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# UHPLC method for multiproduct pharmaceutical analysis by Quality-by-Design

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Highlights:

- An innovative analytical development based on QbD and green chemistry is proposed
- The approach is based on a systematic modeling of all time intervals between peaks
- A UHPLC method was developed for the analysis of 16 pharmaceutical compounds
- The robust experimental domain of the method was determined

## Abstract

An innovative Analytical Quality-by-Design (AQbD) methodology was followed to develop a specific and robust UHPLC method for the simultaneous separation of 16 active pharmaceutical ingredients (APIs). In the context of pharmaceutical repositioning, these molecules have been selected as good candidates for buccal per mucous (BPM®) administration route. Given the structural and physico-chemical diversity of compounds, an innovative development strategy based on QbD was applied. The main advantage of QbD is to ensure the robustness of the method. During a first scouting phase, the C18 chromatographic column was selected. Throughout the study, acetonitrile and ethanol based-mobile phases were investigated and compared. Ethanol was chosen as an alternative to acetonitrile due to its green properties coming from its lower toxicity and sourcing from renewable sources. Screening designs were performed to identify critical process parameters (CPPs). In ethanol media, temperature turned out to be a critical factor on peak retention and separation. Response surface methodology was then carried out to optimize CPPs and define the experimental domain of the method where complete separation between all peaks was obtained. Because changes in the elution order of the compounds occurred when modifying the experimental conditions, time differences between peaks were chosen as critical quality attributes, and an original data treatment was developed. It consisted in a systematic modelling of the time intervals between all possible pairs of peaks over the whole 3D experimental domain. Finally, a desirability analysis based on the smallest predicted time interval between peaks enabled to find optimal conditions only with ethanol based-mobile phases. Optimal conditions using ethanol, a Xbridge BEH Shield RP18 column and a 500 µL starting isocratic step, were determined by maximizing the desirability value and corresponded to a gradient slope of 2.57 %/min, a pH of 4.85, and a temperature of 33.7°C. A baseline separation of the 16 APIs was achieved with resolutions superior to 2.4 and the robustness of the method was experimentally validated.

Keywords: Quality-by-design; Pharmaceutical analysis; Green chemistry; Design of experiments Robustness