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DEVELOPMENT OF UHPLC METHOD FOR THE ANALYSIS OF PIMAVANSERIN AND ITS IMPURITIES USING AQbD PRINCIPLES

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Introduction

Pimavanserin is chemically described as N-[(4-fluorophenyl)methyl]-N-(1-methyl-4-piperidinyl)-N'-[[4-(2-methylpropoxy)phenyl]methyl]-(2R,3R)-2,3-dihydroxybutanedioate (2:1).

It is an atypical antipsychotic that has been approved for the treatment of Parkinson's disease, and its use for the treatment of Alzheimer's disease, psychosis, schizophrenia and major depressive disorder is being investigated [1].

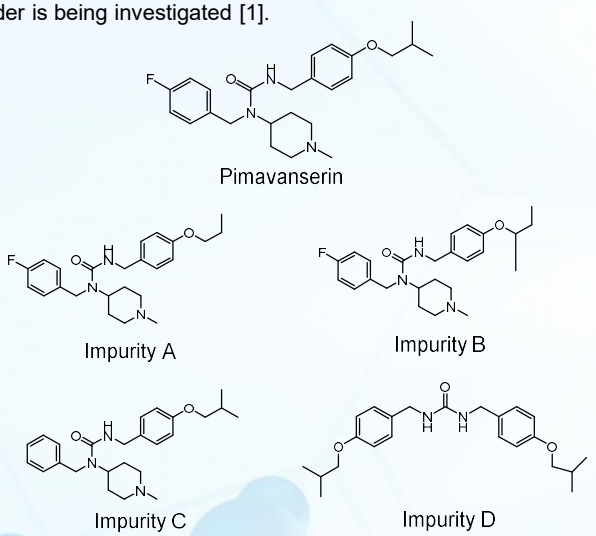

Figure 1: Chemical structure of pimavanserin and its related impurities.

Experimental

For the experiments an Agilent 1290 Infinity II LC system (Agilent Technologies, Santa Clara, United States) equipped with 1290 Infinity Quaternary Pump (dwell volume, Vd = 125 µL, extra column-volume, Vec = 0.004 mL), cooled autosampler (4 ˚C), active heated column oven, DAD detector (190-400 nm) was taken into service.

A reversed phase UHPLC method for determination of pimavanserin and its impurities was developed following analytical-quality-by-design (AQbD) principles as a risk-based strategy [2].

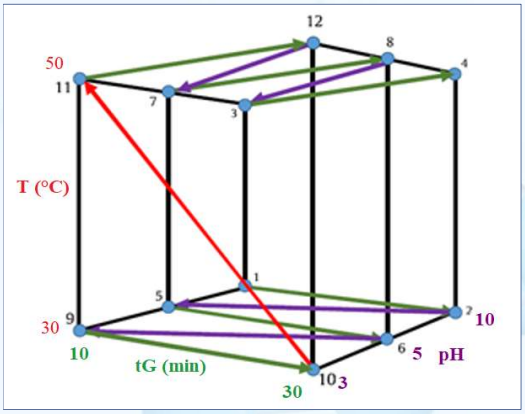

Figure 2: Automated experimental design (Design of Experiments, DoE) and conditions of tG-T-pH model. Twelve preliminary experiments were carried out with gradient range 55% → 90% eluent B (composition of eluent B was acetronitrile: THF = 7:3) and flow rate of 0.2 mL/min.

Results

The method was optimized using DryLab® (version 4.3.2., Molnar-Institute, Berlin, Germany) software modelling package and multivariate experiments. Multivariate analysis of critical method parameters (gradient time, pH, column temperature) was used to determine method operable design region (MODR).

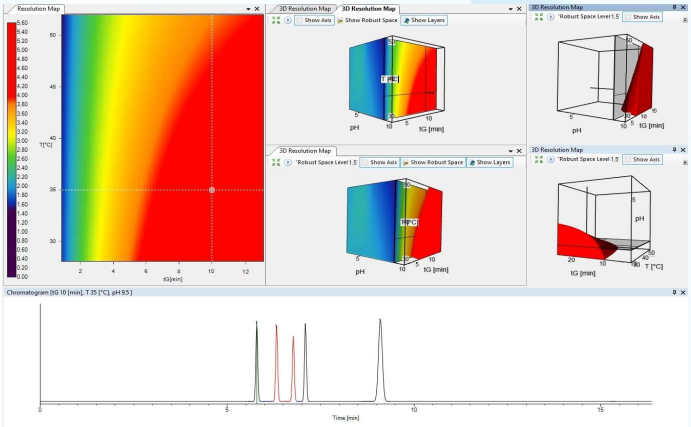

Figure 3: Visualization of the method operable region (MODR) and selection of the working point. Different perspectives of the 3D resolution cube and predicted chromatogram at selected working point (column BEH C18 150 x 2.1 mm, 1.7 µm , eluent A pH 9.5, column temperature T_C 35°C and gradient time t_G 10 min).

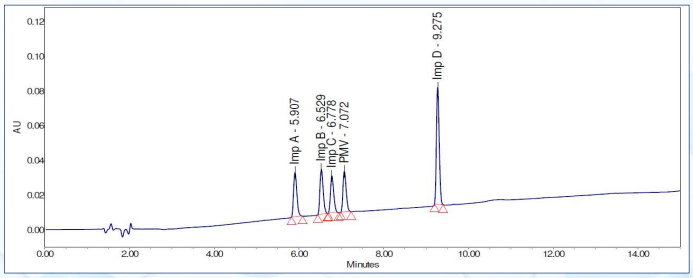

Figure 4: Experimentally obtained chromatogram of pimavanserin and its related impurities at selected working condition.

Conclusion

Analytical method represents a critical lifecycle parameter of a pharmaceutical product due to their role in the early phase of the product development as well as their key role in the finished product quality control. Traditional approach to method development based on varying one-factor-at-a-time (OFAT), especially from the industry point of view, is time-consuming and therefore extremely expensive process. In recent years, development of analytical methods is based on the principles of analytical-quality-by-design (AQbD) as a part of a full risk assessment strategy. A robust final method was obtained with a column BEH C18 150 x 2.1 mm, 1.7 µm, column temperature 35°C, eluent A pH 9.5 and gradient time t_G 10 min.

References

[1] M. P. Cruz, Pimavanserin (Nuplazid): A Treatment for Hallucinations and Delusions Associated With Parkinson's Disease, *P&T* **42** (2017) 368-371.
[2] A. Dispas, H.T. Avohou, P. Lebrun, P. Hubert, C. Hubert, 'Quality by Design' approach for the analysis of impurities in pharmaceutical drug products and drug substances, *Trends Analyt. Chem.* **101** (2018) 24-33.