Development of a soft sensor for solute monitoring and supersaturation feedback control of batch cooling crystallization

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Introduction

Technological advancements in the past decade have significantly enhanced process analytical technology (PAT), which is now crucial for real-time monitoring and control of critical process parameters, highlighting one of the main aspects of Quality by Design (QbD) and Quality by Control (QbC) principals. This research aims to develop a methodology for continuous solute monitoring and control of the supersaturation level during cooling crystallization, a critical step in production of active pharmaceutical ingredients (APIs). This research further describes the development of a soft sensor for monitoring solute concentration and supersaturation control during the cooling crystallization of the ceritinib.

Materials and Methodology

Materials

- Ceritinib (model compound)
- Tetrahydrofuran

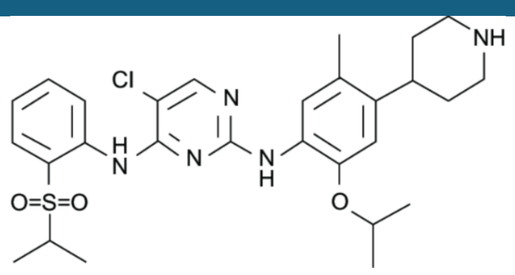

Figure 1. Ceritinib molecule

Equipment setup

1. Reactor
2. Temperature probe
3. ATR-UV/Vis
4. Turibidimeter
5. Agitator
6. PC
7. Thermostat

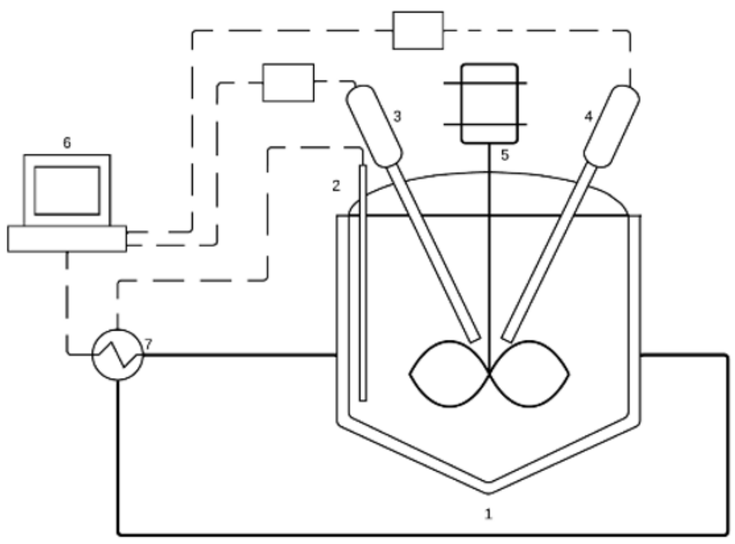

Figure 2. Schematic of equipment setup

Solubility Determination

- Constant heating rate 0.15 °C/min
- Turbidity measurement Blaze 900 process microscope
- Solubility model - modified Apelblat model

UV/Vis Spectra and Temperature Collection for Model Building

- UV/Vis spectra in the 200 – 800 nm range
- Calibration data set – Sepctra and temperature for 9 different concentrations
- Validation data set – Sepctra and temperature for 3 different concentrations

Data Preprocessing

1. Truncated Spectra and standardized temperatures
2. Truncated + smoothed Spectra and standardized temperatures
3. Truncated + derived Spectra and standardized temperatures

Model Building

- Artificial Neural Network (ANN)
- Partial Least Square Reggresion (PLSR)
- Test set validation

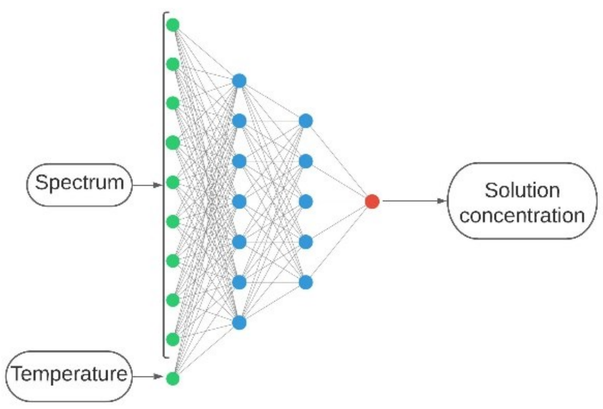

Figure 3. ANN for solution concentration prediction

Supersaturation control expiriment

- Constant superstaturation – 50 g/kg solution
- Starting concentration – 235 g/kg solution

Results

Solubility

- High accuracy of solubility model – $R^2 = 0.99$

Solubility model

$$C^* = \exp\left(30.41 - \frac{109.02}{R \cdot T} - \frac{-113.00}{(R \cdot T)^2}\right)$$

UV/Vis Spectra and Temperature Collection

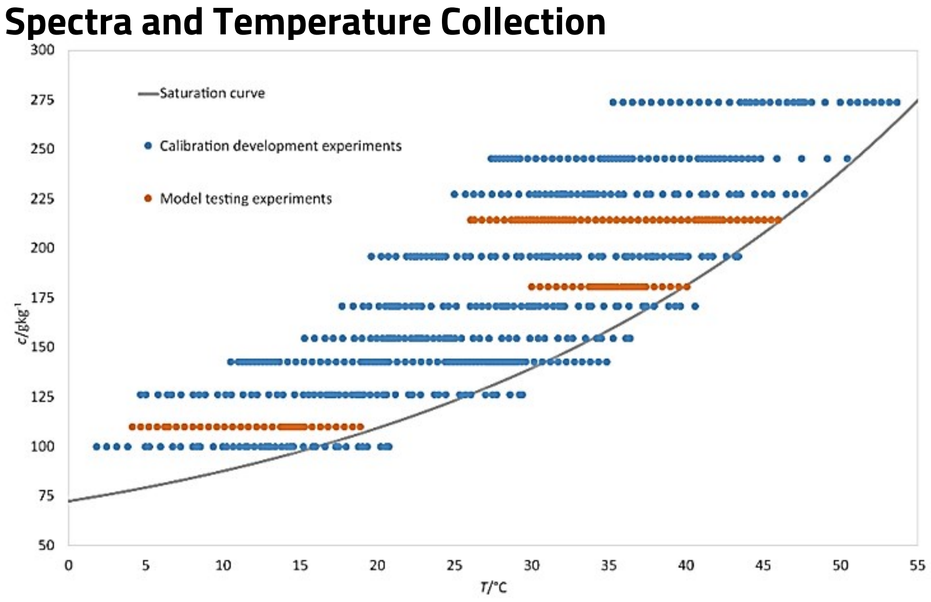

Figure 4. Collected data for ANN and PLSR model building and testing

Data Preprocessing

- Preprocessed spectra - First derivative (Savitzky-Golay filter)
- Preprocessing removed noise and baseline shifts

Model Building

- High accuracy models, ANN models showed higher accuracy

Table 1. Comparison of RMSEP for ANN and PLSR models

Type of used method	RMSEP (g/kg solution)
ANN	0.4
PLSR	1.3

- Both (ANN and PLSR) models are usable for supersaturation control

Supersaturation control

- Constant supersaturation during whole experiment
- Controlled process without significant oscilations
- Promoted crystal growth, supresed secundary nucleation

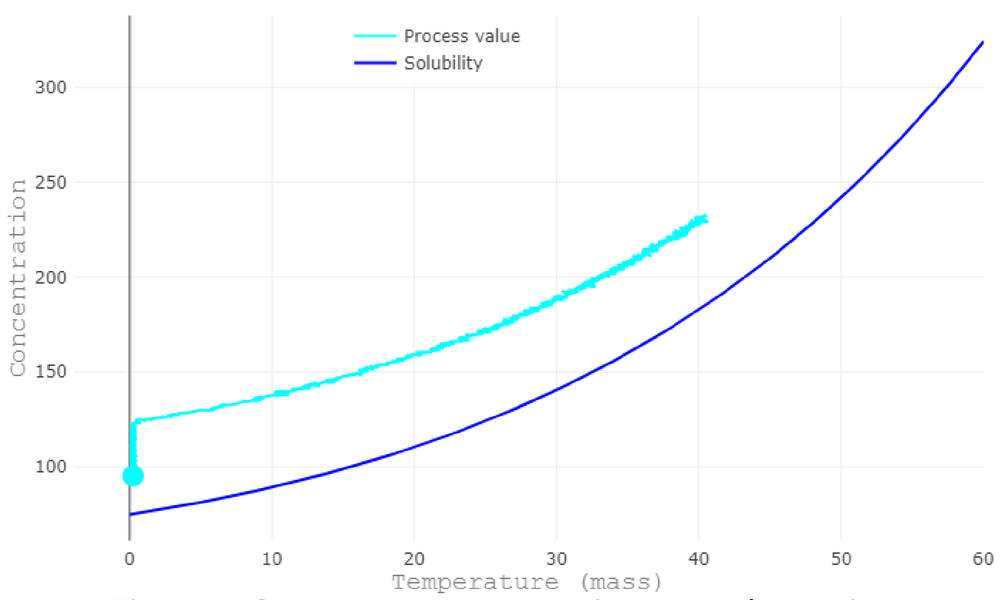

Figure 5. Constant supersaturation control experiment

Conclusion

The developed soft sensor played a key role in the successful execution of a supersaturation control strategy during crystallization, Implementing this methodology during the development of the cooling crystallization process results in a deeper understanding and development of the more robust process.

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