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Common Problems in Stress Testing of Pharmaceutical Preparations

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Stress testing which is also called force degradation study is performed to evaluate the inherent stability of the drug substances and drug products and also to reveal the main degradation pathways as well as to introduce a stability indicating method. According to ICH guidelines identification of the degradation products are only limited to those which are similarly produced in accelerated conditions. Stress conditions are defined as oxidation, hydrolysis at various pH values and photolysis reactions [1-3] In the available guidelines for performing the stress tests, the details such as the type of suitable stresses and the amount of total degradation indicating the end of the experiment has not been mentioned. On the other hand the available information in the literature is contrary [2,4-10] but there is a very useful review in this area by Singh et al. [1]

In practice there are some problems and difficulties in performing the stress tests. One of the important and challenging subjects in hydrolytic stress conditions (acidic, alkali or neutral) is the reactant selection.

Analysts face with some problems like that which hydrolyzing agent is suitable and what concentration should be used and also how much the exposure time is to be used with these reactants?

This should be kept in mind that hydrolytic stress uses bot extreme pH values in aqueous media and elevated temperatures as stress conditions.

Herein different stress conditions have been summarized:

1-Acidic pH in hydrolytic stress is gained with hydrochloric acid or sulfuric acid at the concentrations of 0.1 and 1N respectively.

2- Basic pH is commonly provided using sodium hydroxide (0.1-1N). It is less common to use potassium or ammonium hydroxide or a more concentrated sodium hydroxide solution.

3-Natural hydrolytic stress is performed in distilled water at room temperature or reflux condition.

4-The temperature range used in hydrolytic stress test is 40-110˚C. A most common technique in this area is refluxing of the sample in the boiling point.

The temperature range in stress testing is almost wide, thus choice of appropriate temperature is consequential. In the first steps, when desired results is not achieved in the special studied temperature the analyst should decide on the extent of increments or decrement in the temperature to reach the desired results as well as suitable duration of the study. Considers should be made on the fact that the results are directly depended on the inherent stability characteristics of the drug molecule, i.e. some drugs show no degradation even at boiling temperature and for several weeks.

5- The duration of test is as less as 5 minutes to a maximum of 2 months leading to total decomposition and or a minimum of 3% and a maximum of 70 % of drug molecule loss. Although there is no written instruction in this area but it is useful to reach to 20 % loss in order to have a defined end point. Some drug molecules are too stable and even exaggerated stresses may only lead to trace losses.

6- Oxidation of drug molecule is performed in the aqueous solutions of H_2O_2 (1-30 %) and the most common condition is reached using 3% of hydrogen peroxide. In the oxidation stress, various temperatures are used from room temperature to reflux condition. It should be noted that, using a high concentration of reactant in minimum time period may change the reaction mechanism and may cause practical problems in direct injection to HPLC analyzing system [1]

There is another problem with Metal ions that catalyze oxidative reactions up to several thousand times and some of them even have been implicated in hydrolytic reactions and sometimes their presence in the test condition may lead to new degradation pathways [11]

7-In photolysis, drugs are exposed to short/long wavelength UV/visible or fluorescent light, generally at room temperature, therefore type of light sources and lighting intensity, calibration of light source as well as period of exposure range from a few hours to several months should be considered to get a realistic description of a drug photo reactivity [12,13] UV light (254 nm) and or Fluorescent light is commonly utilized according to ICH photo stability guidelines.

8-Another problem is the concentration of drugs during stress conditions. The suggested concentration in different literature is 1 mg/ml-1 [5] but in some studies a concentration that is expected to be present in the final formulation is utilized in stress testing, because some polymeric degradation products are not formed at lower drug concentration [14].

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