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Editorial

Significance of Stability-Indicating LC Methods in Pharmaceuticals

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Stability Indicating Methods (SIM) is collective analytical procedures that indicate stability of samples and are required to be fully validated. Despite of all the requirements from the regulatory and governing entities, there is still not a clear consensus of what constitutes a stability-indicating method. For the development of the HPLC method of drug substance and drug product, the FDA requires that the following parameters should be calibrated:

1. Accuracy
2. Detection and quantitation limit
3. Linearity
4. Precision
5. Range
6. Recovery
7. Robustness
8. Sample solution stability
9. Specificity/Selectivity
10. System Suitability

The acceptance criteria for each of these parameters are clearly mentioned in the regulatory documents that serve as a gold standard for the validation of all the HPLC methods in academia and industry. However, the guidance documents do not provide the details about scope and degradation study practices [1].

The assay specification and definition of a "major change of the content" from ICH Q1A should be taken into consideration when determining a proper amount of degradation. Thus, a validated LC method should meet all the acceptance criteria and should be sensitive and reproducible enough for the acceptable study of pharmaceutical drugs in unknown samples. Over the years, LC methods have become the first choice in the process of separation of analytes and SIM for pharmaceuticals, when compared to other methods due to several reasons; (1) the modifications that could be achieved in the mobile phase (2) a greater choice of stationary phases which enable good separation and (3) availability of specific and sensitive detector systems such as spectrofluorometer, Diode Array Detector (DAD), electrochemical detector and other hyphenated systems LC-MS and LC-NMR which enable thorough detection of degradation products [2].

The parent drug stability test guidelines issued by the International Conference on Harmonization ICH Q1A (R2) and Q5C suggest that stress studies should be carried out on a drug to ascertain its inherent stability characteristics [3]. It is important to understand the changes in the quality of a drug substance with time and the nature of degradation products formed under various storage conditions as these affect the efficacy and safety of pharmaceuticals. Trissel [4], reported that the failure to recognize the degradation products is the most common factor that leads to erroneous reporting of the data on the stability studies. Most of the studies dealing with stability of pharmaceutical drugs ignore this point. A proper identification of degradation products would hence support the suitability of the proposed analytical procedures.

Stability testing involves forced degradation or stress-studies indicating hydrolysis, oxidation, photolytic and thermal degradation etc. As an example, hydrolysis is studied at various experimental conditions such as 0.1N HCl, 0.1 N NaOH, at different pH's 2, 4, 6, 8, acid control (no API), base control (no API), control API (no base or acid) at 40°C and 60°C; oxidation is studied at 25°C and 60°C in H_2O_2, Azobisisobutyyronitrile (AIBN) at 40°C and 60°C, peroxide control and AIBN control; thermal degradation at room temperature, 60°C(75% RH), 80°C(75% RH), 60°C, 80°C.The results of forced degradation of the drug should show clear chromatographic separation of the degradation product from the parent drug. Degradation of drug substances between 5-20% has been accepted as reasonable for validation of chromatographic assays [5,6]. Some pharmaceutical scientists think 10% degradation is optimal for use in analytical validation for small pharmaceutical molecules for which acceptable stability limits of 90% of label claim is common [7]. Others suggested that drug substance spiked with a mixture of known degradation products can be used to challenge the methods employed for monitoring stability of drug product [8]. No such limits for physiochemical changes, loss of activity or degradation during shelf life have been established for individual types or groups of biological products [7]. Degradation products that exceed the ICH thresholds for identification or qualification encountered in stability studies require special attention, including complete identification. For unknown degradation products, any combination of HPLC coupled with Diode-Array Detection (DAD), LC–MS, LC coupled to Nuclear Magnetic Resonance (LC-NMR), and Gas Chromatography (GC) coupled to MS can give complete structural information. These serve as powerful tools for the rapid identification of degradation

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products with spectral information useful for structure clarification.

Thus, LC methods play a significant role in pharmaceutical drug development to study the stability of A Pausing stress studies under a variety of ICH recommended test conditions. Adequate formal guidelines are not available for the development of stability-indicating LC method. A sensitive stability indicating LC method should be able to detect the API along with the degradation products. Liquid chromatography being a versatile separation technique, when coupled with the latest advances in detection serves as a valuable tool for stability monitoring of pharmaceuticals.

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