies.

7.2. Scientific Basis

Forced degradation should be one of the activities performed early in the development process to ensure that the method is discriminating before a lot of time, effort and money have been expended. The guidance documents do not indicate detailed conditions, so the conditions and interpretations are left up to the development scientist. Suggested forced degradative conditions are summarized in Table 2. Trial and error are needed to find the proper combination of stress agent concentration and time to effect a degradation, preferably in the 20–30% range. Depending on the API, not every stress agent may effect a degradation, but each agent has to be evaluated to determine whether degradation results.

Additional comments are warranted.

Adequate k'. The initially developed method should achieve a suitably retained peak, with a k' of about 4 to 10. This range allows a suitable time space in the chromatogram for degradants to elute before or after the active (major) peak. Since the polarity of the degradants relative to the major peak is not known, the k' of the major peak eluting in the middle of the chromatogram adds some assurance that the degradants would elute on either side of the main peak.

Degradation conditions. Unfortunately this is a trial and error process. Typical degradative conditions involve hydrolysis, photolysis, acid/base reactions, and temperature. The goal is to obtain about 20–30% degradation and not complete degradation of the active compound. Achieving 100% degradation would be too strenuous and could possibly cause secondary degradation, giving degradation products of the degradation product(s), which are not likely to be formed under normal storage conditions. Depending on the API, not all of the degradation conditions effect degradation, and after a reasonable effort (varying concentrations and time) to produce a degradation product with no success, one can move on to the next condition. For example, when chlorhexidine digluconate, an antimicrobial agent in mouthwash, was subjected to each of the above conditions, only degradants were isolated from heat, acid and light (12). While it was impervious to the other conditions, this was not known up front, so each of the conditions had to be tried.

Acid/base. Generally the concentration of the API is doubled to enable the reaction solution to be neutralized before injecting into the HPLC system to prevent damage to the silica-based chromatographic column.

Controls. Refer to Table 2. It is important that corresponding matrices and appropriate controls be treated in a similar fashion to identify possible interferences.