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DoE-Optimized Process for Residual Ethanol Reduction in Codaewon-S Syrup

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Introduction

Liquid formulations containing natural-derived ingredients may retain residual ethanol during manufacturing, necessitating a reduction strategy to ensure regulatory compliance. In this study, a Design of Experiments (DoE) approach was employed to systematically optimize the ethanol reduction process and incorporate the findings into the Common Technical Document (CTD) for regulatory approval. Critical process parameters and their interactions were analyzed to determine the optimal manufacturing conditions. This work focuses on a DoE-driven ethanol reduction strategy and evaluates its impact on regulatory compliance and product quality.

Methods

1. Critical process parameters for Ethanol Reduction

To effectively reduce ethanol content while maintaining product quality and process stability, it is essential to identify and optimize key process parameters. Several factors, including temperature, heating time, additional purified water volume, preparation tank pressure, and batch scale, influence ethanol reduction efficiency. This section outlines the critical process conditions that were optimized to ensure consistent and reproducible ethanol reduction.

1) Temperature

As temperature increases, ethanol reduction efficiency improves; however, previous studies have shown that excessive heat can lead to product quality degradation and instability. Therefore, to maintain process consistency and ensure product stability, the maximum temperature was limited to 80°C

2) Heating time

The required heating time varies depending on the type and performance of the equipment used, and an optimal balance between temperature and exposure time must be maintained to ensure effective ethanol reduction. If the heating time is too short, ethanol removal may be insufficient, whereas excessively long heating durations can lead to unnecessary energy consumption, alterations in product characteristics, and increased solvent loss. Therefore, the point at which the target ethanol reduction is achieved must be clearly defined and incorporated into process control.

3) Additional Purified Water Volume

During the ethanol reduction process, solvent loss (ethanol and water) may lead to phase separation of the raw material. To prevent this phenomenon and maintain process stability, the addition of purified water was necessary.

4) Preparation Tank Pressure and Batch Scale

Ethanol reduction efficiency is influenced by batch size (scale) and tank pressure, requiring adjustments to establish optimal process conditions. Lower tank pressure enhances ethanol reduction efficiency and can shorten processing time. Additionally, since process conditions may vary depending on batch size, batch size must be considered to ensure consistent outcomes.

To systematically analyze the process parameters described above, they were defined as factors.

Category	Factor
Independent Variables (Factors)	Heating Temperature
	Heating Time
	Additional Purified Water Volume
Dependent Variables (Responses)	Residual Ethanol Content
	Appearance (Precipitation / Phase separation)
Fixed variables	Batch Scale : 3 kg
	API Lot No.
Noise Factors*	Tank Pressure
Experimental Range	Temperature (50-80°C)
	Time (30-90 min)
	Water Volume (20-70%)

* A factor that affects the dependent variable but can not be identified or controlled.

2. Preliminary Experiment

To establish an ethanol reduction process for the DoE study, a preliminary experiment was conducted to determine the independent variables, specifically the heater's transfer fluid temperature and the internal temperature of the preparation tank.

1) Ethanol Reduction Process

· **Preparation of Feed solution:** Ethanol was added to the raw material solution to achieve a final concentration of 13% w/w, simulating the initial process conditions.

· **Preheating process:** The prepared solution was transferred into the preparation tank, where the transfer fluid temperature of the heater was adjusted to a setpoint to achieve the target internal temperature.

· **Vacuum Degassing process:** The degassing process commenced once the internal temperature reached the target setpoint, with the vacuum pump activated to initiate ethanol reduction, while the internal temperature (°C) and pressure (mmHg) were recorded at different time intervals.

2) Result

· **Stabilization of Internal Temperature During Degassing:** The heater's transfer fluid temperature was controlled to maintain the internal temperature at the target level during the degassing process.

Time (min)	0	1	2	4	5	12	19	23	60
Internal Temp. (°C)	80	81	82	77	75	77	79	80	81
Internal Pressure (mm·Hg)	760	600	500	395	380	395	410	410	390
Remark	SV : 135 °C	Foaming	boiling						

* The internal temperature remained stable throughout the degassing process, confirming effective temperature control.

· **Influence of Heater Transfer Fluid Temperature on Internal Temperature:** The internal temperature of the preparation tank varied depending on the setpoint of the heater's transfer fluid temperature.

Heater set temp. (°C)	Internal Temp. (°C)	Internal Pressure (mm·Hg)
70	50	120
100	60	210
135	80	390

* Adjusting the heater's transfer fluid temperature allowed precise control of the internal temperature to meet target conditions.

· **Influence of Additional Purified Water volume on Heater Temperature Setpoint:** An increase in the amount of additional purified water led to a higher evaporation rate and stabilized the vacuum level, resulting in a rise in internal temperature, which consequently necessitated a lower heater transfer fluid set temperature to maintain the target internal temperature.

Additional Purified Water (%)	Heater set temp. (°C)	Internal Temp. (°C)	Internal Pressure (mm·Hg)
20	145	80	360
45	140	80	375
70	135	80	390

3) Discussion

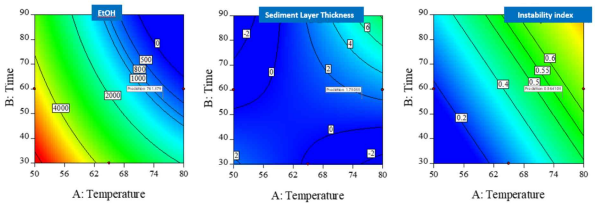
The internal temperature of the preparation tank was selected as an independent variable for the DoE study and was confirmed to remain stable under vacuum conditions. By setting the additional purified water volume at 70% and adjusting the heater's transfer fluid temperature to 135°C, the internal temperature was effectively maintained. This experiment demonstrated that the ethanol reduction process could be stably conducted while maintaining the target temperature.

Results

1. Contour Plot Analysis of Ethanol Reduction Process

A Box-Behnken Design-based Response Surface Methodology (RSM) was employed to evaluate the influence of key process variables and to establish a design space for ethanol reduction.

- Pelargonium sidoides extract, which contains 9.0–13.0% w/w ethanol, was processed to ensure that the residual ethanol content remained below 900 ppm.
- During the ethanol reduction process, solvent (ethanol and water) loss led to the formation of insoluble particles, which needed to be minimized to maintain product stability.



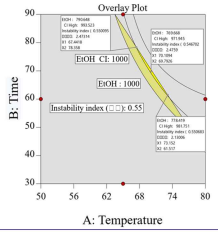
Contour plots were generated to illustrate the effects of temperature (A) and time (B) on key response variables, including residual ethanol content, precipitation thickness, and instability index.

2. Optimization and Model Verification

An overlay contour plot was used to simultaneously visualize acceptable regions for residual :

- Residual ethanol content (EtOH ppm < 1,000),
- Sediment layer thickness (< 3 mm)
- Instability index (< 0.55)

The acceptable design space was identified in the range of ~75°C and 60 minutes, with desirability values > 0.80, satisfying all critical quality attributes.



3. Numerical Optimization and Reproducibility

Using desirability-based optimization, five combinations were shortlisted. Two representative conditions were experimentally verified. All observed values were consistent with the model-predicted range :

Condition	EtOH (ppm)	Sediment (mm)	Instability Index	Desirability
75°C / 60min / 70% DW	780 (pred: 657.7)	3.0 (pred: 2.16)	0.548 (pred: 0.571)	0.851
75°C / 70min / 70% DW	720 (pred: 774.3)	3.0 (pred: 2.47)	0.577 (pred: 0.546)	0.828

This validation confirms the statistical reliability and experimental reproducibility of the predictive DoE model.

4. *Scale-Up and Validation*

Pilot-scale and mid-scale validation studies were conducted to assess the scalability of the optimized process. Processing parameters were extrapolated to match ethanol evaporation dynamics at increasing batch sizes.

- A. Ethanol Extract-Based System

Filling Ratio	Condition (Temp / Time)	EtOH (ppm)
10%	75°C / 60 min	530
34%	80°C / 180 min	550
68%	80°C / 380 min	460

- B. API Solution System

Filling Ratio	Condition (Temp / Time)	EtOH (ppm)
10%	75°C / 60 min	780
34%	80°C / 180 min	670
68%	80°C / 380 min	670

5. *Scale-up Time Modeling*

Processing time was linearly correlated with Filling ratio. The predicted time for a 556 kg full-scale batch was 8.7 hours, assuming similar heat transfer efficiency as in lab-scale equipment.

Filling Ratio	Processing Time (hr)
10%	0.9 (actual)
34%	3.0 (actual)
68%	6.3 (actual)
100%	8.7 (predicted)

These result validate the process robustness across multiple scales and support its industrial implementation for compliant ethanol reduction.

Conclusion

This study employed a DoE approach to optimize and scale up an ethanol reduction process for Codaewon-S Syrup. The validated process effectively minimized residual ethanol while preserving formulation stability, meeting regulatory requirements. The successful 500 L commercial-scale validation demonstrates industrial feasibility, offering a robust strategy for large-scale pharmaceutical liquid formulations. Long-term stability studies confirmed product consistency over time.

Acknowledgement

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