Application of the DoE Concept for Peptide API Process Development at Bachem

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Introduction

ICH guideline Q11 [1] describes approaches to developing process and drug substance understanding. In a traditional approach, set points and operating ranges for process parameters are defined, and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and more extensive scientific knowledge are used to select process parameters and unit operations that impact critical quality attributes (CQAs) for evaluation in further studies to establish design space(s) and control strategies applicable over lifecycle of the drug substance [1].

Results and Discussion

The design of experiments (DoE) concept is applied at various stages of peptide API manufacturing processes at Bachem for design space definition. For unit operations with multiple process parameters the impact of each parameter on the relevant product and process quality attributes can be assessed utilizing DoE software [2]. Two case studies taken from the manufacturing process of different peptide APIs are presented to demonstrate the benefit of DoE for process development. Both, optimization of reaction conditions and process economy can be addressed by DoE.

Case study #1 comprises the optimization of TFA cleavage conditions for an Eptifibatide intermediate. The objective was to optimize the cleavage variables in order to maximize product purity and minimize the formation of cleavage related impurities.

Optimal TFA cleavage conditions (cleavage cocktail composition and cleavage duration) were predicted by DoE software with regard to maximized product purity and minimized contents of cleavage related impurities (Figure 1). Predicted results were confirmed at small and medium scale (from grams up to several 100 grams), as well as at large scale (multi kg manufacturing campaigns).

Table 1. Scope of DoE case study #1. TFA cleavage of Eptifibatide intermediate.

<i>DoE setup</i>		<i>Parameters</i>	
Variables		EDT vol. %, TIS vol. %, H ₂ O vol. %, cleavage time at RT	
Response		Product purity [%], crude recovery [mg], peptide content [mg], PbF adduct [%], EDT adduct [%], tBu adduct [%], des-Acm Eptifibatide intermediate [%]	

Case study #2 had the objective to optimize the anti-solvent filtration rate of a precipitated Bivalirudin crude suspension without negative impact on product quality. Filtration optimization is a typical economic concern in large scale peptide manufacturing; it improves overall process duration and reduces production equipment allocation times. The impact of precipitation and filtration conditions (temperature during addition of anti-solvent to the peptide solution, temperature during aging of precipitated suspension, ratio of anti-solvent to peptide solution, and aging time) on product filtration rate and product quality attributes (product purity, peptide content, and crude recovery) was evaluated using DoE.

Fig. 1. Example of DoE results for case study #1. Impact of scavenger percentage on product purity (black line). Confidence interval of DoE results described by blue and green lines.

Table 2. Scope of DoE case study #2. Bivalirudin crude precipitation and filtration.

DoE setup	Parameters
Variables	Addition temperature, aging temperature, aging time, ratio anti-solvent to cleavage cocktail volume
Response	Filtration rate [$\mu\text{L/s}$], aspect of filtration [semi-qual.], product purity [%], peptide content [%], crude recovery [%]

Both the temperatures during anti-solvent addition and during aging were identified as variables with a significant impact on Bivalirudin crude filtration rate, with increased filtration rate at higher addition and aging temperatures; other variables, for example aging time, turned out to be insignificant (Figure 2).

Fig. 2. DoE surface plot for case study #2. Impact of temperatures on filtration rate.

Summary

The concept of DoE is regularly used at Bachem for process development at different stages of peptide API manufacturing, particularly for the optimization of process steps with multiple variables. Different types of DoE are applied depending on the objective. The information obtained by application of the DoE concept has been proven essential for peptidic API manufacturing process characterization and qualification to satisfy regulatory expectations.

Acknowledgments

We thank Andreas Stadelmaier and Ralf Eisenhuth for their valuable contributions.

References

1. ICH guideline Q11 on development and manufacture of drug substances
2. DoE software MODDE 10.1 by UMETRICS