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Resolution-based scoring function and design of experiment for green oriented UPLC method development in pharmaceutical analysis

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PURPOSE

Green analytical chemistry is a part of a sustainable pharmaceutical development concept. Analytical chemistry has recently turned its attention to the use of ecologically friendly solvents. Miniaturisation of analytical methods and shortening analysis time while obtaining reliable analytical results are important aspects of green analytical chemistry. Using Design of Experiment (DOE) for method development, optimization and assessing robustness, can increase the scientific understanding of the method in short time frames.

In this study, a combination of Green Chemistry principles and DOE approach using a new resolution-based scoring function is presented through the development of an UPLC method for the quantitative analysis of ibuprofen and two main degradation products in a commercial tablet formulation. The Method Operable Design Region (MODR) was identified with the DOE approach and Analytical Eco-Scale metric tool was applied to assess method greenness.

METHODS

Mixed standard solutions containing ibuprofen and impurities J and E from EP were prepared from commercial standards. Ibuprofen tablets were acquired from the market. Bioethanol, a non-synthetic ethanol produced from corn (Merck), was used in the mobile phase as a green alternative. Phosphoric acid (WVR) as aqueous additive and phosphate salts (Merck) were chosen for their low environmental impact and hazard (GHS classification).

Three consecutive DOE were performed: I – screening, a reduced combinatorial linear design of 10 experiments, to select the factors; II – optimization, a full-factorial interaction design of 8 experiments, to identify the most suitable operating conditions; III – robustness, a fractional factorial res III design of 4 experiments, to define the operable region domain. Each design included replicated trials for the experimental error assessment and data were fitted by Multiple Linear Regression (MLR) using MODDE® software (Sartorius).

The following factors were investigated after a preliminary knowledge assessment: stationary RP phase (C18, Amide, Hexyl-phenyl), flow (0.4ml/min, 0.6ml/min), column temperature (40°C, 60°C), organic solvent percentage (20%, 40%) and pH (3.0, 7.0). UHPLC-DAD 1290 binary pump system (Agilent) with 264nm detection wavelength and 0.1µl injection volume was used. Analysis was performed on 1.7µm particle size UPLC Analytical columns (Waters) 50x2.1mm I.D.

RESULTS

Screening Design

The following scoring function R_{score} was used as response vector for the MLR analysis:

$$Rscore = \left(\frac{1}{N-1}\sum_{i=1}^{m} Rsi\right) \cdot a \cdot b$$

Resolution values (R_{si}) were assigned to avoid the contribution of unacceptable resolutions:

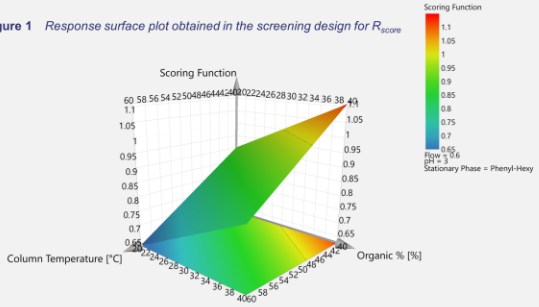
- R_{si} = 0 if the resolution is ≤ 1.5 (R_{min})
- R_{si} = 1 if the resolution is ≥ 3 (R_{opt})
- If $R_{min} < R_{si} < R_{opt}$ then $R_{si} = (R_i - R_{min})/(R_{opt} - R_{min})$

Weighing factors *a* and *b* account for the run time to ensure a green oriented fast analysis:

- a = 0 if the k' is ≤ 0.5 (k 'referred to the first peak)
- a = 1/k' if the k' is > 0.5 (k' referred to the first peak)
- b = 5/(RT-t_0) (RT referred to the last peak)

A robust model (R^2 = 0.99; Q^2 = 0.86) was developed for the screening DOE. The proposed scoring function identified as best condition the Hexyl-phenyl column and the aqueous mobile phase with pH 3. A strong linear trend was highlighted for the R_{score} function and investigated with an optimization DOE using the Hexyl-phenyl column and the pH 3 aqueous phase.

Figure 1 *Response surface plot obtained in the screening design for R_{score}*



Optimization Design

A robust model was obtained also for the optimization design (R^2 = 0.98; Q^2 = 0.96). It allows the identification of the best chromatographic conditions using, as response, R_{score}.

The function shows a cusp shape: the highest R_{score} value identifies the chromatographic conditions corresponding to a well-resolved, fast analysis. High ethanol% and flow is preferred because for run time shortening, without strong impact on peak resolution and operating pressure. Column temperature has a severe influence on peak retention, probably due to heat-related modification on logP coefficient: this leads to loss of retention on higher temperature and lower R_{score} value.

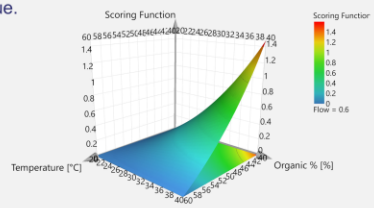


Figure 2 *Cusp shape surface plot obtained in the optimization design for R_{score}*

Robustness Design

Finally, a robustness DOE was performed using as set point the condition identified by the optimization design. The MODR was identified using Monte Carlo simulations and the developed responses models.

Final conditions, considering MODR for robustness and method life-cycle management were:

- Hexyl-phenyl column as stationary phase
- Ethanol and Phosphate buffer pH 3 as mobile phase
- Ethanol% = 39% ±1%
- Temperature = 39°C ±3°C
- Flow = 0.6 ml/min ±0.03 ml/min

The system can be defined robust inside the region tested, since all the parameters were within specification.

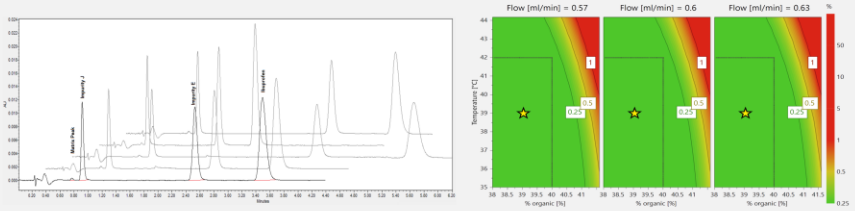


Figure 3 *Chromatograms of MODR and final conditions, and Design space*

Greenness Assessment

Analytical Eco-Scale metric tool was applied for the greenness evaluation. Starting from a value of 100, selected approach assigned penalty points for reagents, their amounts, generated waste, occupational hazard, and energy usage. Analytical Eco-Scale total score was 86, with 14 assigned penalty points, which ranked the method in the best group as excellent green analysis (total score >75).

CONCLUSIONS

A robust UPLC method for the determination of ibuprofen and two of its related impurities in a commercial tablet formulation combining the DOE approach and Green Chemistry principles, was developed. The R_{score} proved to be a useful tool for choosing the best green analytical condition. Furthermore, the method showed to be an excellent green analysis with an Analytical Eco-Scale score of 86.

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