ABSTRACT

A traditional approach to method development could flop to encounter desired separation downstream during test method validation, test method transfer or out of specification studies. In contrast, method development through quality by design (QbD) approach can result in a more rugged/robust method due to greater emphasis on risk management. A design of experiments (DOE) approach which involves both statistical analysis and modeling is used in a QbD approach to understand the impact and interactions between critical method variables. A QbD approach is applied in present study to drug analogs and isomers complex method development using Shimadzu LC Solution Software. The permissible nonconformities of method variables are determined within the design space – the proven acceptable ranges (PARs). The critical method variables in attaining chromatographic resolution for drug analogs and isomers were column chemistry, chromatography type, sample preparation and mobile phase. The prospective intrusion of method variables was determined in terms of desirable method responses, leading to a better method understanding besides achieving anticipated method quality.

Effect of column physical properties (length and inner diameter) on separation and speed was investigated during initial screening experiments. Effect of chemical properties (type of surface, pore size and particle size of stationary phase) on sensitivity and retention factor were studied. Both pH and ionic strengths of the aqueous portion of mobile phase were considered in developing rugged methods that were not sensitive to small variations in conditions.

Unified quantification methods for structural, functional and direct analogs of sartans (angiotensin II receptor antagonists), statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), quinolones, proton pump inhibitors (PPI's) with gastroprokinetic agents and dipeptidyl peptidase-4 (DPP-4) inhibitors with biguanide are developed. Additionally enantiomers of linagliptin, sitagliptin phosphate, cetirizine hydrochloride, solifenacin succinate and montelukast sodium are separated on Diacel Chiralpak IC stationary phase instead of using separate stationary phase for individual enantiomeric separation. The proposed methods were statistically validated in terms of precision, accuracy, linearity, specificity, selectivity and robustness in accordance with guidelines of International Council on Harmonisation (ICH). The newly developed methods proved to be specific, accurate and robust for the unified quantification of drug analogs in commercial pharmaceutical formulations and to

confirm the relative abundance of desired enantiomer in a racemic mixture of active pharmaceutical ingredient.

The advantage of developed methods for unified quantification of drug analogs is that only one sample is prepared and single chromatographic run is required to provide information on the identity, content uniformity, dissolution, potency and purity of active pharmaceutical ingredients. Therefore, these methods can be handy in daily sample handling in routine, when many samples of drug analogs are analyzed in drug testing laboratories. The proposed methods are able to discriminate not only between different drug analogs and enantiomers but are also able to detect counterfeit products.