Poster 21

Efficient HPLC Column and Mobile Phase Screening Protocol for Developing Stability-Indicating Methods: Diphenhydramine Case Study

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Purpose

Stability-indicating HPLC methods are required to establish small-molecule drug stability and must adequately quantify drug-related impurities. Methods must demonstrate that all degradation products are observed and have adequate resolution from each other and the main band. Current method development practices are laborious, requiring the setting of multiple instrument parameters (e.g. column type, mobile phase, gradient). This study enlists automated systems and algorithms to improve the efficiency of stability indicating method development.

Methods

Diphenhydramine (DPH) was used as a model system to assess the efficacy and accuracy of a proposed screening protocol for developing a stability indicating method. DPH was stressed with a single selected forced degradation stress condition, acid exposure. Utilizing compatible column and solvent switching modules, the HPLC system screened six columns with four mobile phases, for a total of 24 combinations. Method combinations were filtered using quantitative parameters (resolution, tailing, retention), then qualitative parameters (elution profiles and baseline quality). Refined analyses were conducted on suitable methods to provide one candidate for optimization.

Results

Automated quantitative analytical filtering of the combinations eliminated twelve methods. Qualitative chromatographic factors reduced the number of suitable methods to four. Of these four, the method with the lowest back pressure was advanced for further optimization. Method viability was confirmed through further analysis, including evaluation of mass balance and peak purity.

Conclusion

A screening process was developed and evaluated for use in the rapid development of stability indicating methods. A set of 24 possible combinations of columns and mobile phases were tested in an automated screening for diphenhydramine as a case study. Options were narrowed using quantitative then qualitative parameters to select a single option for method optimization. Further analysis of the selected method was conducted to confirm its viability. The proposed methodology was successfully demonstrated through development of a method meeting all requirements in three days with three hours of hands-on work.

Keywords: HPLC, Method Optimization, Stability Indicating Method