

IMPLEMENTATION OF DESIGN SPACE CONCEPT FOR THE DEVELOPMENT OF ROBUST ANALYTICAL METHODS

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Nowadays, the concept of quality by design (QbD) and more particularly the design space (DS) has become widespread in the field of pharmaceutical sciences. The ICH Q8(R2) guideline [1] defines the design space as “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality”. Therefore, in the framework of separation sciences, the design space can be considered as a zone of robustness where small but deliberate variations in method parameters do not affect its quality.

The present methodology is based on the use of design of experiments (DoE). The first step consisted in the selection of an appropriate response or criterion which represents the quality of a separation. Previous works have demonstrated that the chromatographic resolution (R_S) is not suitable for the predictive error analysis [2]. Thus, the separation criterion (S) – defined as the difference between the end of the first peak and the beginning of the second peak of the critical pair (i.e. the two most proximate peaks) – was preferred. In a second step, some common chromatographic parameters (i.e. pH of mobile phase, gradient time, temperature...) were selected to optimize S . The retention factors at the beginning, the apex and the end of each peak were then modelled. The selected criterion, S , was finally computed using Monte Carlo simulations in order to pay a special attention to the predictive error propagation. By this way, the design space can be defined using the following equation.

$$DS = \left\{ \mathbf{x}_0 \in \chi \mid E_{\hat{\theta}}[P(S > \lambda) \mid \hat{\theta}] \geq \pi \right\}$$

Where \mathbf{x}_0 is a point in the experimental domain, χ . λ is the acceptance limit for criterion S ; π is the quality level and $\hat{\theta}$ is the set of estimated parameters of the model. P and E respectively correspond to the estimators of probability and mathematical expectation.

This methodology has been applied to several analytical methods in order to optimize the separation and to compute the design space. For example, the separation of a mixture containing 9 compounds was optimized as illustrated on the following figures. Several examples will be presented.

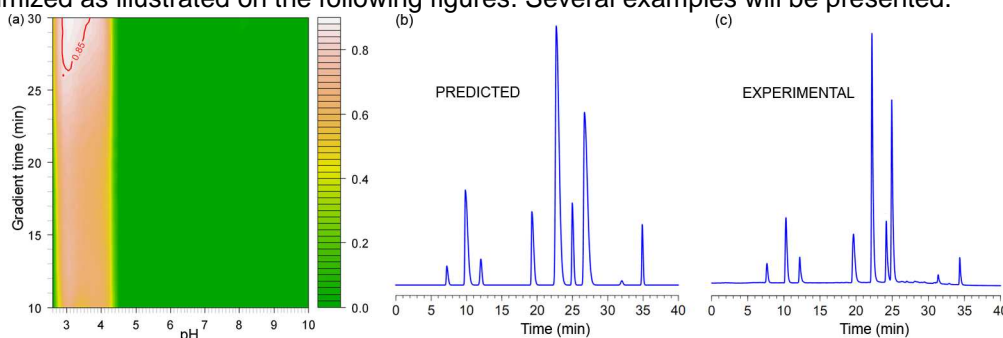


Figure (a) depicts the probability surface to obtain a separation (S) of at least 0 min (baseline resolved peaks). The quality level is set to 85% and the corresponding design space is surrounded in red. Figure (b) displays the predicted chromatogram at pH 3.0 and with a gradient time of 30 min. (within the DS). Figure (c) shows the chromatogram recorded at this operating condition.

References

- [1] ICH Q8(R2), Draft Guidance on Pharmaceutical Development, 2005 (step 5).
- [2] P. Lebrun *et al.* Chemom. Intell. Lab. Syst., 91 (2008) 4-16.