Robustness Studies for Albumin Fractionation Process Based on Design of Experiment (DoE)

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Abstract

Green Cross Corp. (Yongin, Korea) manufactures albumin (human) 20% solution (Albumin-GCC), for which the upper manufacturing process step includes the Cohn fractionation method. Recently, the development of a 25% albumin production process was proceeded based on a qualified small scale, and the whole process included fraction I+II+III, fraction IV and fraction V processes, just as the 20% albumin production process does. To the achieve quality by design (QbD) approached fractionation process, Design of Experiment (DoE) was performed. Critical quality attribute/performance attribute (CQA/PA) were chosen by references and previous knowledge. To confirm critical process parameters (CPPs) for each fractionation process, Preliminary Hazard Analysis (PHA) was conducted as a risk assessment. As a result, pH, ethanol concentration, temperature, membrane capacity, mixing RPM and the amount of filter aid were selected. DoE was applied to create a response surface model (RSM). The test results were analyzed using statistical software (JMP, version 11.2). Factors not significant with a p-value less than 0.05 were eliminated, and then model formulas were calculated with selected parameters. After the selection of a statistically significant factor, the model formulas for each CQA/PA were drawn. Using the formulas, design space was selected to meet the criteria of CQA/PAs, and the normal operating ranges (NORs) were derived from the contour profiler. As a result, the robustness for albumin 25% fraction I+II+III, fraction IV and fraction V processes was established.
Keywords : Quality by Design, Design of Experiment, Fractionation, Albumin

Results

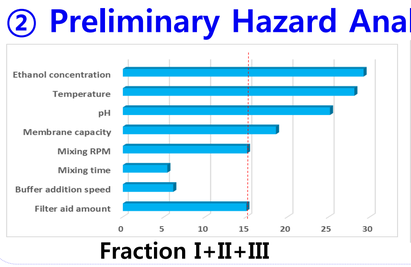
Procedures for process development

CQA/PA and CPPs

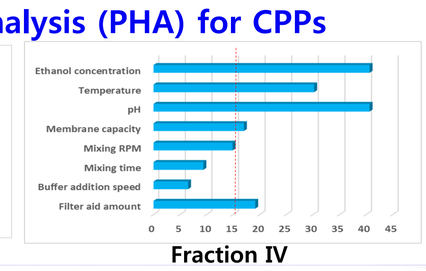
① Critical quality attribute/performance attribute chosen

Fraction I+II+III: Albumin yield, fibrinogen removal ratio, IgG removal ratio, IgM removal ratio, purity
Fraction IV: Albumin yield, IgG removal ratio, transferrin removal ratio, haptoglobin removal ratio, purity
Fraction V: Albumin yield, protein yield, polymers

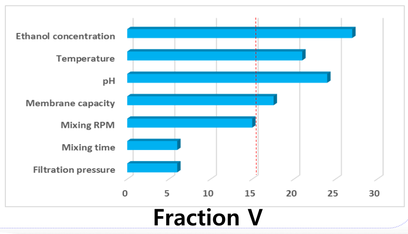
② Preliminary Hazard Analysis (PHA) for CPPs



Fraction I+II+III

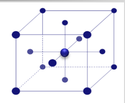
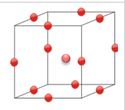
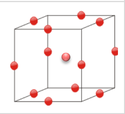


Fraction IV



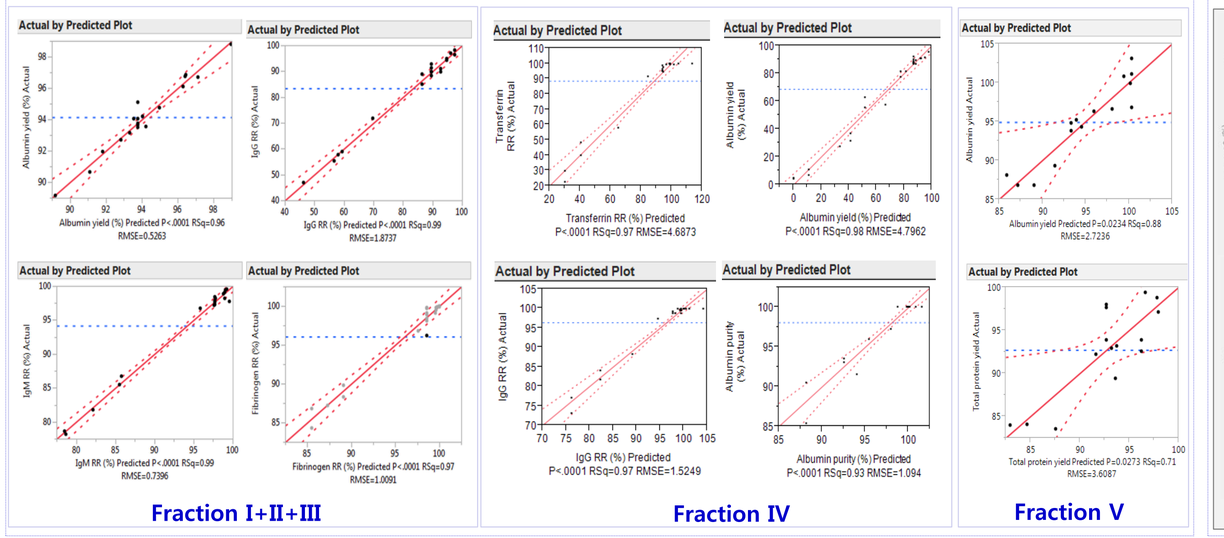
Fraction V

Design of Experiment

Process	DoE model	Experiment no.	Process parameters for DoE	Process parameters for single variable study
Fraction I+II+III	RSM (Central composite face-centered)	20 runs (Center point : 3 runs) 	Ethanol, pH, temperature	Membrane capacity, Filter aid amount, RPM
Fraction IV	RSM (box-behnken)	15 runs (Center point : 3 runs) 	Ethanol, pH, temperature	Membrane capacity, Filter aid amount, RPM
Fraction V	RSM (box-behnken)	15 runs (Center point : 3 runs) 	Ethanol, pH, temperature	Membrane capacity, RPM

Results of Statistical Design of Experiment Analysis

Predicted plot

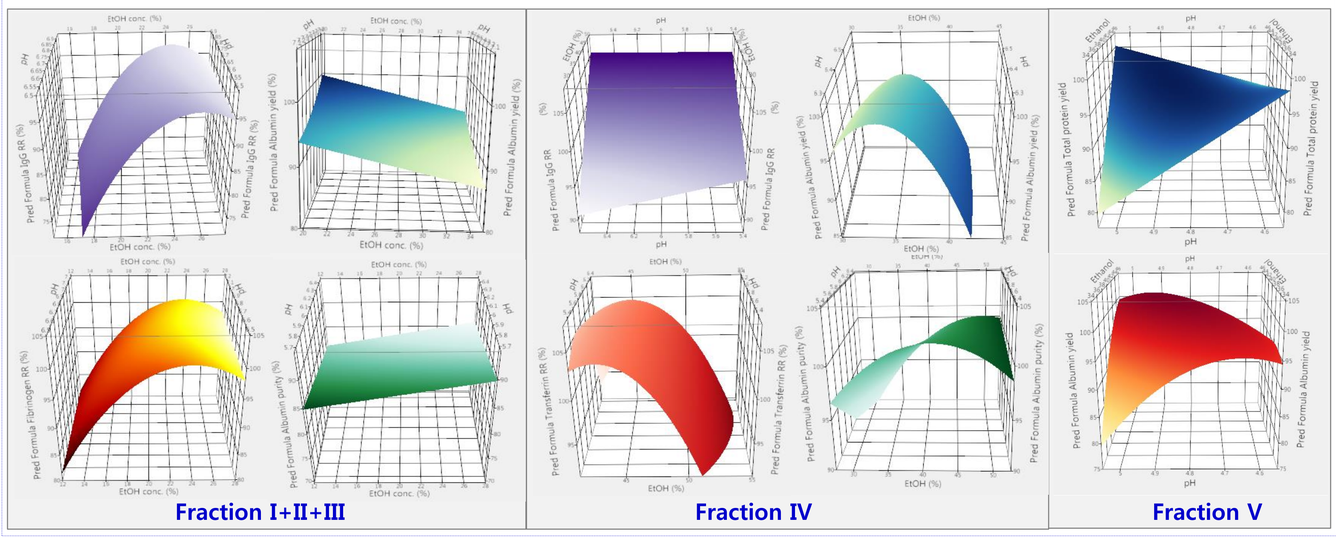


Fraction I+II+III

Fraction IV

Fraction V

Prediction profiler

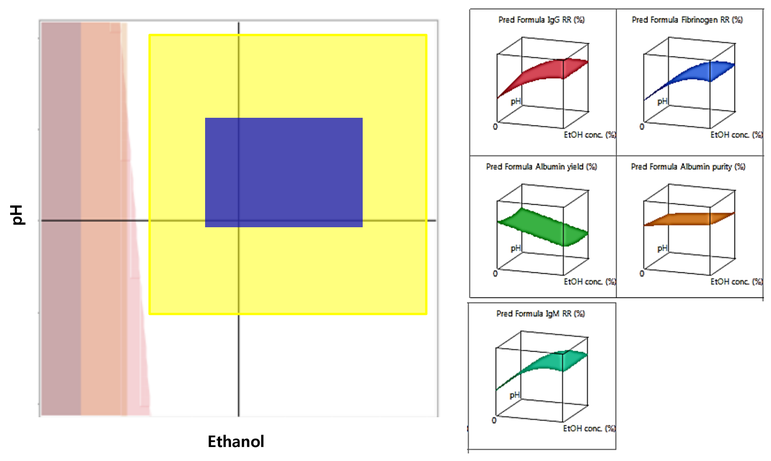


Fraction I+II+III　Fraction IV　Fraction V

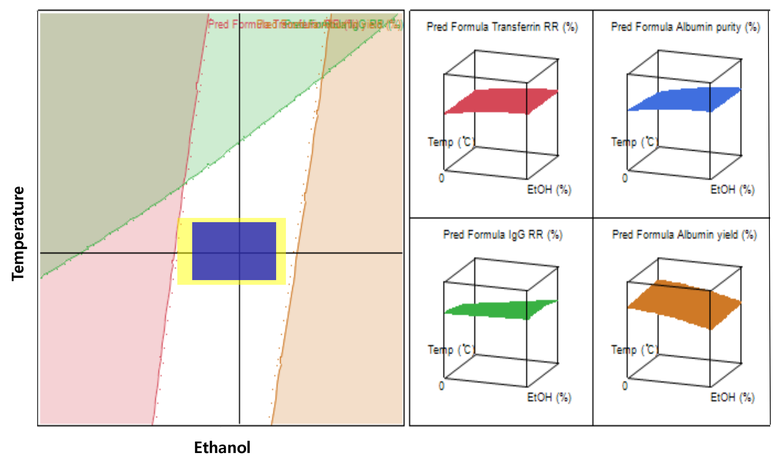
→ Results of statistical DoE analysis. If CQA/PA result were not deduced statistically significant formula, those CQA/PA were removed when set the design space.

Set the Design Space and Normal Operating Ranges

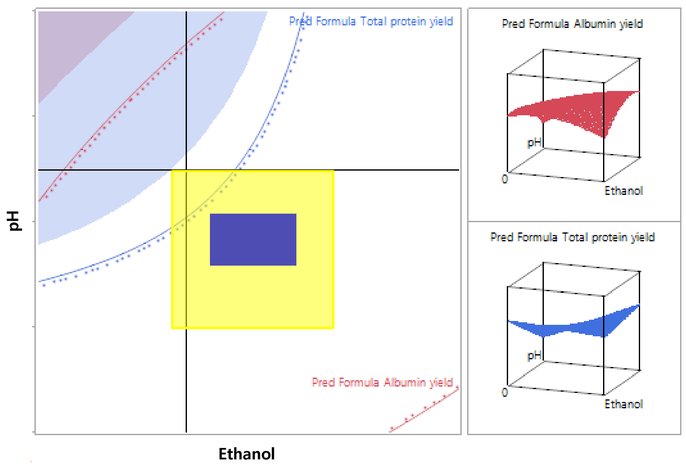
Fraction I+II+III



Fraction IV



Fraction V



→ Design space and normal operating ranges for fraction I+II+III, fraction IV and fraction V.

Conclusions

1. Based on DoE, the design space and normal operating ranges were set for each fractionation process.
2. As a result, robustness for albumin 25% fraction I+II+III, fraction IV and fraction V process was established.

References

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2. L. Yu, Pharmaceutical quality by design: product and process development, understanding, and control. Pharm. Res. 2008;25(4):781–791.