Abstract

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The title of Diploma Thesis:
Development of UHPSFC-PDA method for impurity profiling in active pharmaceutical ingredient atomoxetine

This diploma thesis deals with an optimization of UHPSFC method for determination of atomoxetine and its impurities mandelic acid, o-cresol, phenol, phenoxyatomoxetine, benzylatomoxetine and atomoxetine carbamate. Atomoxetine is used as centrally acting sympathomimetic agent for the treatment of hyperkinetic disorders such as Attention Deficit Hyperactivity Disorder (ADHD).

Measurements were carried out on the UHPSFC system Aquity UPC^2 with PDA detector and Torus Diol 1.7 µm (3.0 x 100 mm) column. ABPR pressure was optimized at 2000 psi and the column temperature at 40°C. Flow rate of mobile phase was 1.5 ml/min. Additional optimization parameters were the mobile phase composition, gradient elution conditions (initial composition of mobile phase, gradient slope, gradient time, gradient curves) and the effect of analysis time on the resolution of critical peak pairs. PDA detector parameters were examined, including comparison of data acquisition in 3 D and 2 D mode, selection of detection wavelength, resolution, sampling rate, filter time constant and mode selected for data acquisition, in order to obtain the maximum sensitivity of the method.

Optimal conditions for the impurity profiling in the drug substance atomoxetine were chosen as folows: CO_2/MeOH + 0.1% NH_4 OH as mobile phase with a gradient from 1% to 40% in 14 minutes. Detection was made in the 3 D of compensated mode at 215 nm with a resolution of 4.8, with a sampling rate of 20 points /sec, the filtering time constant in the normal mode during a 15 minute analysis. The method was validated properly including SST (retention time, peak area, resolution, peak symmetry, peak width at half height) and determination of parameters of precision, accuracy, linearity, selectivity and robustness of the method.

Keywords: atomoxetine; mandelic acid; *o*-cresol; phenol; phenoxyatomoxetine; benzylatomoxetine; atomoxetine carbamate; SFC; mobile phase; PDA detector; optimalization; validation; pharmaceutical analysis