Streszczenie w języku angielskim (Abstract)

Application of statistical methods of Design of Experiments (DoE) in the Quality by Design (QbD) approach for the development of innovative active substances and drug products technologies

The aim of the work was to demonstrate the usefulness of using advanced statistical tools for the design of experiments (DoE) and the QbD approach in various areas of the development of innovative active substances and drug products: developing analytical methods for monitoring the quality of processes and products at various stages of manufacturing substances and drug products, developing and optimizing the composition and formulation of drug products, development and optimization of API synthesis methods at various stages of technology development.

Using AQbD and DoE approaches, including screening, optimization and validation, a UHPLC method was developed to quantify the full profile of nine impurities of the innovative pharmaceutical substance CPL409116 (JAK/ROCK inhibitor). Critical method parameters (CMP) were tested in a wide range: type of stationary phase (8 different columns), pH of the aqueous mobile phase (2.6, 3.2, 4.0, 6.8) and start (20 – 25%) and alloy (85 – 90%) per cent organic mobile phase (ACN). The critical method attributes (CMA) were peak-to-peak resolution (2.0) and analyte peak symmetry factor (0.8 – 1.8). At the screening stage, the impact of different CMP levels on CMA was assessed based on a full fractional design 2^2. The robustness of the method was confirmed using a $2^{(4-1)}$ fractional factorial design. The method operational range (MODR) was generated. Monte-Carlo simulation was used to calculate the probability of meeting the CMA specifications. The final method parameters were as follows: Zorbax Eclipse Plus C18 column, aqueous mobile phase 10 mM ± 1mM aqueous HCOOH solution with pH 2.6, 20% ± 1% ACN at the beginning and 85% ± 1% ACN at the end gradient and column temperature 30°C ± 2°C. The method was validated according to ICH Q2(R1) guidelines. The developed method met the requirements of linearity, precision and robustness. The LOQ was 0.05% and LOD 0.02% for all impurities.

The effective use of the QbD and/or DoE concept to optimize the composition and formulation of drug products is demonstrated in the example of the development of lipid nanoparticles for the various types of RNA delivery. The review summarised research published over the last ten years, presenting the latest trends and regulatory requirements, as well as mathematical and statistical design methods. Most of the optimization work used the DoE approach. Various methods of designing and innovative approaches to DoE were discussed. In addition to the traditional tests and statistical modelling (ANOVA, regression analysis), artificial intelligence and machine learning methods were also used. The full QbD approach was described in a few articles, and a few refer to some aspects of QbD.

The API synthesis is another area where using the DoE approach benefits have been demonstrated. The use of DoE made it possible to learn and effectively optimize two stages of the production process of the innovative active substance CPL302415 (PI3Kδ inhibitor) in flow reactors: the Pd-catalyzed oxidation stage and the ester group reduction stage. The use of various tools of the DoE approach allowed us to find important factors influencing the efficiency of the process and to determine the operational scope allowing for maximum product efficiency. Optimized catalytic oxidation conditions allowed for a product yield of 84%. In the case of the catalytic reduction stage, over 98%, and for reduction using LAH, 83%.

The use of the DoE approach also allowed for the effective optimization of the synthesis parameters of the innovative active substance CPL304110 (pan-FGFR inhibitor) in a flow reactor. Performing seventeen experiments based on the central composition design (CCD) 2^4 with two repetitions at the central point and the response surface methodology allowed the reduction of the reaction time to 2 minutes at 20°C and the equivalent of diethyl oxalate and sodium ethoxide 1.23, with a satisfactory product yield of 84%.

Keywords: Analytical Quality by Design (AQbD); design of experiment (DOE); method operable design region (MODR); pharmaceutical impurity profiling; CPL409116; JAK/ROCK inhibitor; lipid nanoparticle (LNP); RNA delivery; CPL302415; PI3Kδ inhibitor, CPL304110; pan-FGFR inhibitor, flow chemistry