

From Screening to Scale-Up: A Progressive Experimental Workflow for Characterizing Phase Behavior

by Ceresana©
FoB:Pack
Future of Bio Packaging2026

Mona Amrihesari, Ph.D. / Application Specialist

Technobis

Technobis



Crystal BREEDER



Crystal 16

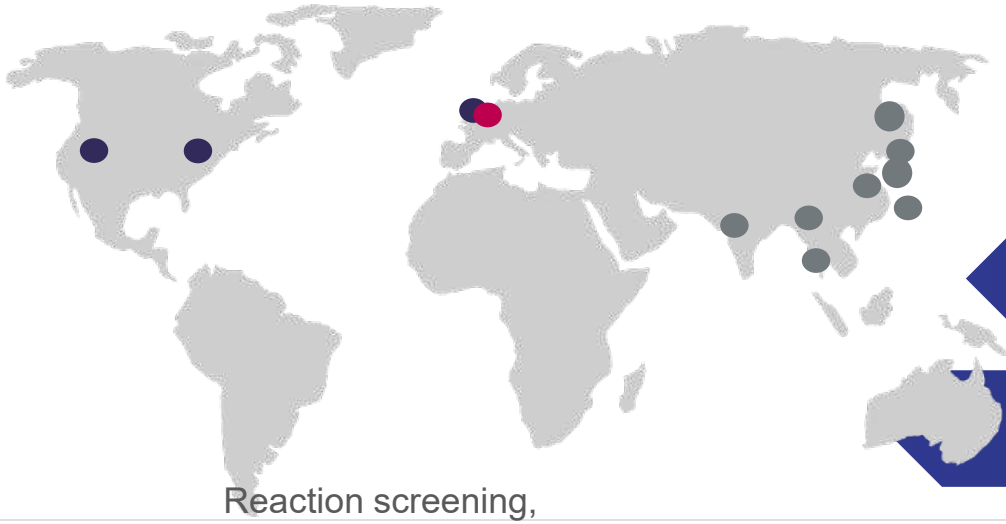


Crystal LINE



React ALL

MERCK, Lilly, UCB, Bayer, Amgen, Novartis, Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, abbvie, sanofi aventis, Bristol-Myers Squibb, Eisai, BASF, Teva, Johnson & Johnson, GSK



- In Business since 2005, 65+ employees on group level
- 800+ systems in the field, 3 product lines in our portfolio
- We have a global reach and presence, including a service organization
- Active in Pharmaceutical, Agrochemical, Food and Personal Care and Academia

Reaction screening,
Crystallization, Process development and Formulation

Technobis

Technobis Portfolio

Product Line:
Crystallization Screening

Crystal BREEDER | Crystal 16 | Crystal LINE







SOON!

2014	2022	2022	2026
CrystalBreeder	**Crystal16 V3**	**Crystalline V2**	**CrystalDose**

NEW!

Product Line:
Reaction Screening

React ALL | Dose ALL

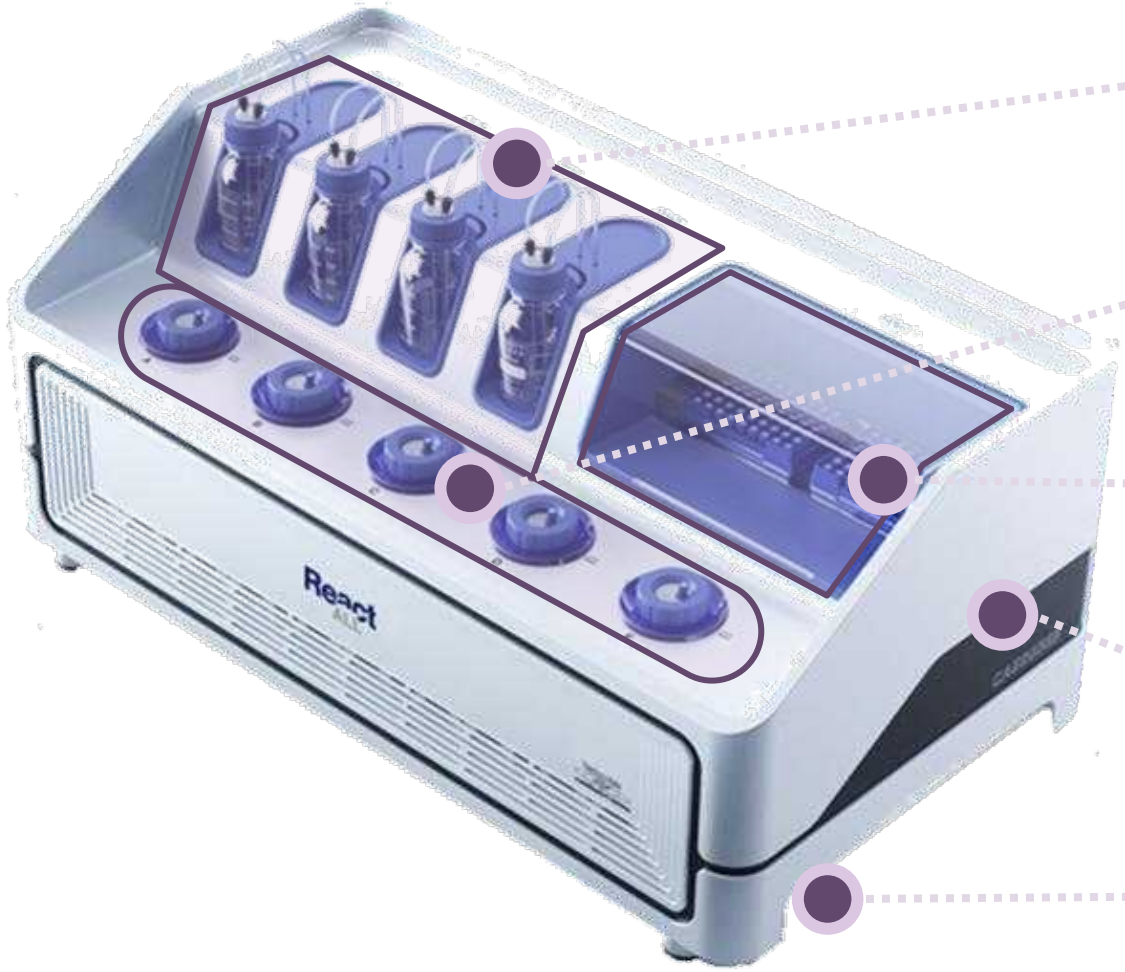




2024	2025

Technobis

Reaction Screening Product line - ReactALL



Quench-Dilute-Rinse & Waste Station

4 solvent- and waste reservoirs for ***individualized choice of QDR-solvents***

Reactor Blocks

5 identical, independent reactor blocks with ***automated sampling***

Sample Preparation

Dispensing of samples to ***staandard HPLC vials***

Software User Interface

Intuitive, user-friendly, tile-based drag & drop-programming

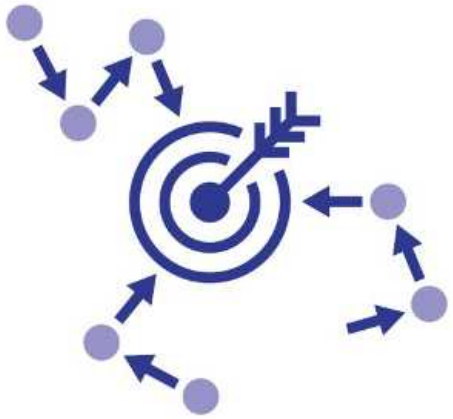
Small Footprint

Designed to ***fit in standard fume hood***

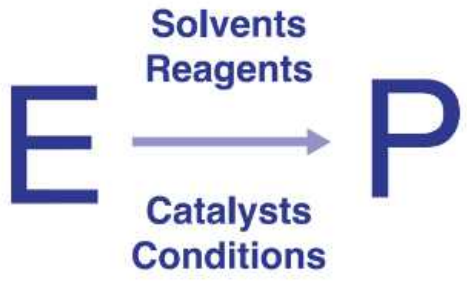
Technobis

ReactALL – Target Applications

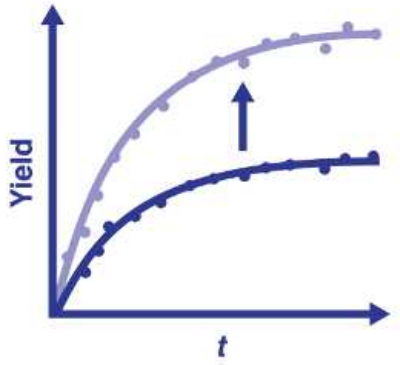
Route Scouting



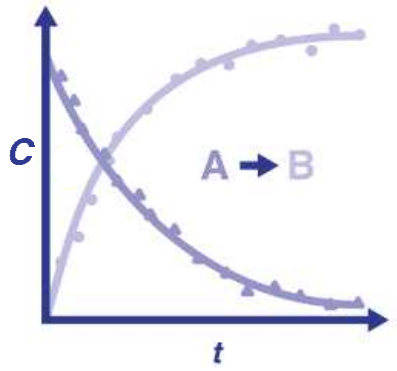
Reaction Screening



Reaction Optimization



Reaction Profiling & Kinetics



Technobis

Crystallization Products Line

Crystal BREEDER



0.06 – 0,2 ml
32 reactors



Crystal 16



0.5 – 1 ml
16 reactors



Crystal LINE



2.5 – 5 ml
8 reactors



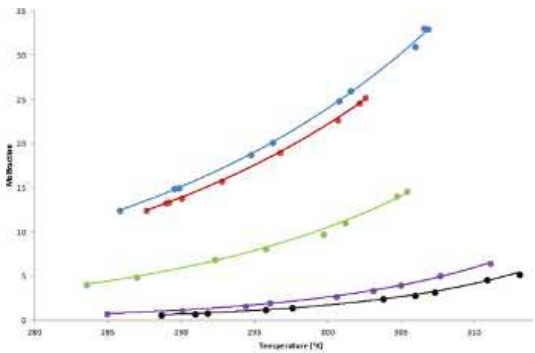
Discover

- Single crystals
- Solvent screening
- Solubility
- Solid state screening



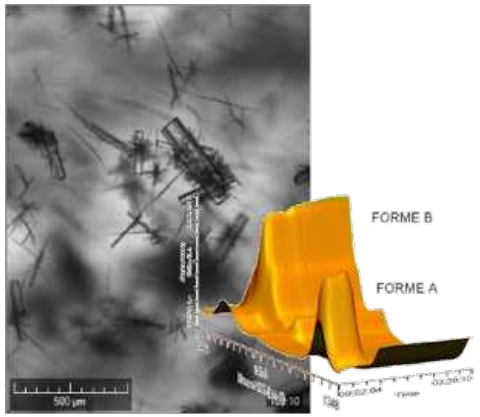
Screen

- Solubility, MSZW
- Nucleation rate
- Induction time measurements
- Phase diagrams
- Polymorphs, Salt and
- Co-crystals screening



Optimize

- Habit control
- Particle size
- Process optimization
- Formulation



Technobis

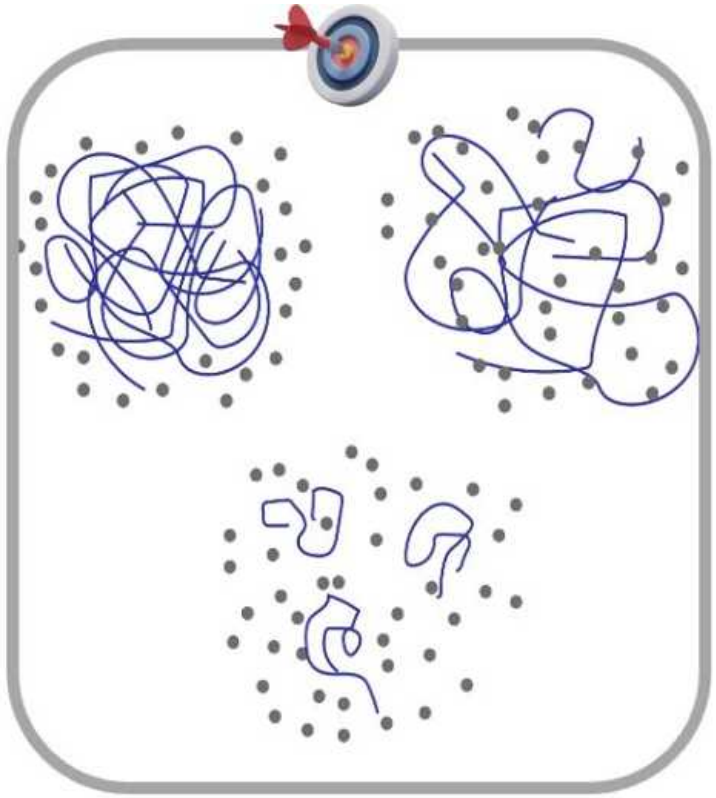
Greener future is possible with research



“Help Research Succeed”

https://www.un.org/sustainabledevelopment/blog/2015/09/why-should-you-care-about-the-sustainable-development-goals/

Accelerating polymer solubility screening for more sustainable process development

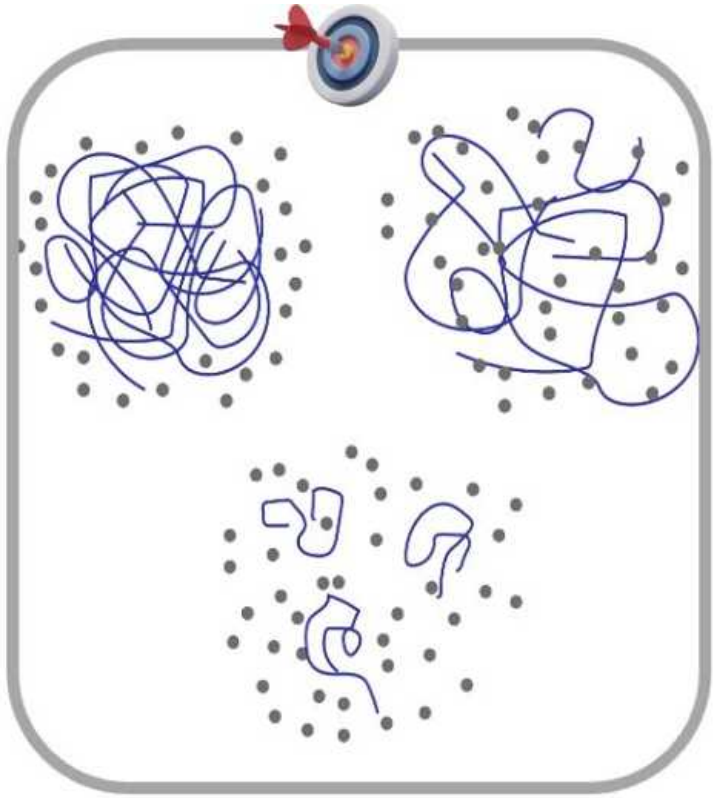


Polymer solubility screening

Accelerating polymer solubility screening for more sustainable process development



Swap dangerous/unsustainable solvents for green solvents



Polymer solubility screening

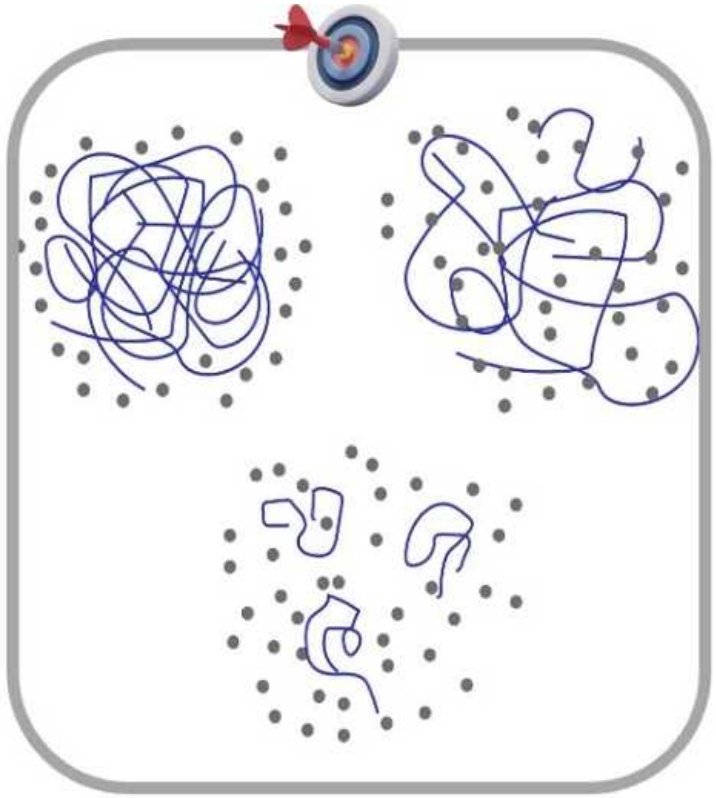
Accelerating polymer solubility screening for more sustainable process development



Swap dangerous/unsustainable solvents for green solvents



Replacing solvents that commercially banned



Polymer solubility screening

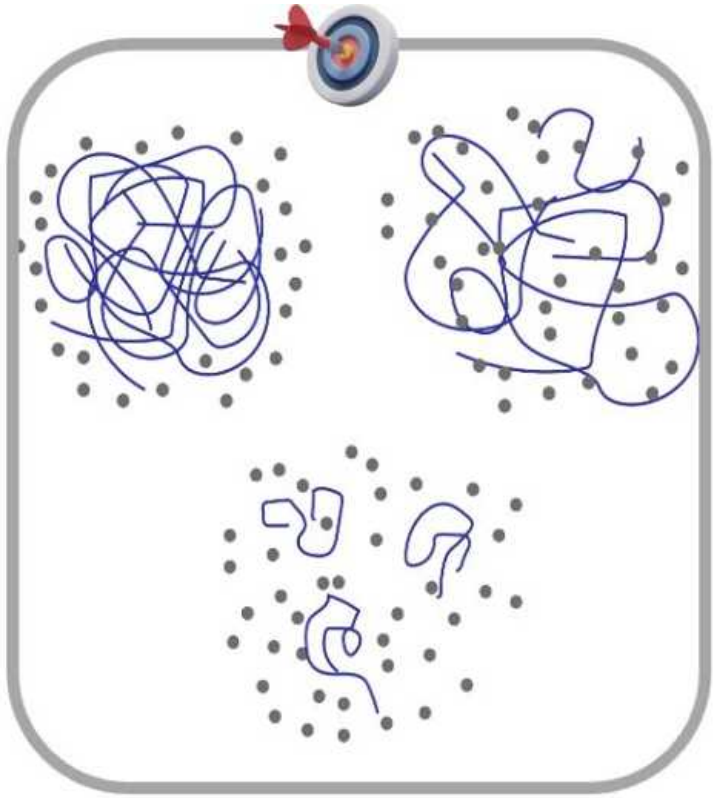
Accelerating polymer solubility screening for more sustainable process development



Swap dangerous/unsustainable solvents for green solvents



Replacing solvents that commercially banned



Polymer solubility screening



Decrease solvent usage

Technobis

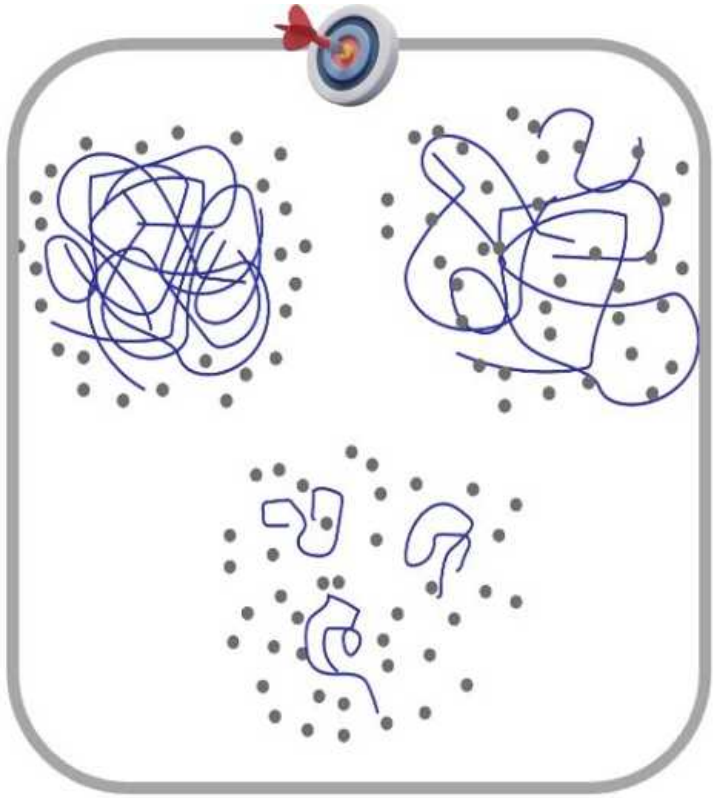
Accelerating polymer solubility screening for more sustainable process development



Swap dangerous/unsustainable solvents for green solvents



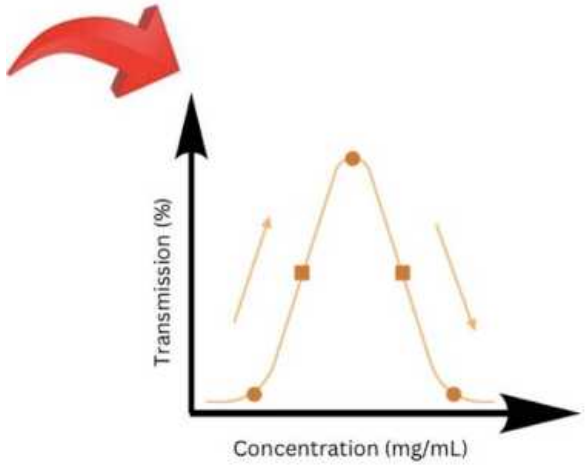
Replacing solvents that commercially banned



Polymer solubility screening



Decrease solvent usage



New dissolution/precipitation processes for separation

Technobis

How can polymer solubility screening be accelerated?

1

How do we generate reliable solubility screening process?
A comprehensive dataset on polymers!

What is the comprehensive data anyway?



There is no comprehensive data that captures all the factors that impact measured solubility

A comprehensive dataset should include key factors influencing the target property

Temperature



Concentration



Molecular weight

Measurement parameters



There is no comprehensive data that captures all the factors that impact measured solubility

A comprehensive dataset should include key factors influencing the target property

Temperature



Concentration



Molecular weight

Measurement parameters

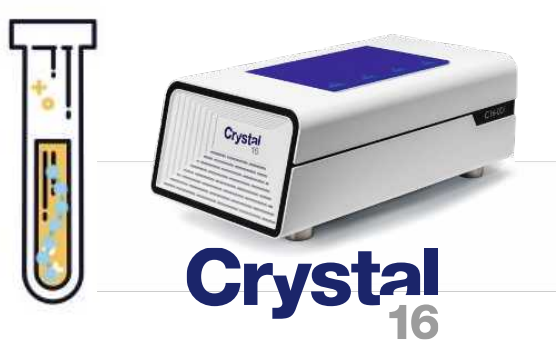


Developed a standardized method and built a dataset



Temperature-resolved turbidity measurements enable quantitative monitoring of polymer dissolution and precipitation

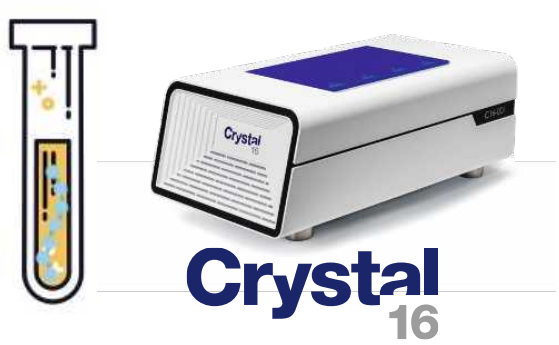
Turbidity measurement

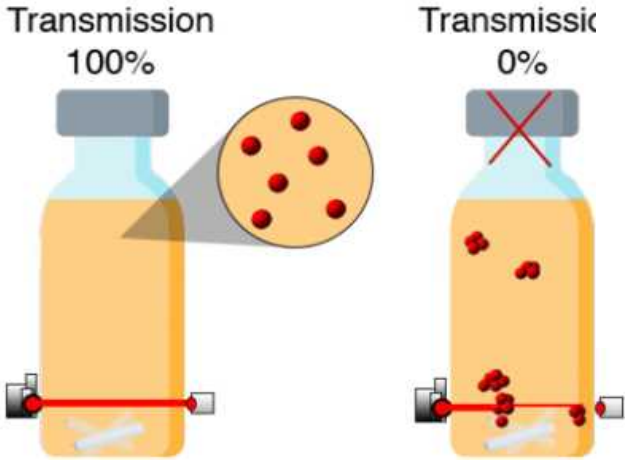


Amrihesari et al., Polymer, 2023

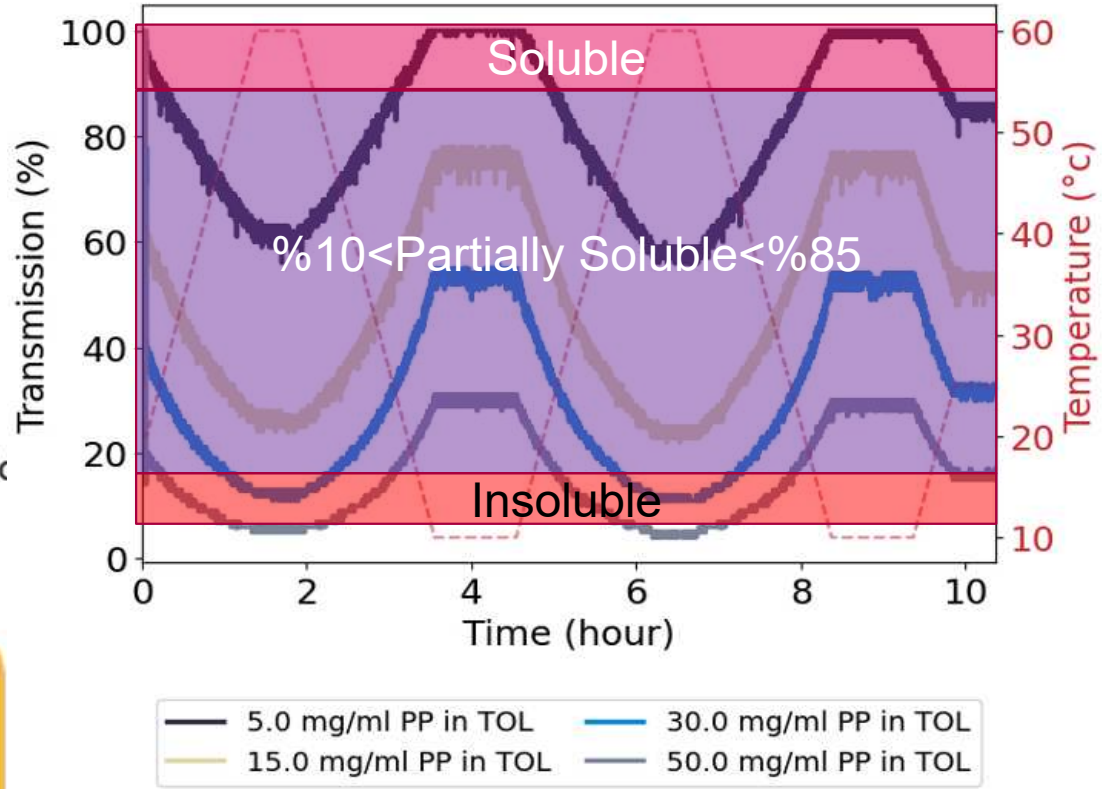
Temperature-resolved turbidity measurements enable quantitative monitoring of polymer dissolution and precipitation

Turbidity measurement





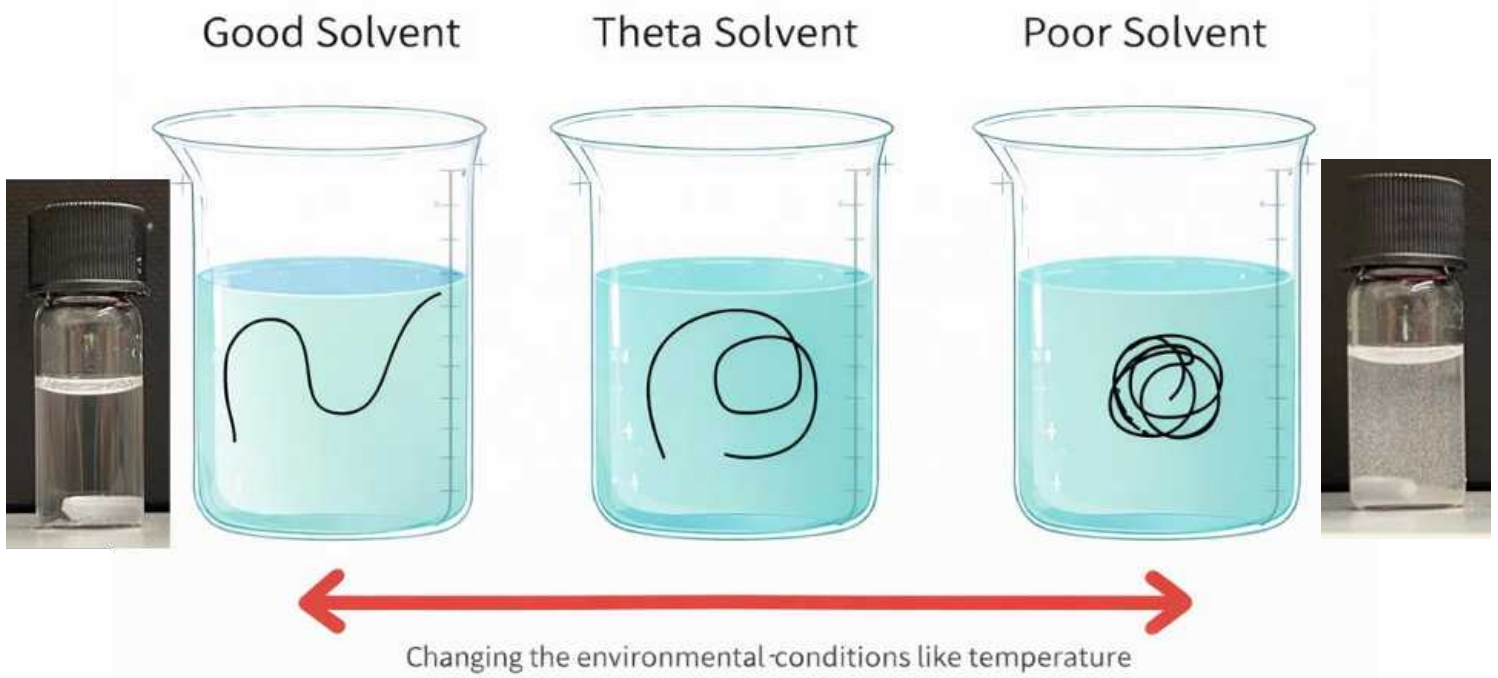
Polypropylene in toluene



Amrihesari et al., Polymer, 2023

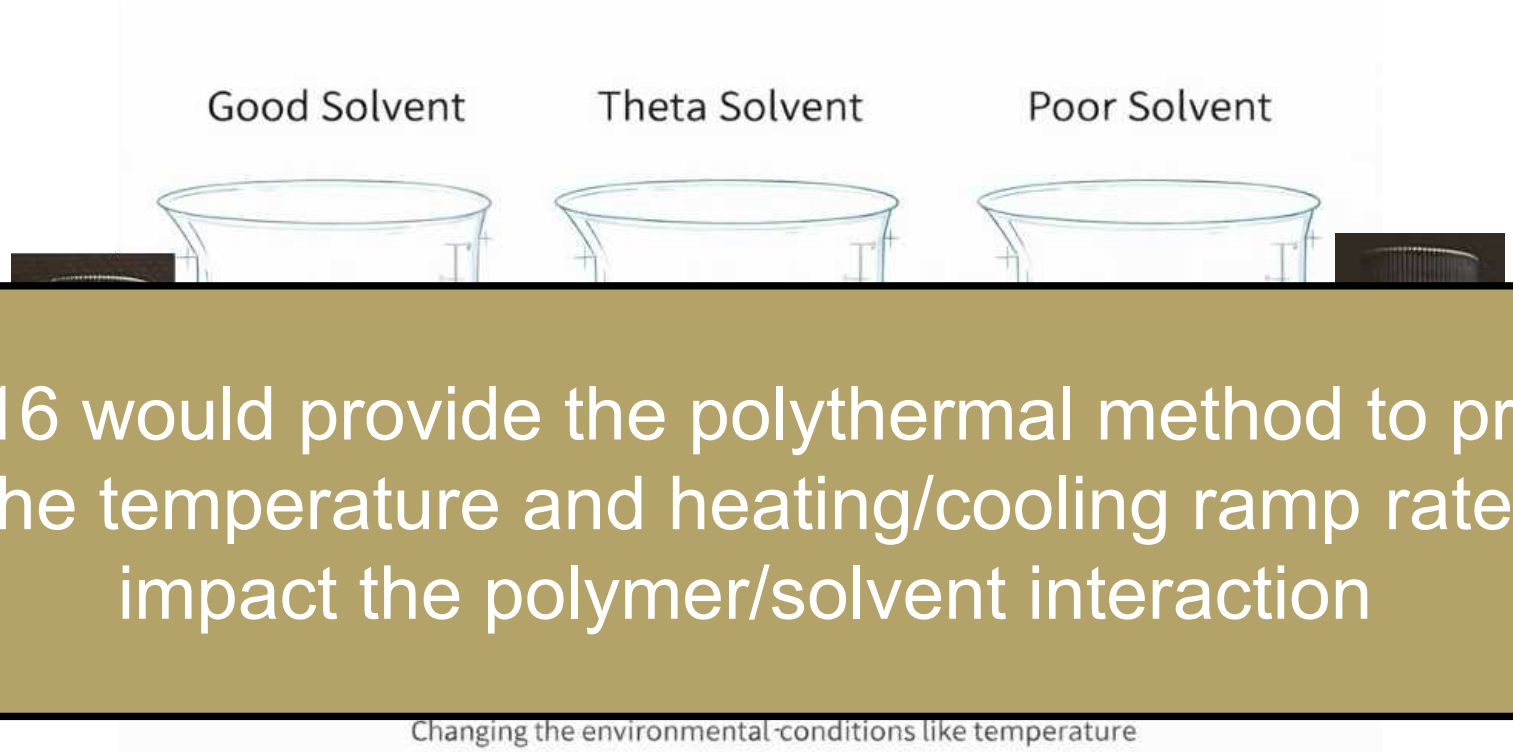
Technobis

Changing the environmental condition would lead to dissolution or precipitation of polymers



- Polymers are large molecules and move slowly
- Both kinetics and thermodynamic is important for phase separation

Changing the environmental condition would lead to dissolution or precipitation of polymers

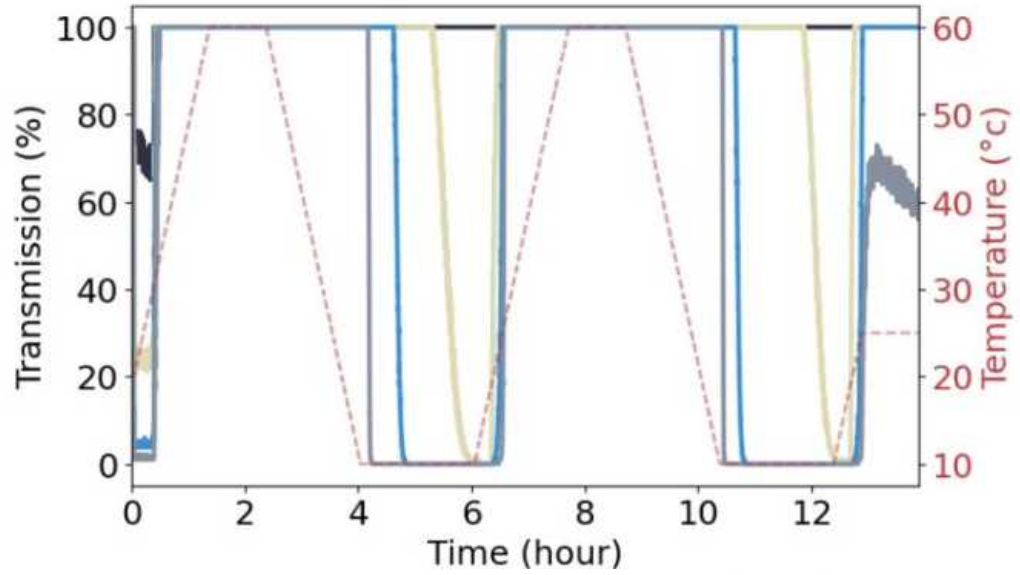


Crystal16 would provide the polythermal method to precisely control the temperature and heating/cooling ramp rates which impact the polymer/solvent interaction

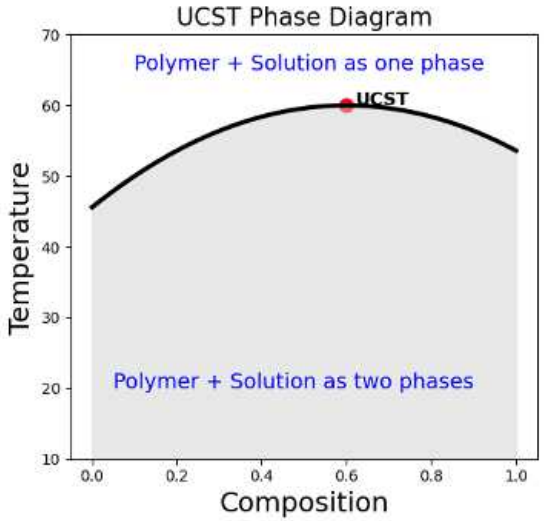
- Polymers are large molecules and move slowly
- Both kinetics and thermodynamic is important for phase separation

Capturing the phase behavior of polymers require an understanding of unique behavior of polymer solutions

Polyethylene glycol (PEG) in ethyl lactate



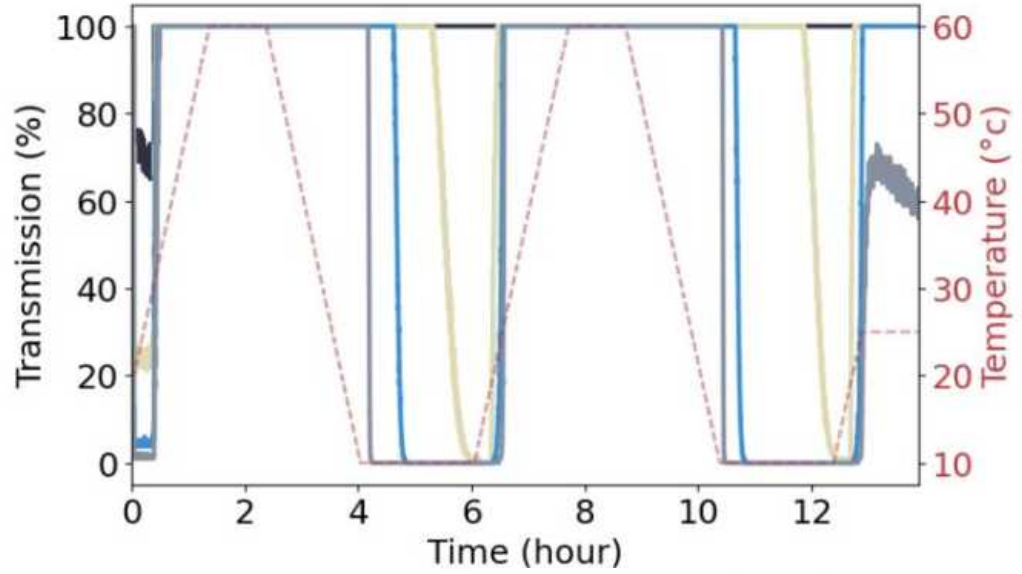
UCST: Upper Critical Solution Temperature



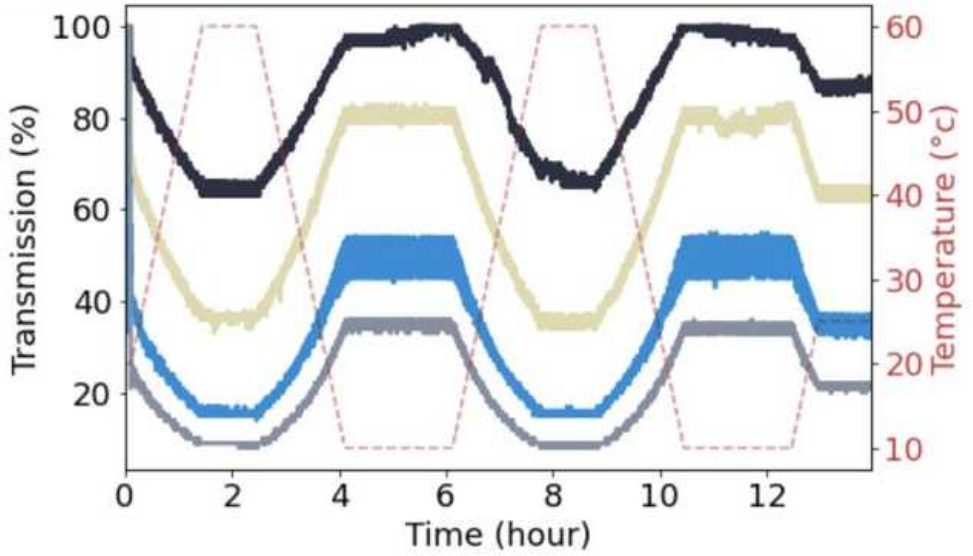
Technobis

Capturing the phase behavior of polymers require an understanding of unique behavior of polymer solutions

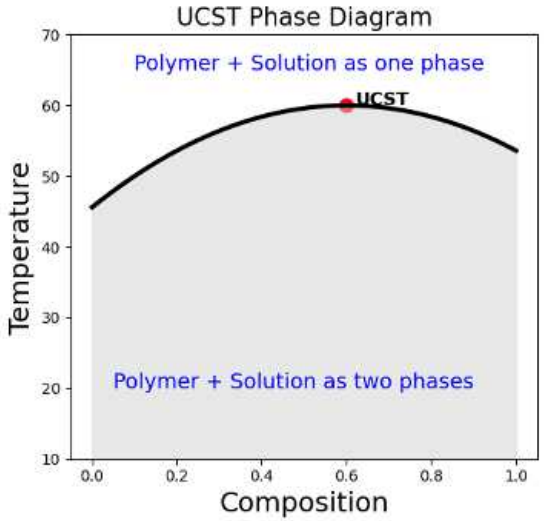
Polyethylene glycol (PEG) in ethyl lactate

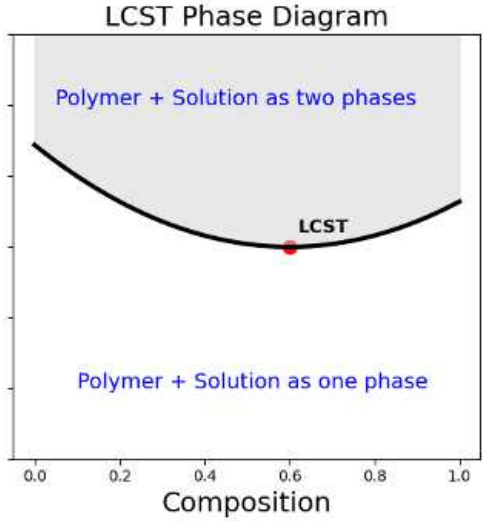


Polypropylene (PP) in 2,4,6-trimethylpyridine



UCST: Upper Critical Solution Temperature

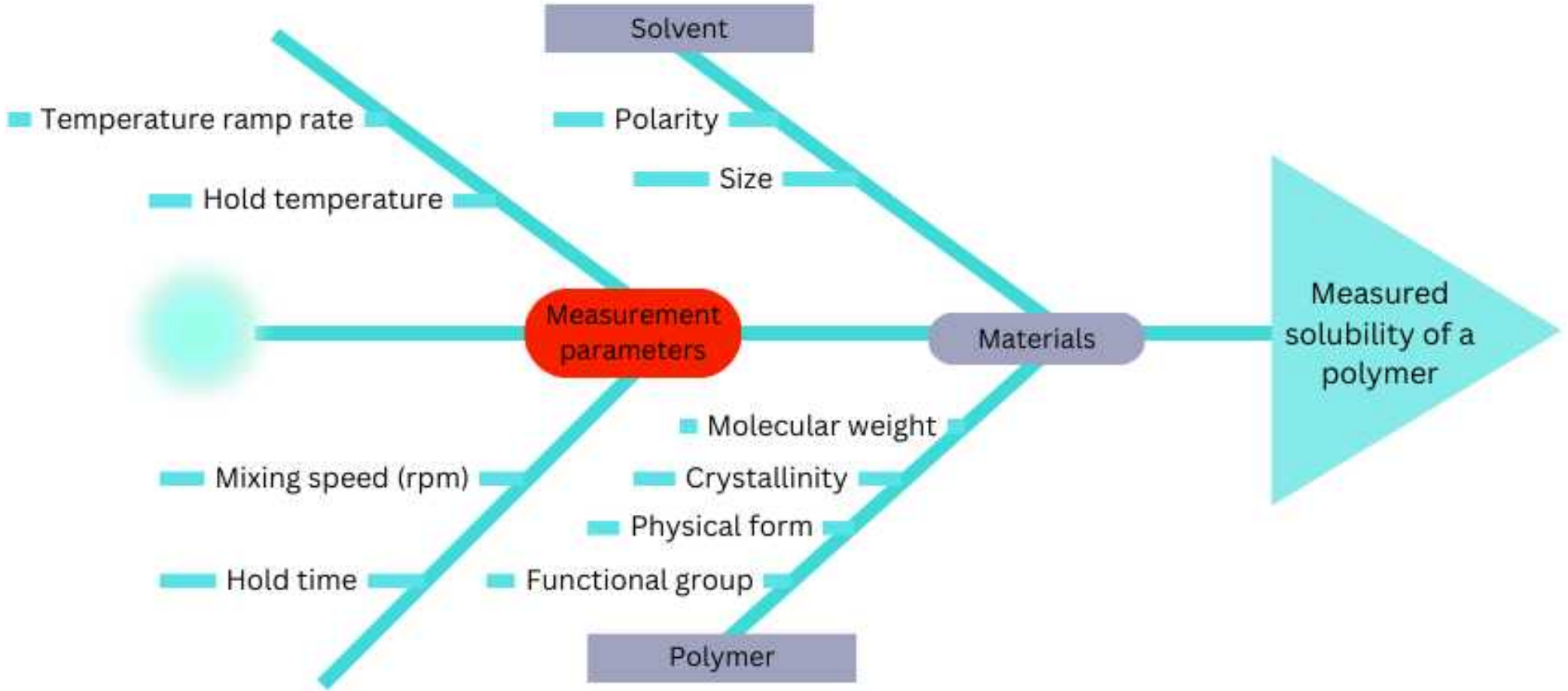




LCST: Lower Critical Solution Temperature

Technobis

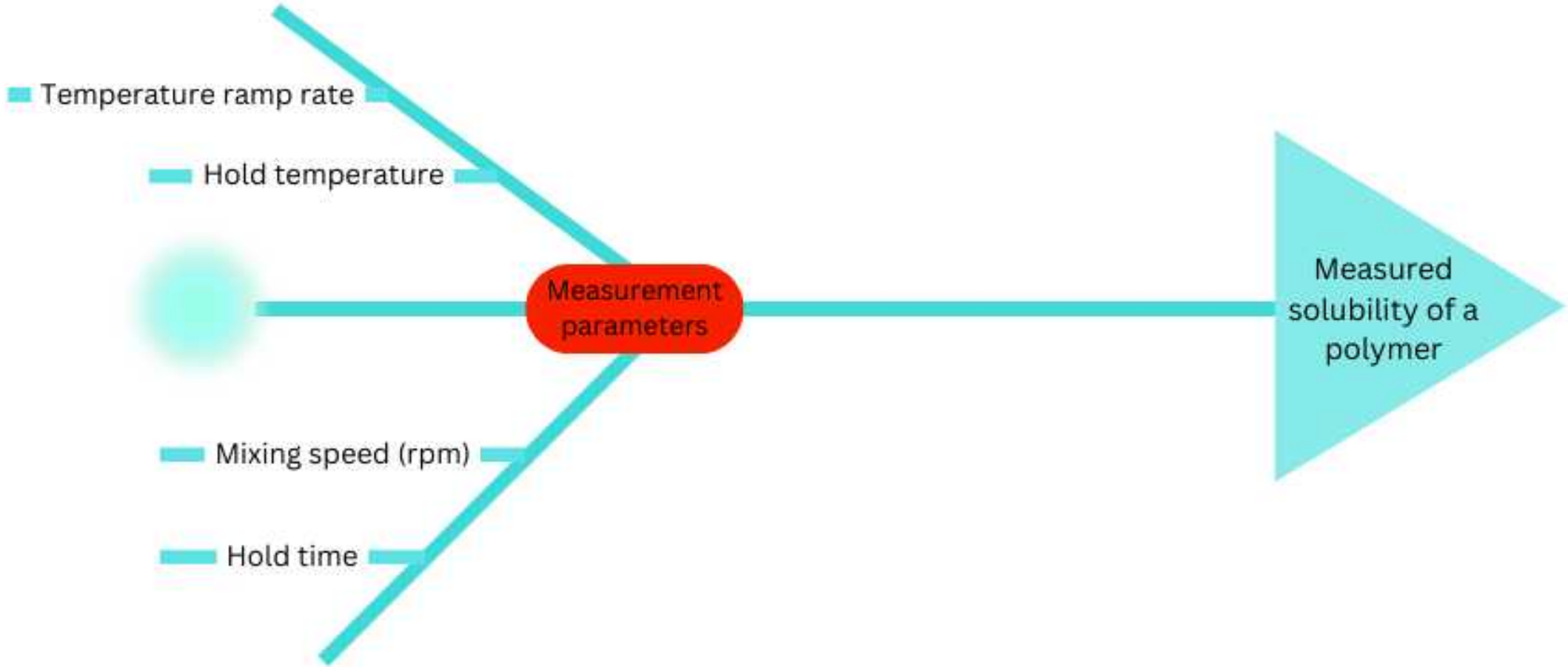
Standardized measurement parameters to enhance high-throughput data collection



Amrihesari et al., Polymer, 2023

Technobis

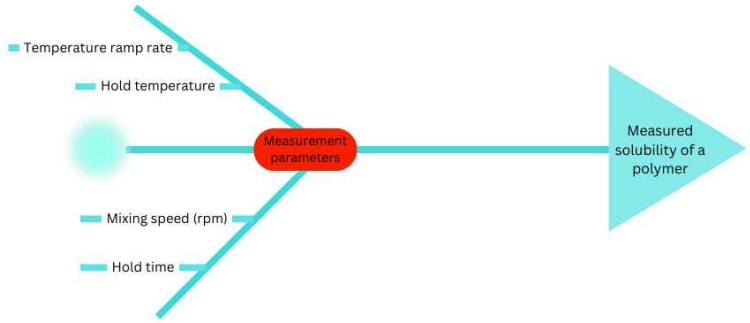
Standardized measurement parameters to enhance high-throughput data collection



Amrihesari et al., Polymer, 2023

Experimental design space for polymer solubility screening

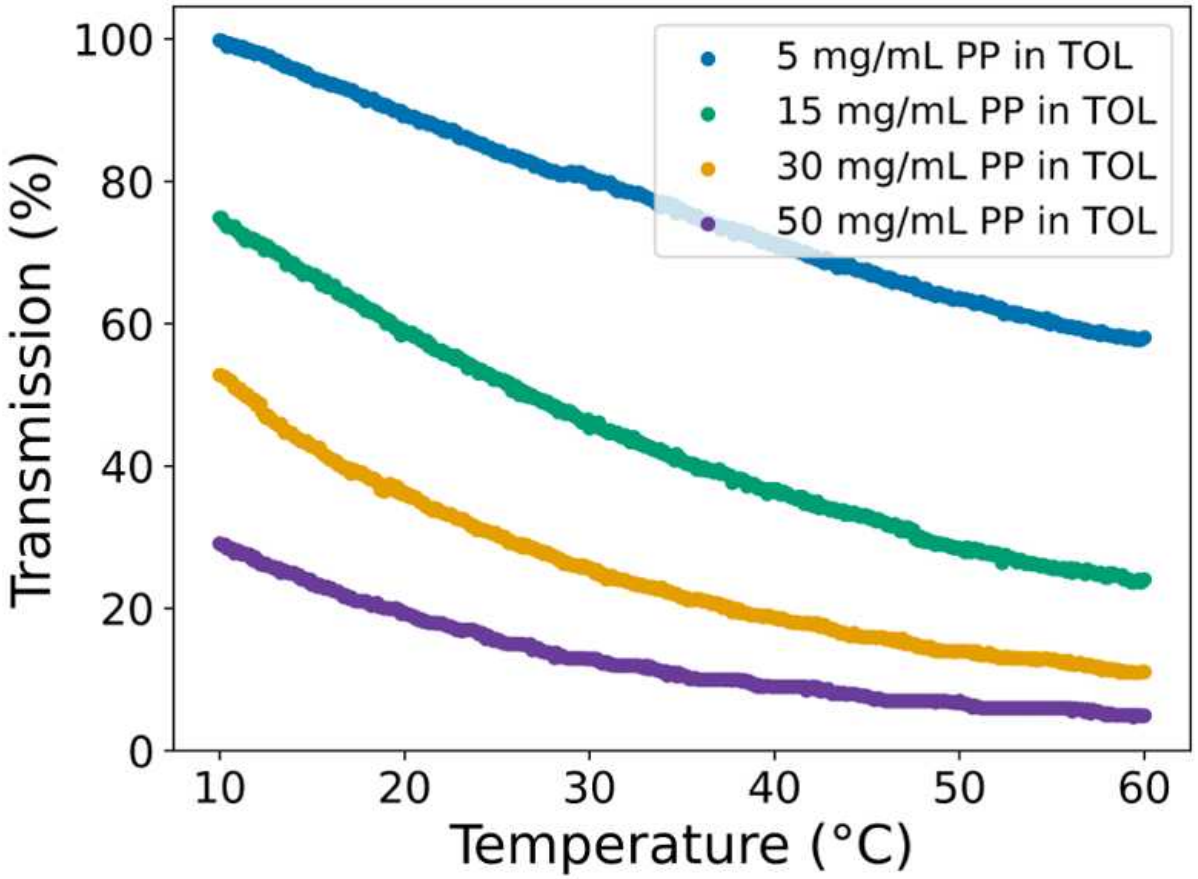
Parameter	Value 1	Value 2	Value 3	Value 4	Value 5	Value 6
Heating Ramp Rate ($\frac{℃}{min}$)	0.1	**0.5**	1	5		
Cooling Ramp Rate ($\frac{℃}{min}$)	0.1	**0.5**	1	5		
Number of Cycles	1	**2**				
Mixing Rate (RPM)	300	500	600	700	800	**900**
Hold time (min)	15 min hot 15 min cold	15 min hot 30 min cold	30 min hot 30 min cold	30 min hot 60 min cold	**60 min hot 120 min cold**	
Concentration ($\frac{mg}{mL}$)	**5** $\frac{mg}{mL}$	**15** $\frac{mg}{mL}$	**30** $\frac{mg}{mL}$	**50** $\frac{mg}{mL}$		



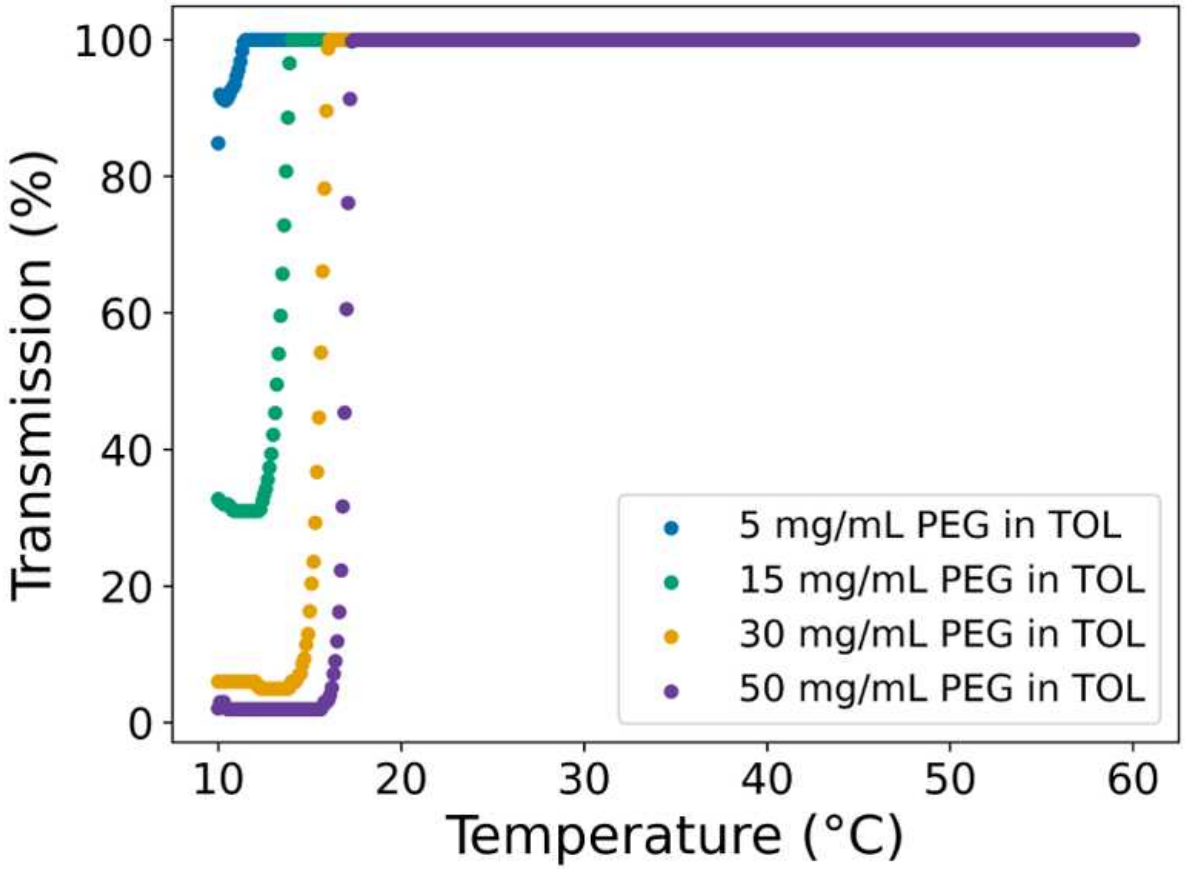
Technobis

Standardized screening requires comparing transmission during the ramp and isothermal hold

Polypropylene in toluene



Polyethylene glycol in toluene

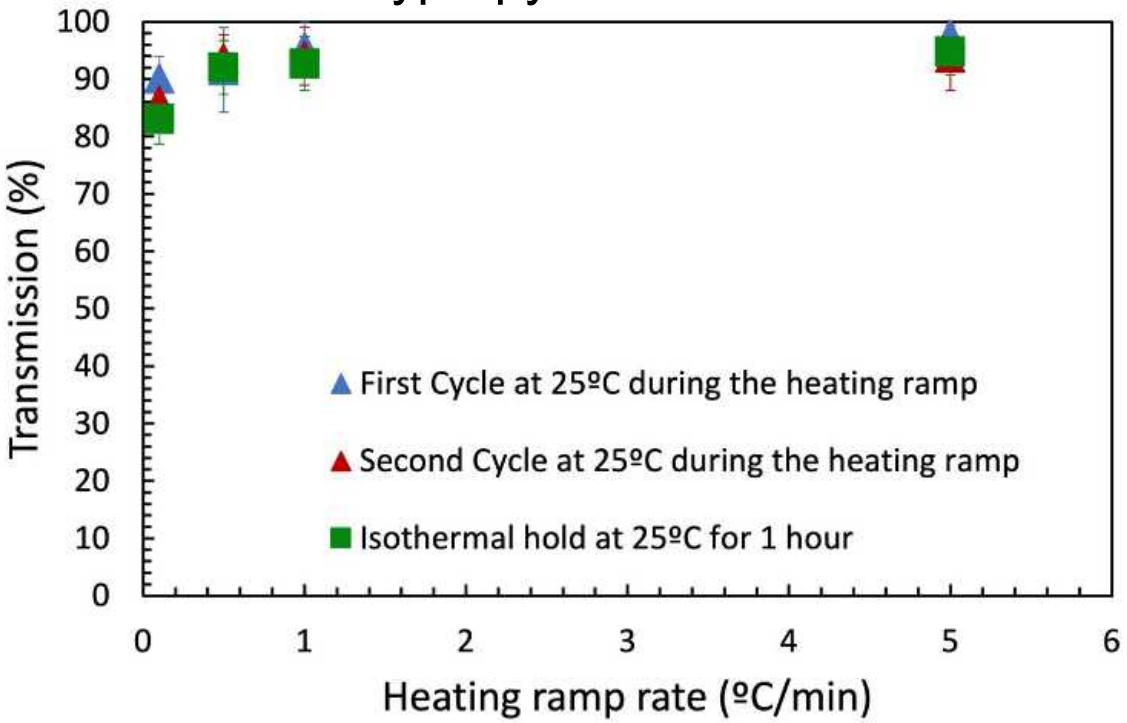


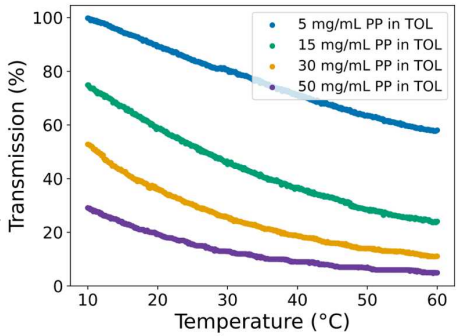
Amrihesari et al., Polymer, 2023

Technobis

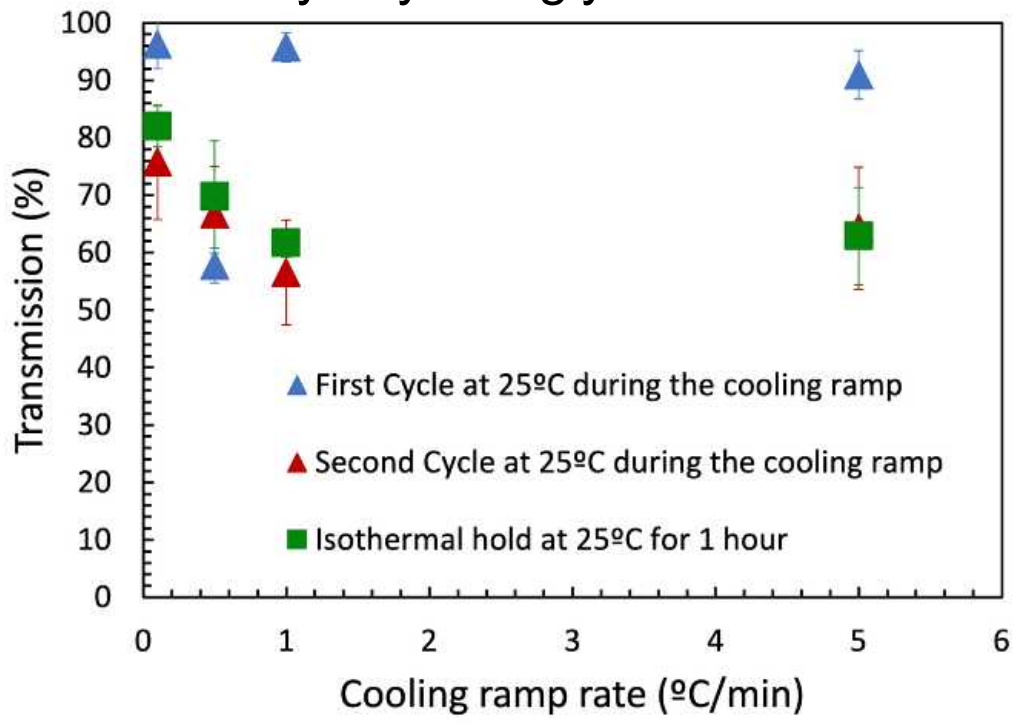
Standardized screening requires comparing transmission during the ramp and isothermal hold

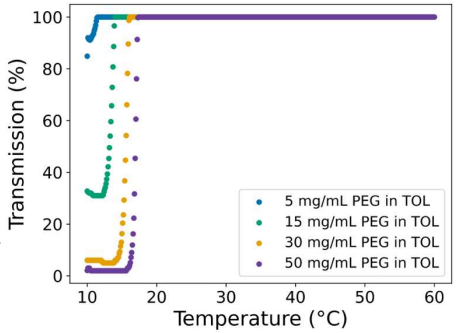
Polypropylene in toluene





Polyethylene glycol in toluene





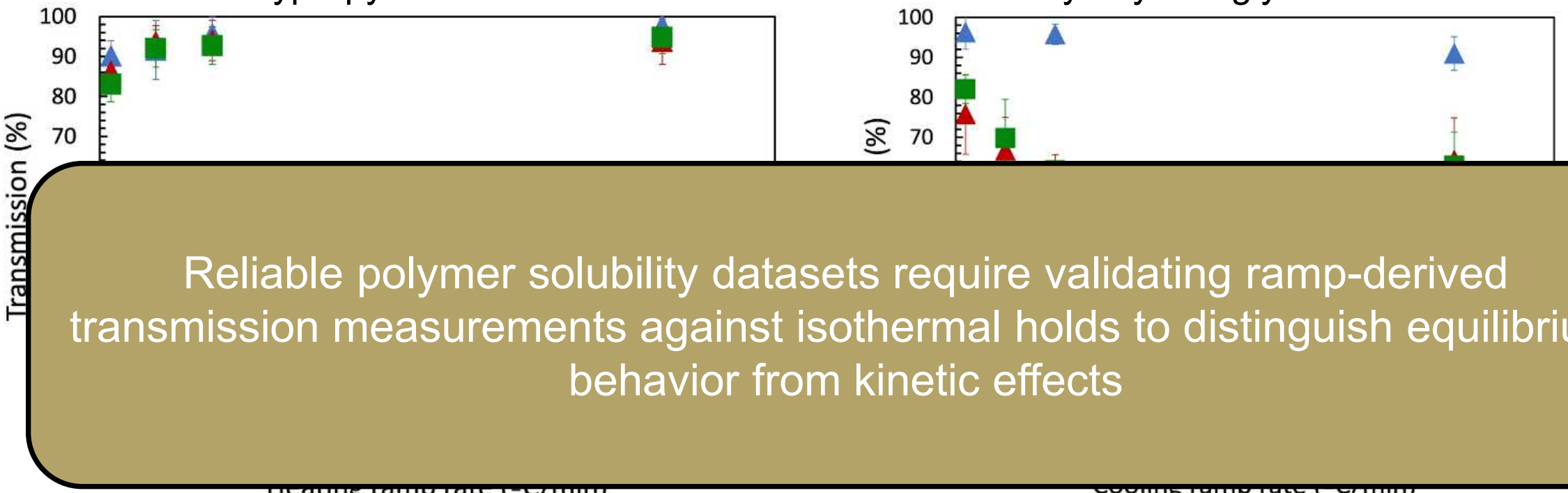
Amrihesari et al., Polymer, 2023

Technobis

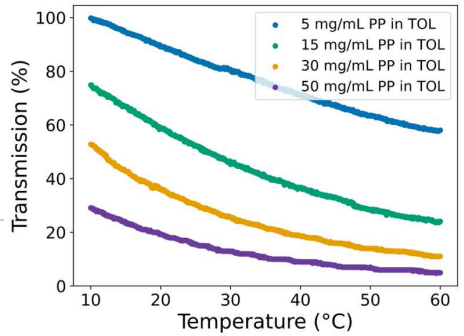
Standardized screening requires comparing transmission during the ramp and isothermal hold

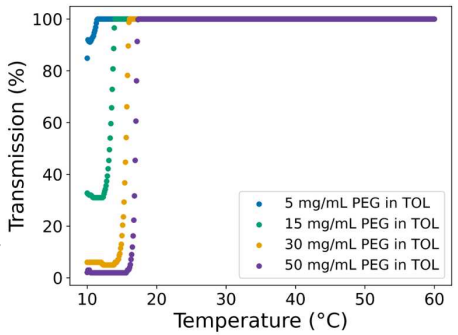
Polypropylene in toluene

Polyethylene glycol in toluene



Reliable polymer solubility datasets require validating ramp-derived transmission measurements against isothermal holds to distinguish equilibrium behavior from kinetic effects





Amrihesari et al., Polymer, 2023

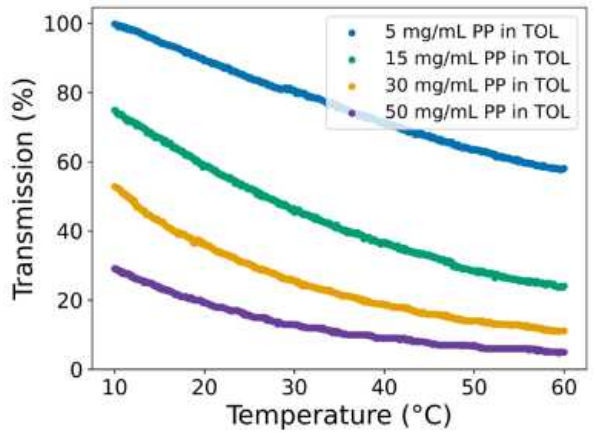
Technobis

How can polymer solubility screening be accelerated?

1. How do we generate reliable solubility screening process?
   A comprehensive dataset on polymers!
2. What are some practical ways to use this data to guide the decision making for polymer dissolution/precipitation?

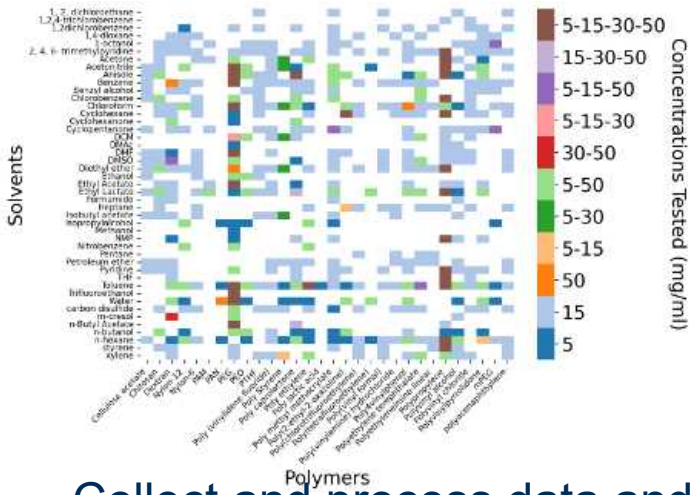
Use Case: Enabling machine learning with turbidity data collected on polymer solutions using Crystal16

1.



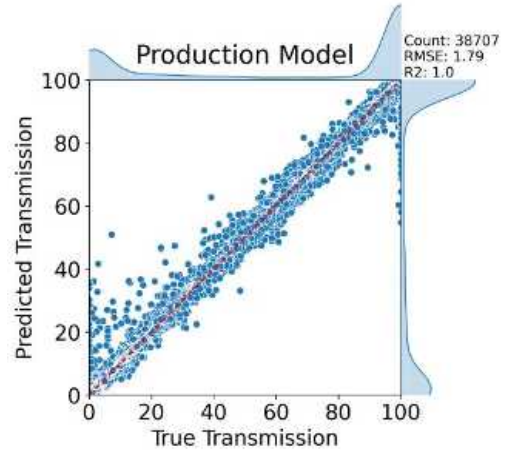
Develop improved data collection

2.



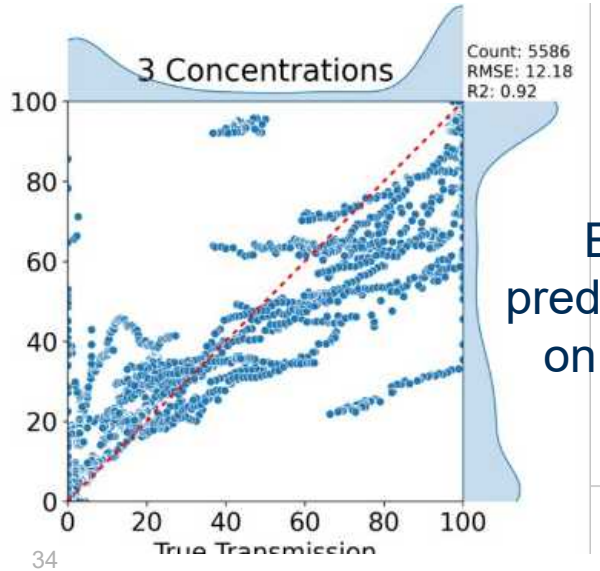
Collect and process data and generate dataset

3.



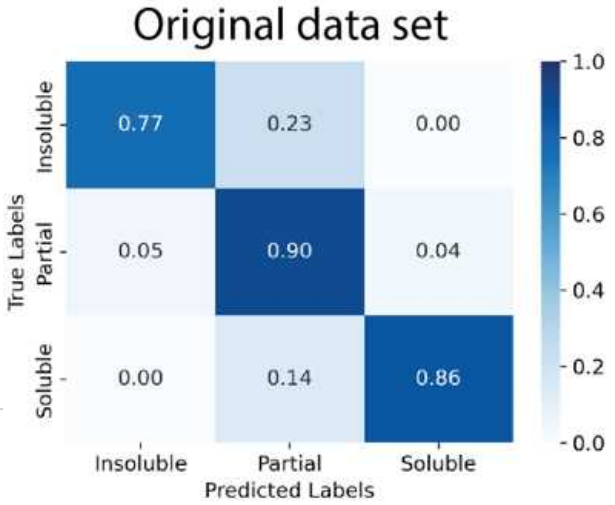
Select and train a model

4.



Evaluate model predictive performance on transmission vs. time data

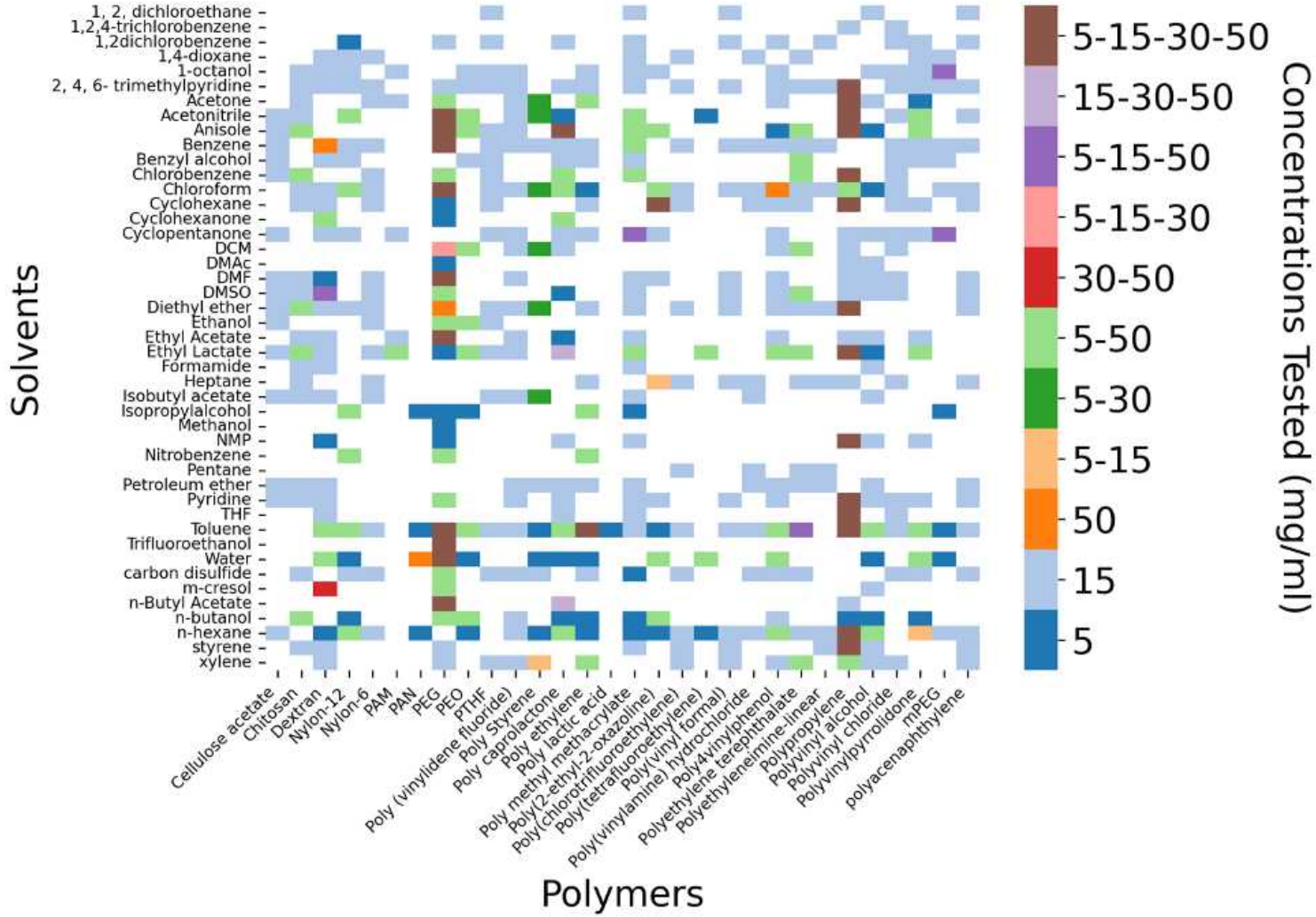
5.

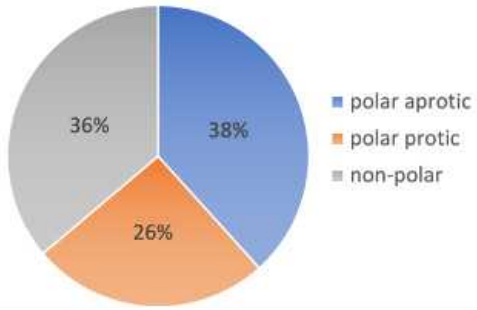


Translate transmission percent to classification and evaluate model performance

Amrihesari- Kern, et al. (2024)- In revision

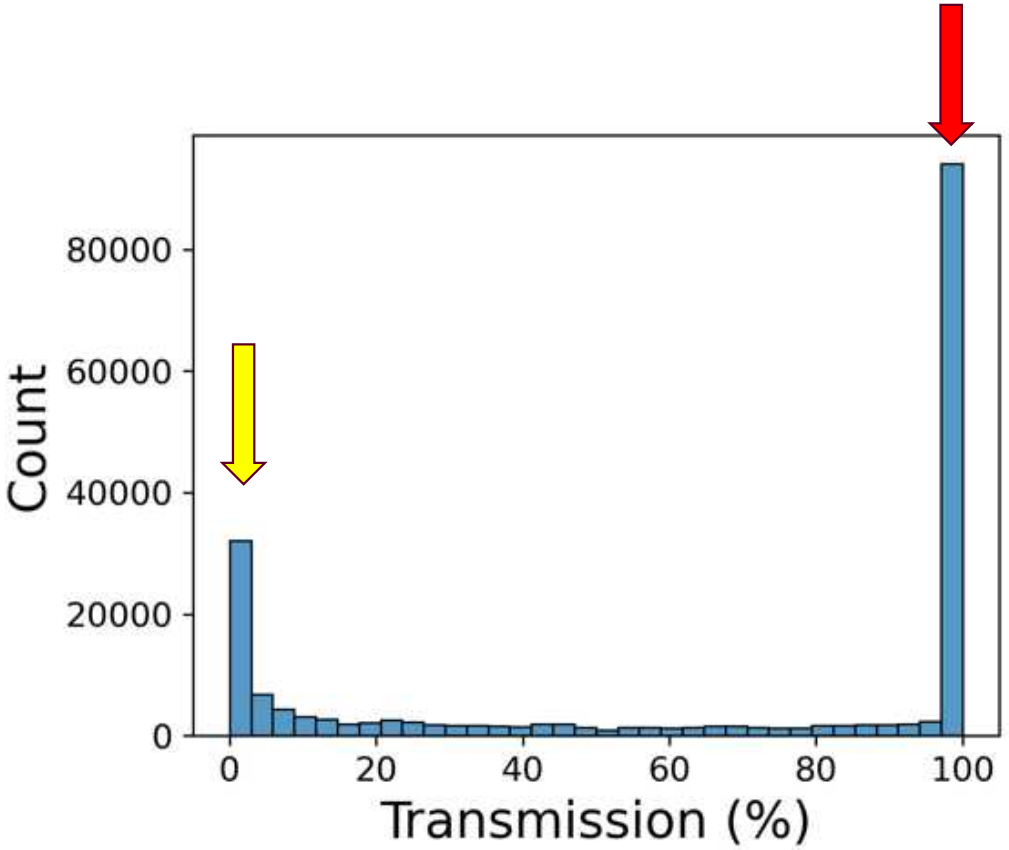
Heatmap with the data collected over 30 polymers and 48 solvents -> This means 900 unique polymer/solvent pairs

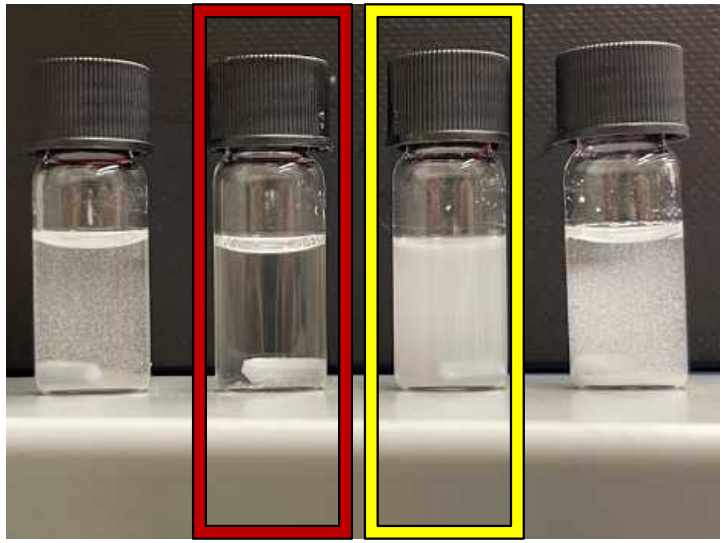




Technobis

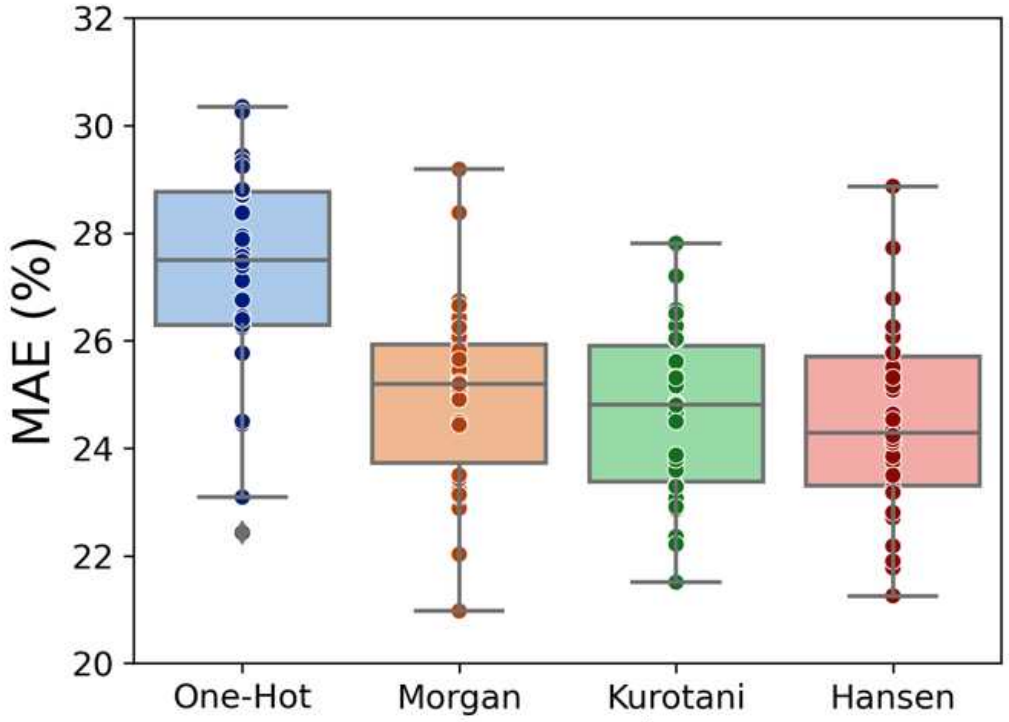
Data set is biased towards 0 and 100 % transmission





Technobis

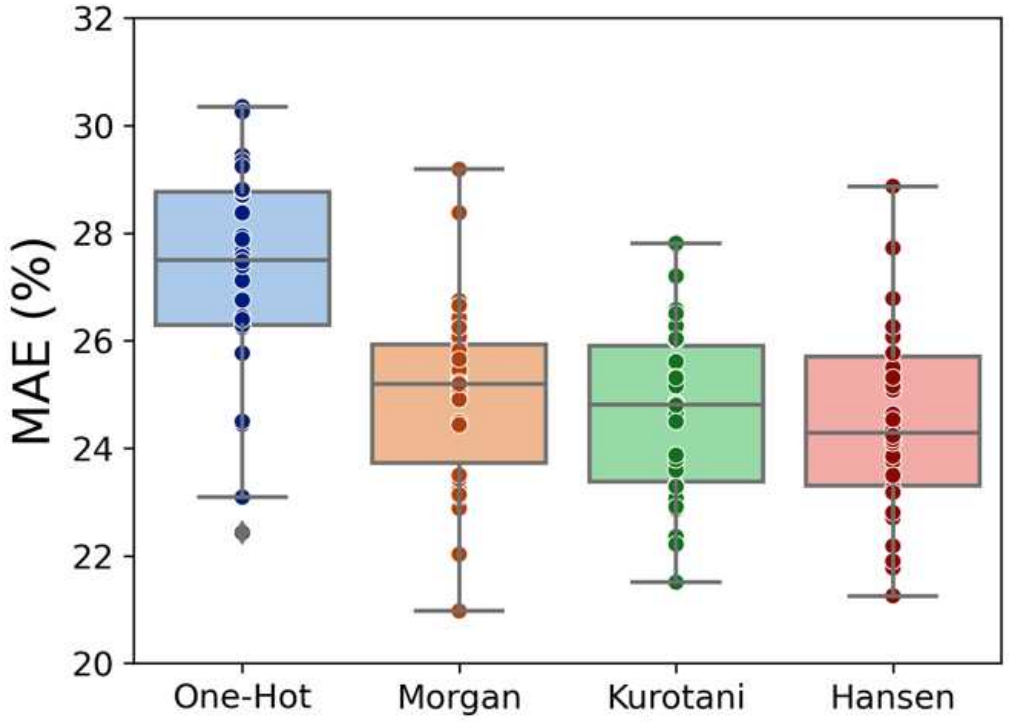
The production model is built using the Morgan fingerprinting and XGBoost machine learning model



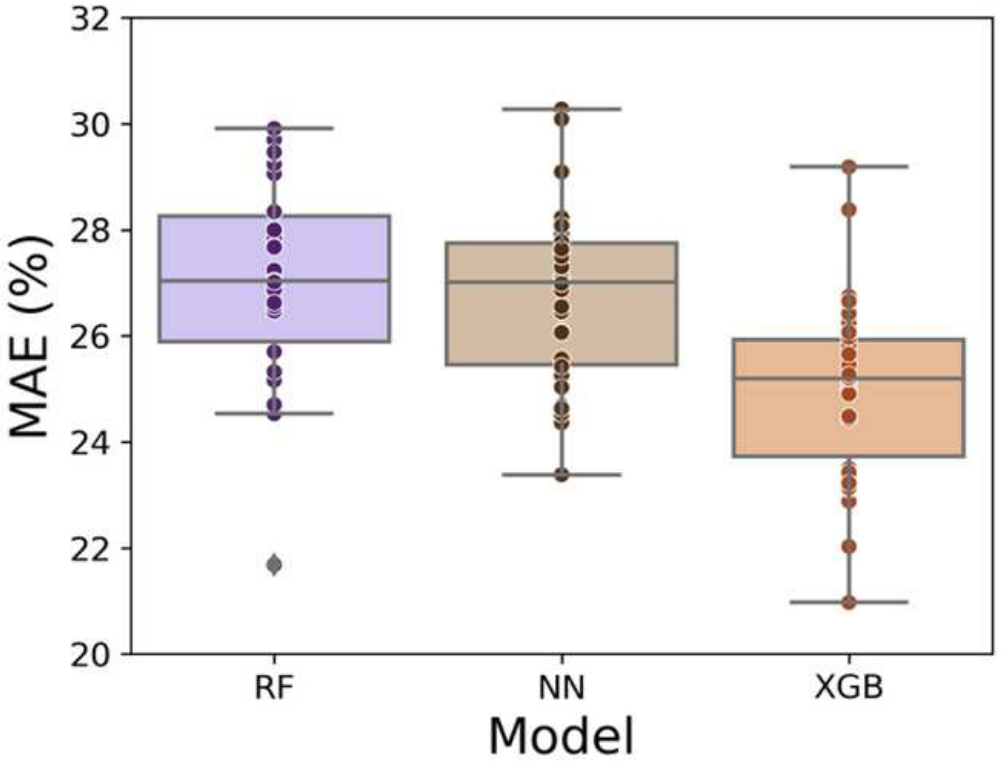
Fingerprinting Methods

- One-Hot encoding was utilized to represent the polymer/solvent association.
- Results are gathered from 30 models with 50/50 train/test splits
- Morgan fingerprinting was used further for model comparison

The production model is built using the Morgan fingerprinting and XGBoost machine learning model

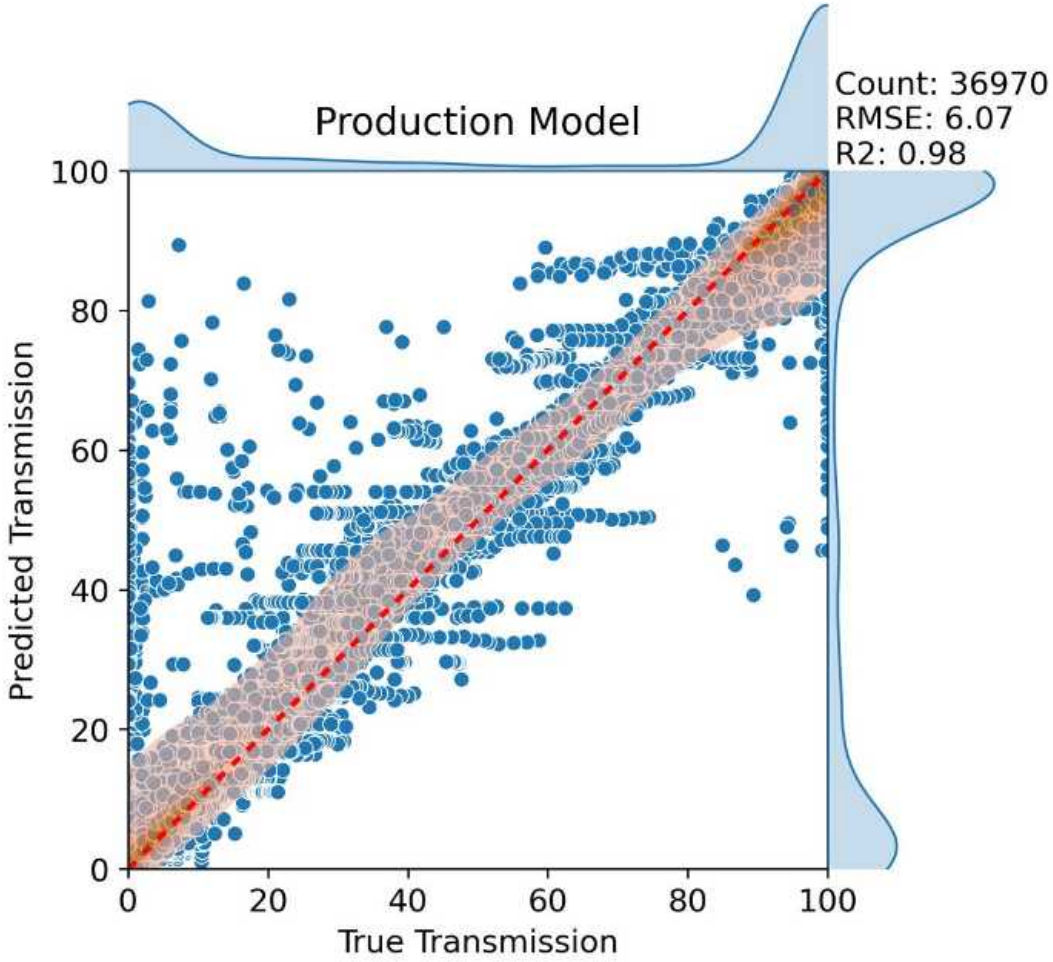


Fingerprinting Methods



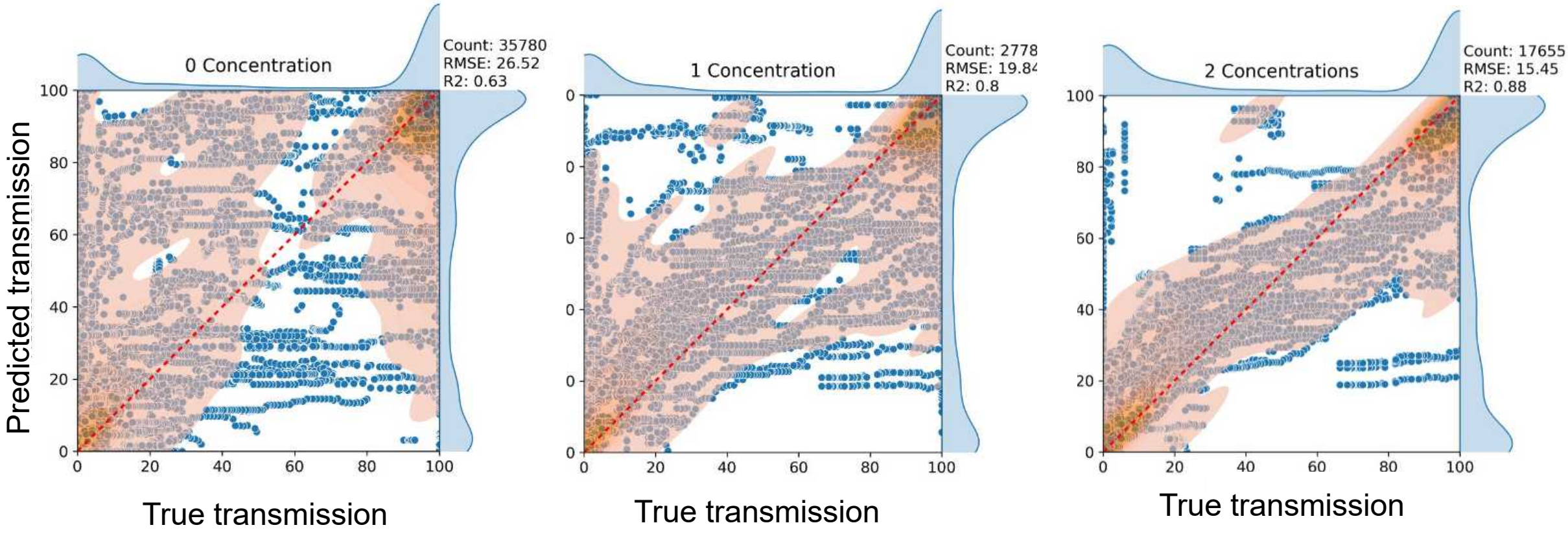
Machine Learning Models

Our production model achieved RMSE: 6% and R2: 0.98, indicating it was not underfitted



Technobis

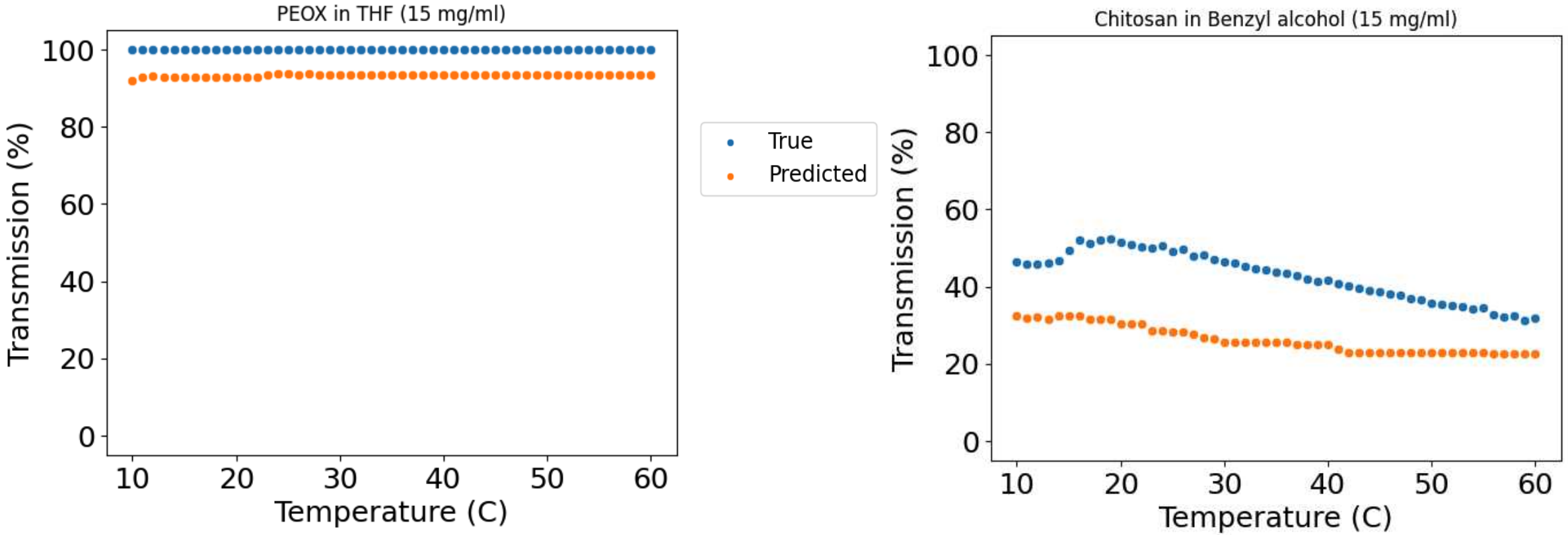
Leave-one-out analysis of the model's performance shows improvements as more polymer-solvent concentrations were added to the training data



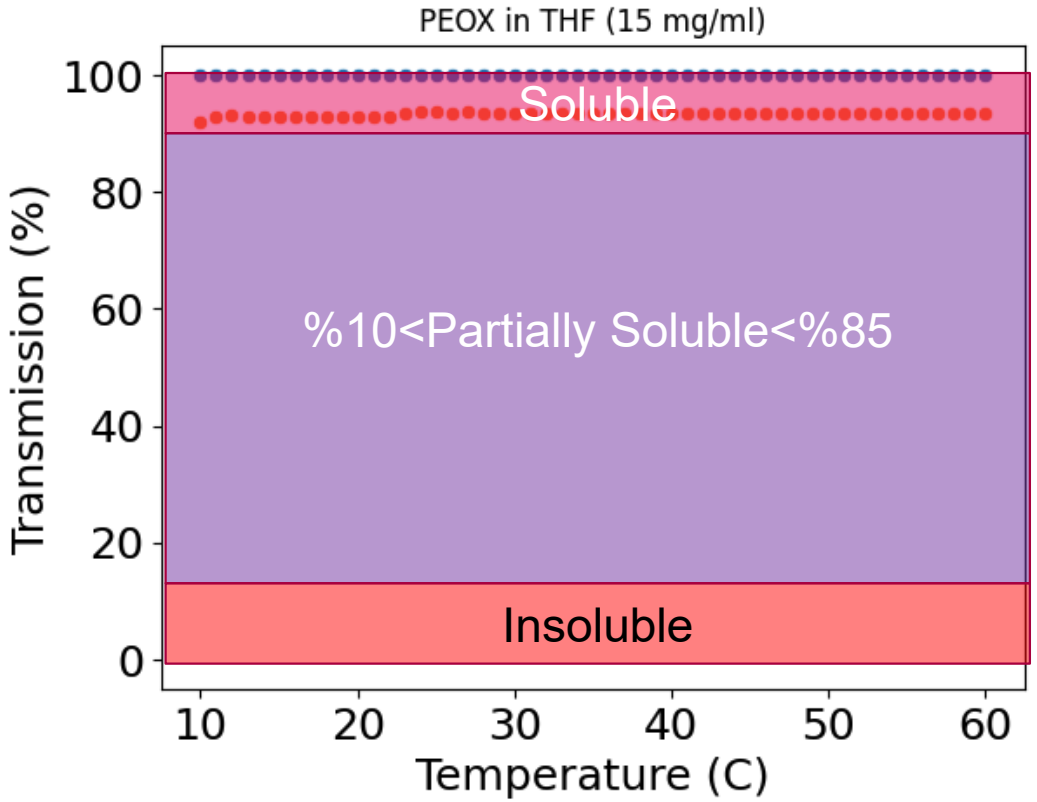
- New polymer-solvent pair: performance is moderate
- Polymer-solvent pair seen at least once before at a different concentration: performance is dramatically improved

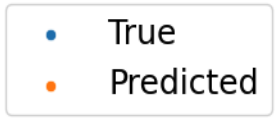
Technobis

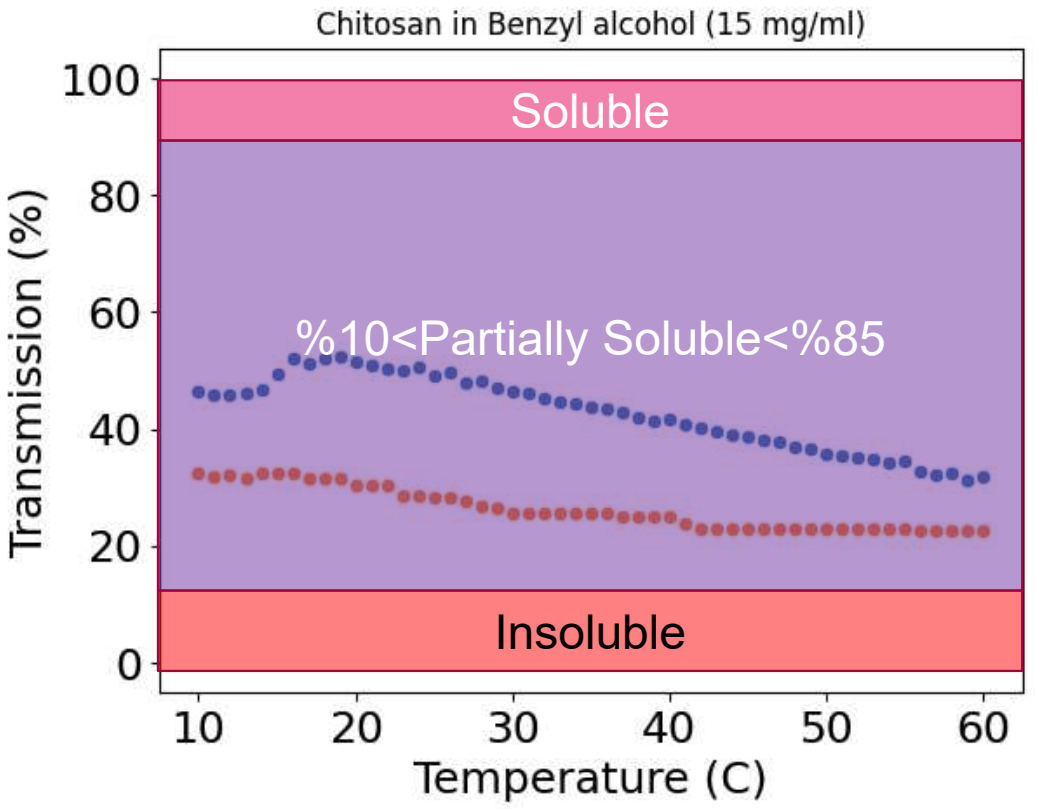
Testing the model predictions shows the good expansion for unseen polymer/solvent pairs



Testing the model predictions shows the good expansion for unseen polymer/solvent pairs







How do we generate reliable polymer solubility screening process? A comprehensive dataset!

1. Standardizing experimental methods for polymer solubility measurement

2. The prediction model for polymer solutions across different temperature and concentration

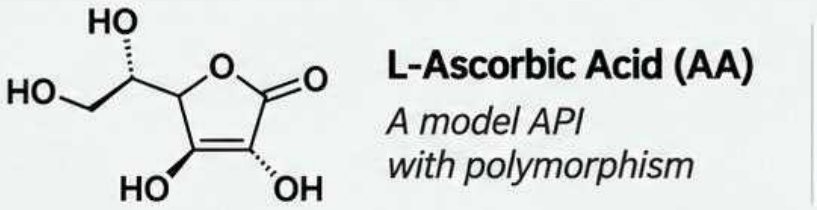
The standardized data collection produce well controlled, well-detailed and reproducible data

A reliable predicting model for polymer solubility is possible with reliable, data rich data collection method

How can solubility screening guide the crystallization processes ?

1

Solvent selection and solubility assessment



L-Ascorbic Acid (AA)

A model API with polymorphism

Solubility Screening

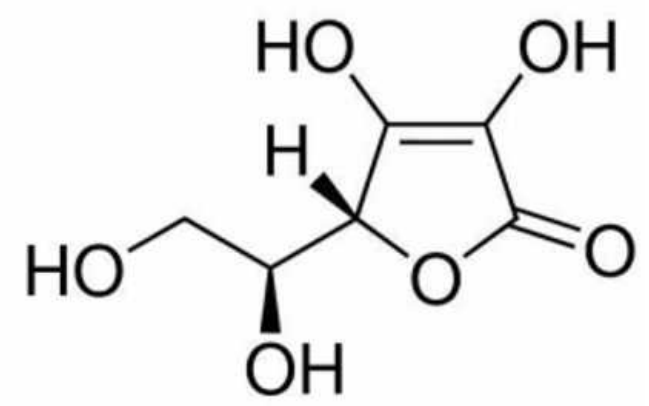
Crystallization (Solvent–Antisolvent)

Real-Time Monitoring (Imaging & Raman)

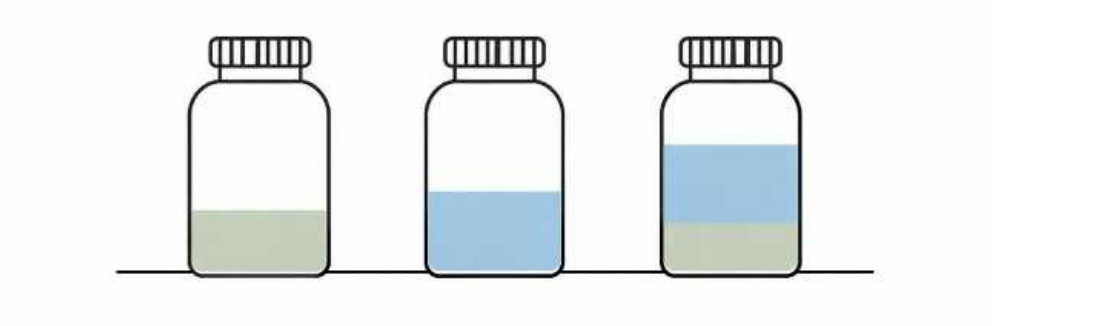
Technobis

Use Case: Linking Thermodynamics, Nucleation Kinetics, and Crystal Habit to Guide Solvent Selection for L-Ascorbic Acid Crystallization

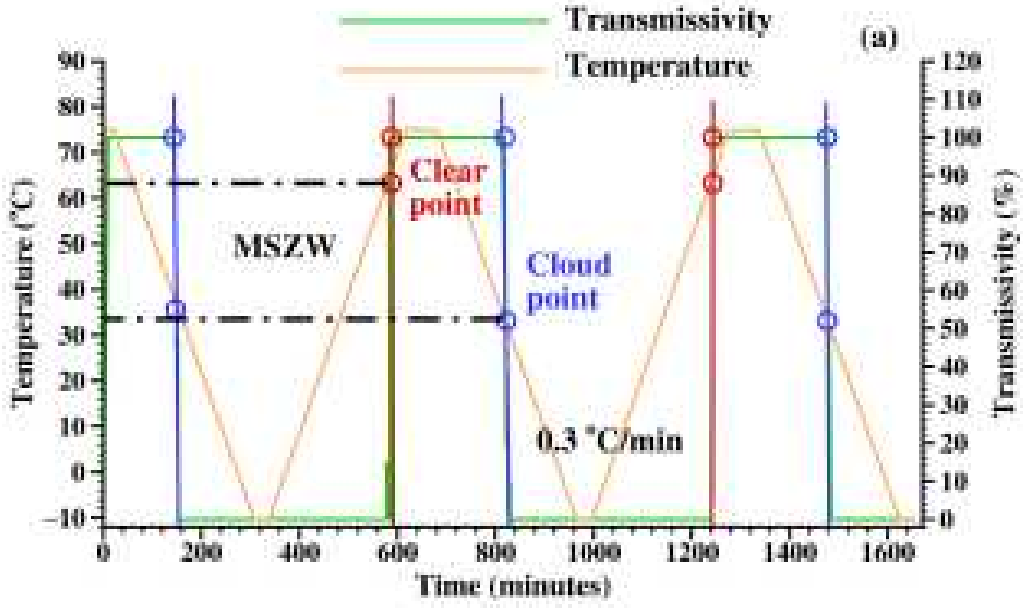
- Determine solubility and metastable zone width across different solvent systems.
- Quantify supersaturation-dependent nucleation kinetics using induction-time measurements.
- Evaluate solvent-dependent crystal morphology to support crystallization process design.



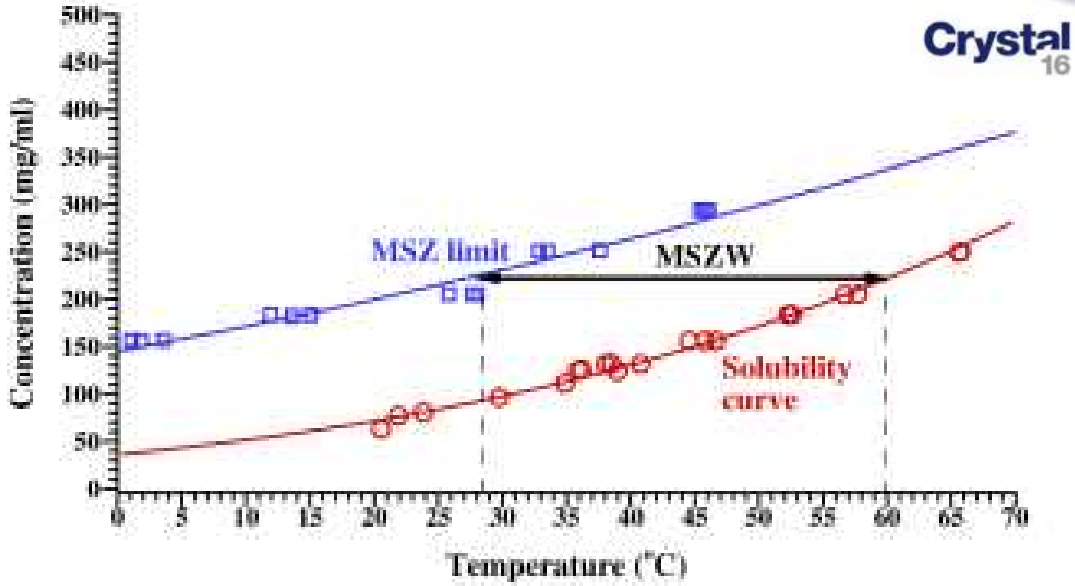
Structure of L-ascorbic acid



Measured clear points, cloud points, and MSZW using Crystal16 V2 across 10–60°C



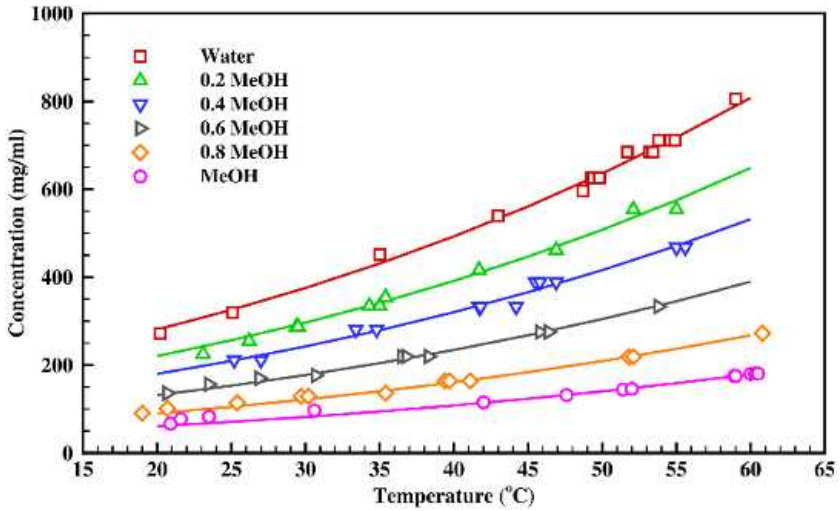
Experimental design for detection of clear and cloud point



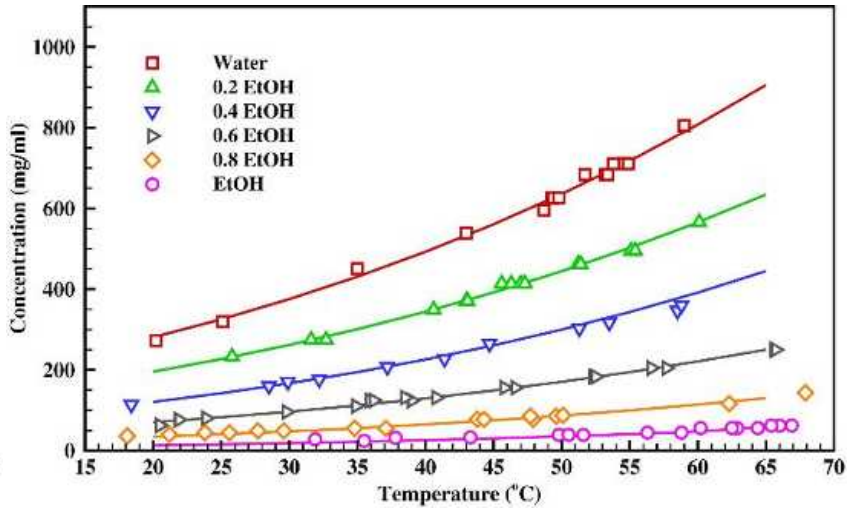
MSZW limit

Solubility of *L-ascorbic acid* in binary solvent systems

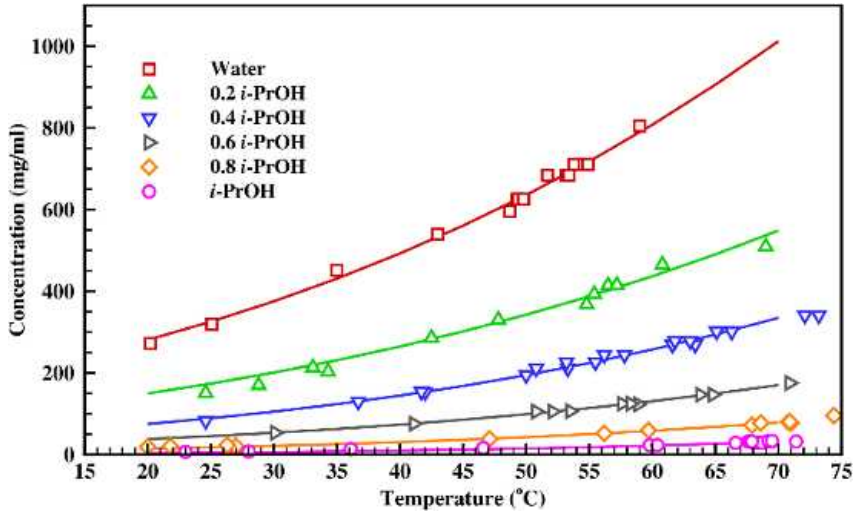
Water-Methanol



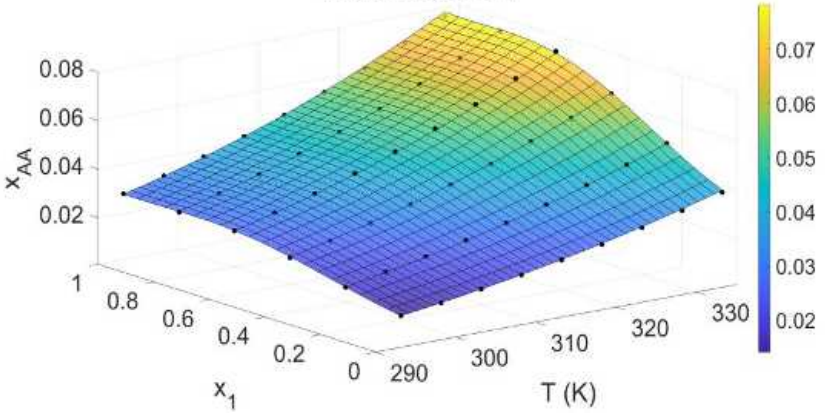
Water-Ethanol



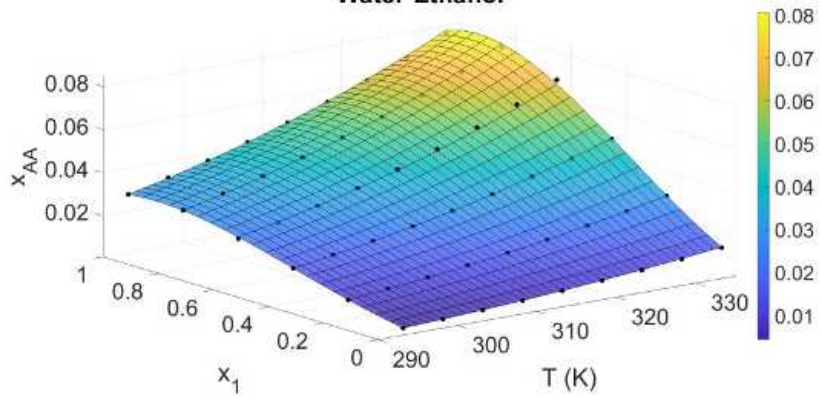
Water-Isopropanol



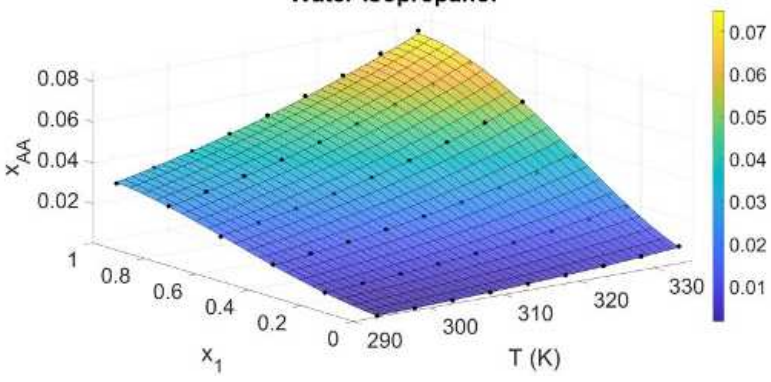
Water-Methanol



Water-Ethanol



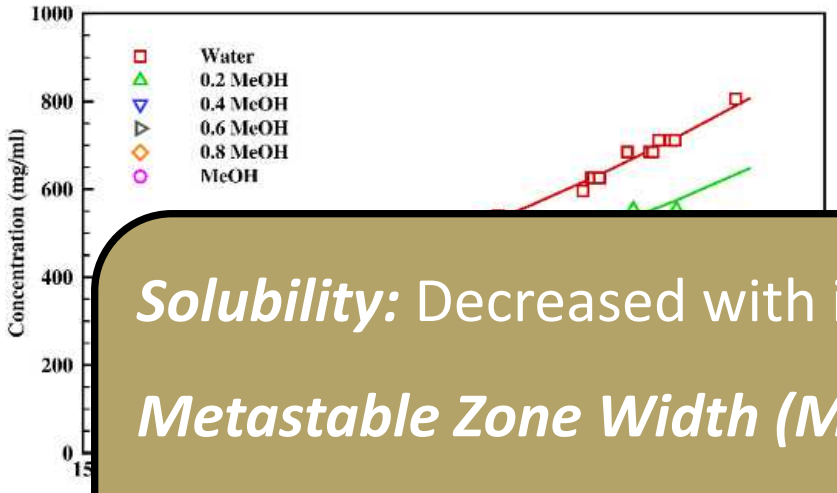
Water-Isopropanol



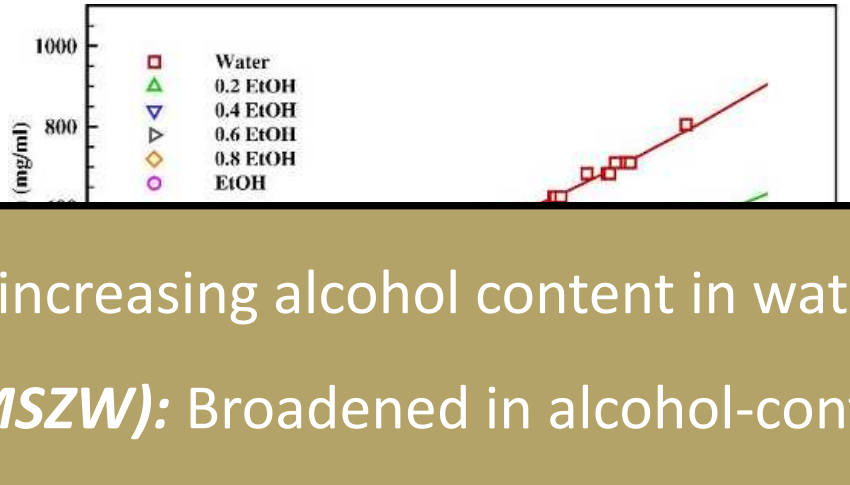
Technobis

Solubility of *L-ascorbic acid* in binary solvent systems

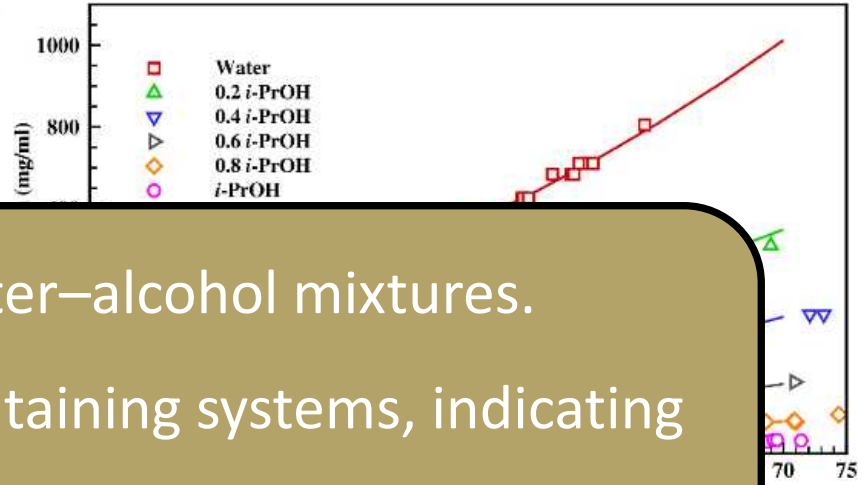
Water-Methanol



Water-Ethanol

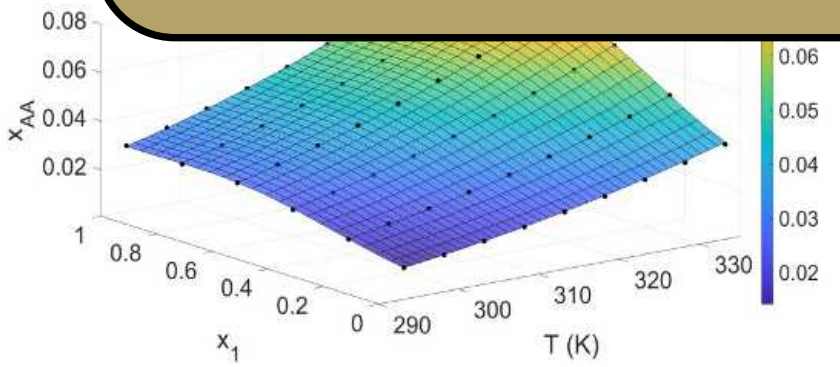


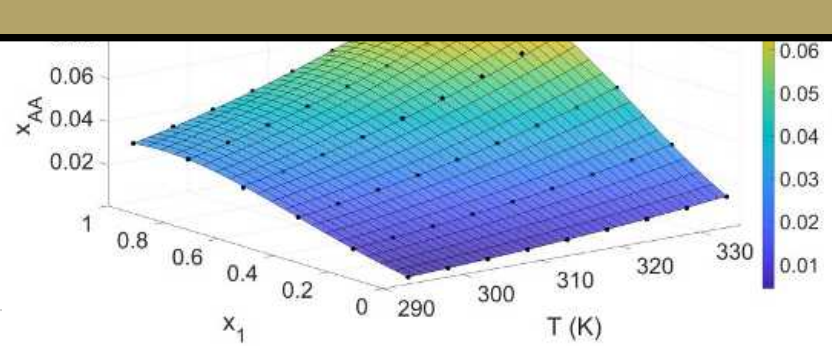
Water-Isopropanol

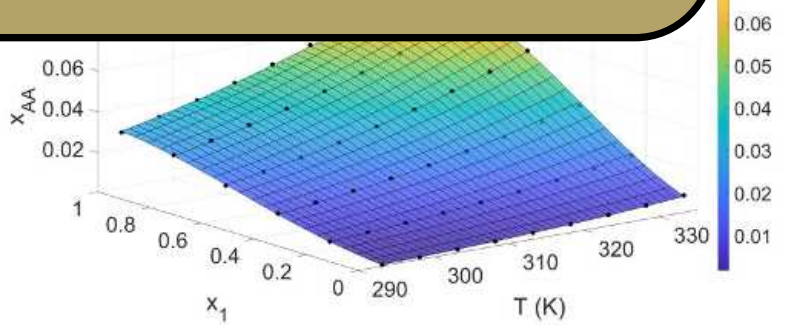


Solubility: Decreased with increasing alcohol content in water–alcohol mixtures.

Metastable Zone Width (MSZW): Broadened in alcohol-containing systems, indicating greater undercooling before detectable nucleation.







Technobis

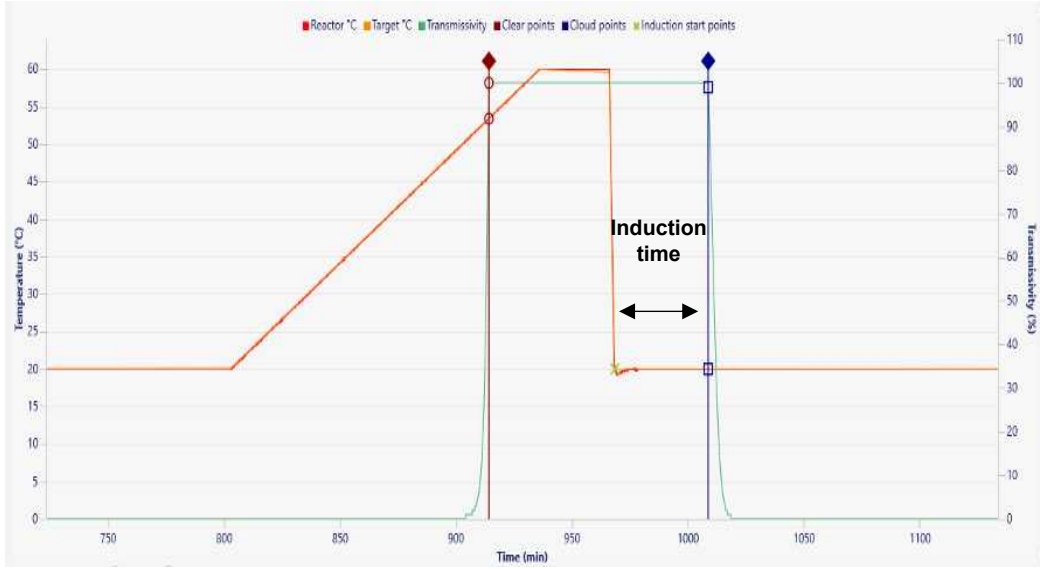
induction-time experiments at controlled supersaturation ratios in selected solvent systems



Different supersaturations

HPLC vials

$$P(\mathrm{t}) = 1 - exp(-JV(t - t_g))$$



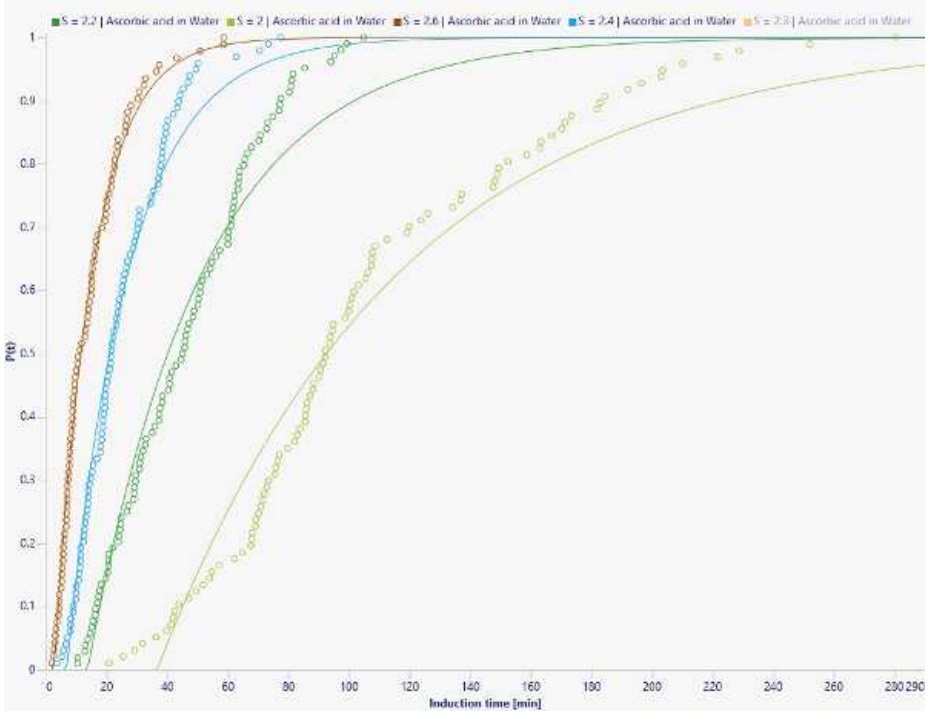


Fig: Probability distribution vs induction time.

P: Probability
J: nucleation rate
V: Volume
t: induction time
t_g: growth time
.

S. Jiang, & J.H. ter Horst, *Crystal Growth & Design*, **2011** *11*(1), 256-261.
C. Brandel, & J.H. ter Horst, *Faraday discussions* **2015**, *179*, 199-214.

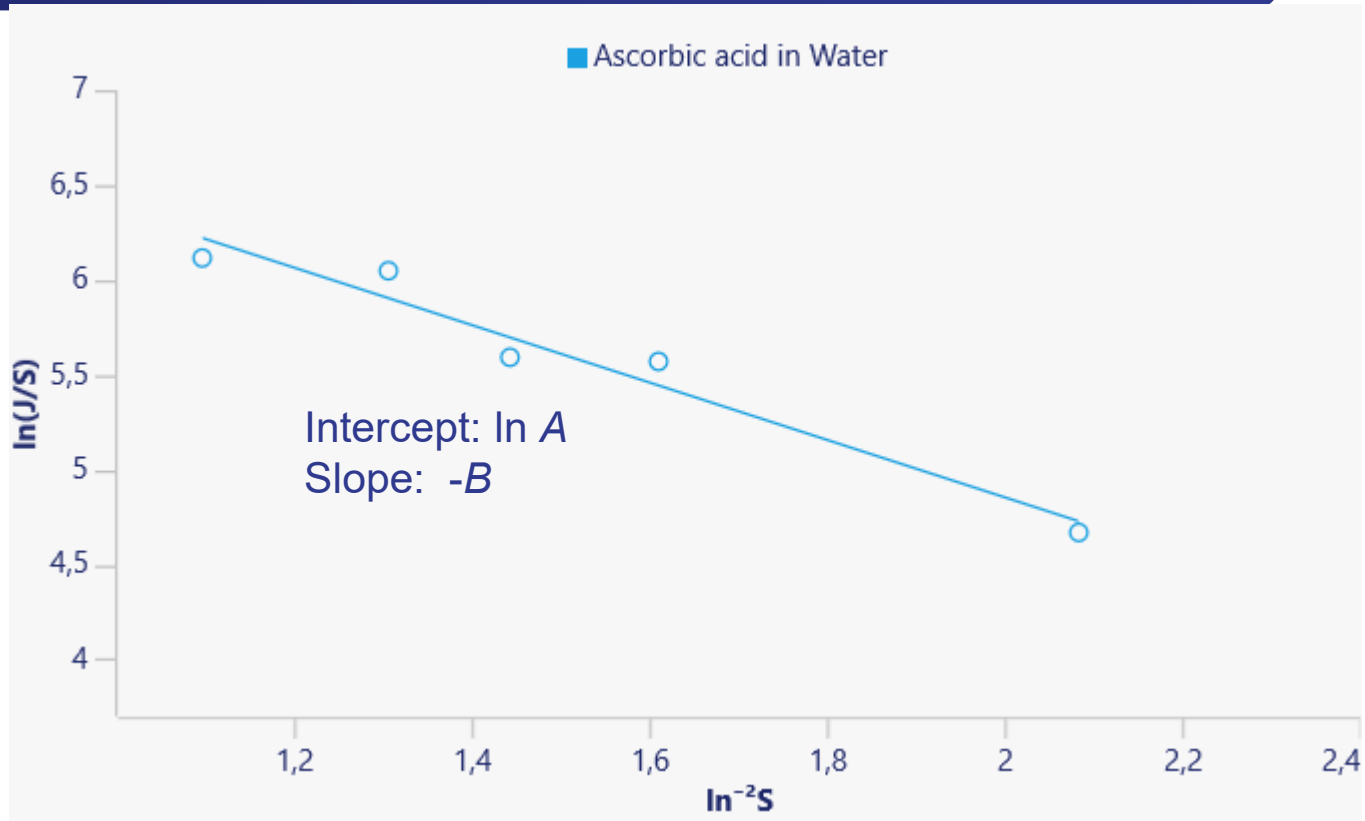
Technobis

Experiments: Induction Time and Nucleation Rate

Supersaturation	Fitted function	J [m^{-3} s^{-1}]	tg [s]
2.4	P(t) = 1 – exp(–1015,84 * 1e-6 * (t – 555,06))	1015.84	555.057
2.2	P(t) = 1 – exp(–577,38 * 1e-6 * (t – 721,43))	577.38	721.433
2.6	P(t) = 1 – exp(–1177,13 * 1e-6 * (t – 158,11))	1177.13	158.112
2	P(t) = 1 – exp(–213,12 * 1e-6 * (t – 2234,98))	213.124	2234.98
2.3	P(t) = 1 – exp(–617,01 * 1e-6 * (t – 409,17))	617.005	409.169

$$ln\left(J/S\right) = lnA - \frac{B}{ln^2 S}$$

$$y = c + mx$$

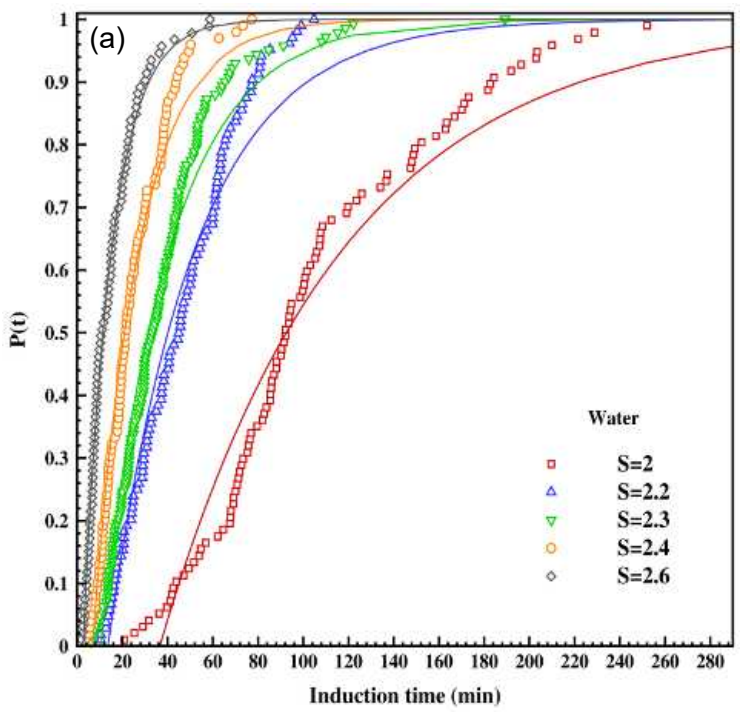


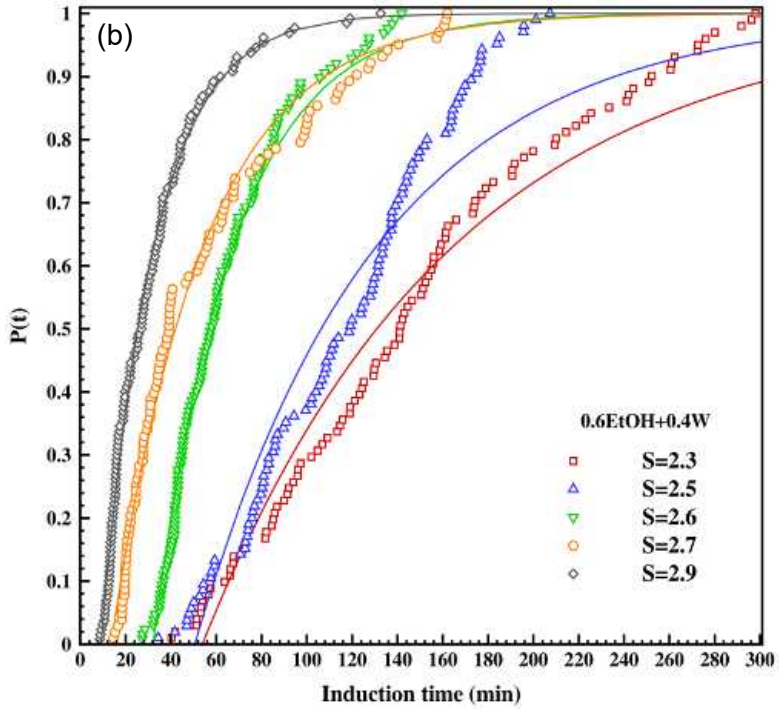
Nucleation rates table

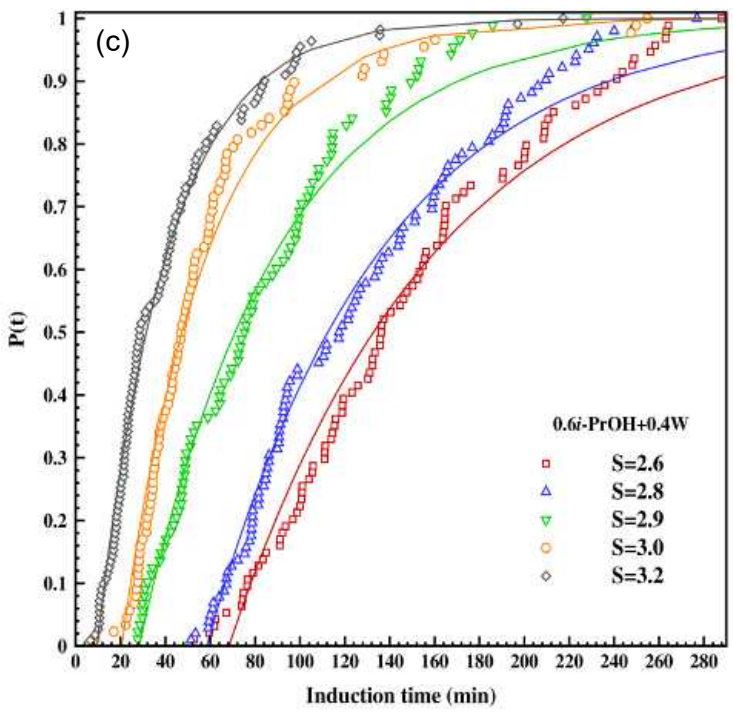
Compound	Solvent	Color	Fitted function]	A [m^{-3} s^{-1}]	B	R2	Adj R2
Ascorbic acid	Water		J(S) = 2642,314 * S * exp(–1,5141 / ln²(S))	2642.31	1.51405	0.9533	0.9065

Technobis

Analyzed induction-time distributions using Classical Nucleation Theory (CNT) for different binary systems

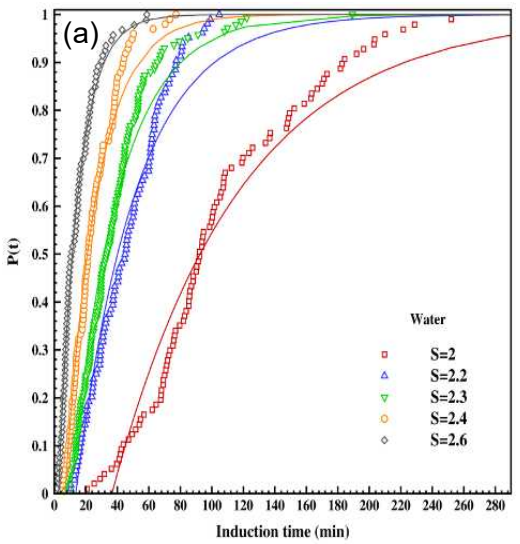


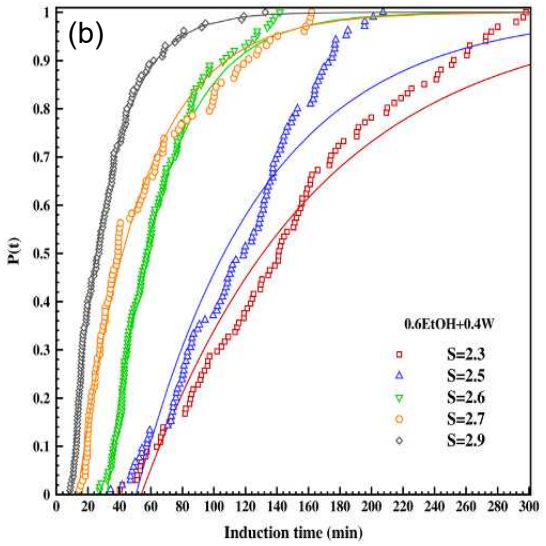


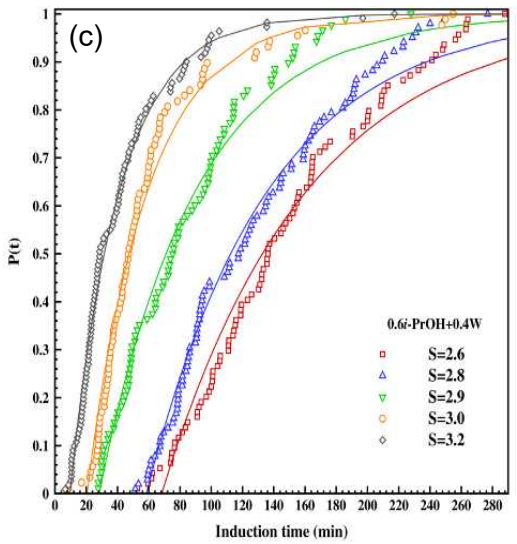


Yadav, J., Kendall, T., Dumitrescu, D. G., Guguta, C., & Patel, S. A. (2024). Nucleation Kinetics of Ascorbic Acid in Various Aqueous Solvents. *Industrial & Engineering Chemistry Research*, *63*(6), 2812-2821.

Analyzed induction-time distributions using Classical Nucleation Theory (CNT) for different binary systems

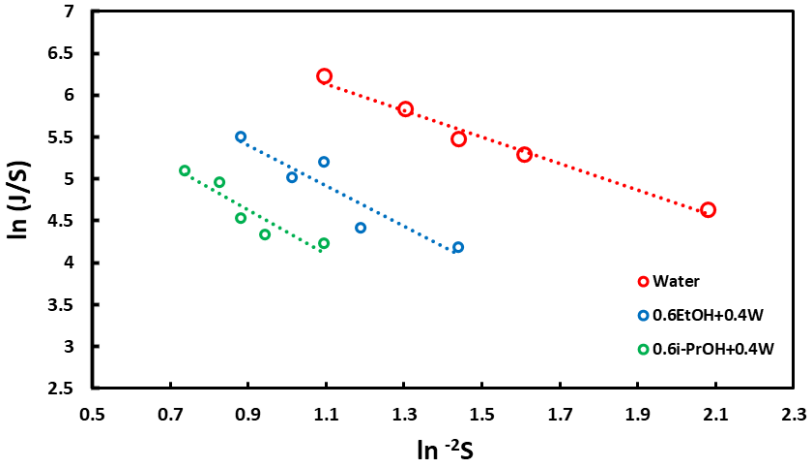






Classical Nucleation Theory

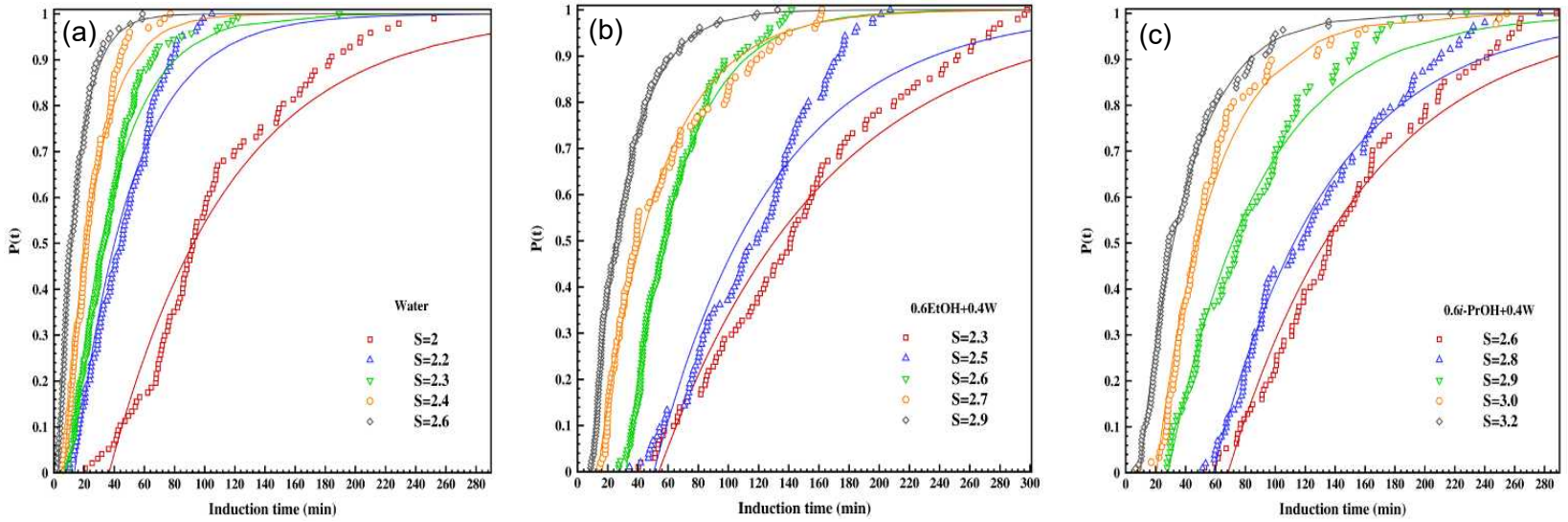
$$ln\left(J/S\right) = lnA - \frac{B}{ln^2 S}$$



Solvent	*A*	*B*	R^2
Water	2662.48	1.589	0.986
0.6EtOH+0.4W	1981.20	2.425	0.856
0.6iPrOH+0.4W	1092.94	2.633	0.847

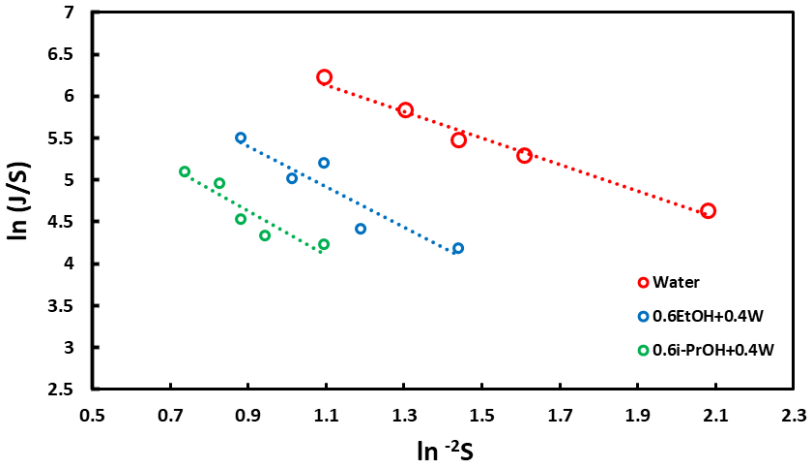
Yadav, J., Kendall, T., Dumitrescu, D. G., Guguta, C., & Patel, S. A. (2024). Nucleation Kinetics of Ascorbic Acid in Various Aqueous Solvents. *Industrial & Engineering Chemistry Research*, *63*(6), 2812-2821.

Analyzed induction-time distributions using Classical Nucleation Theory (CNT) for different binary systems



Classical Nucleation Theory

$$ln\left(J/S\right) = lnA - \frac{B}{ln^2 S}$$



Nucleation Kinetics: Increased with supersaturation, while alcohol-containing mixtures exhibited slower nucleation and larger fitted CNT barrier parameters.

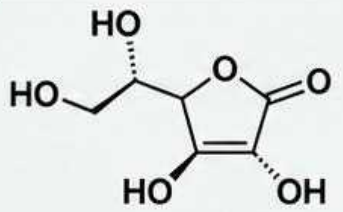
Solvent	*A*	*B*	R^2
Water	2662.48	1.589	0.986
0.6EtOH+0.4W	1981.20	2.425	0.856
0.6iPrOH+0.4W	1092.94	2.633	0.847

Yadav, J., Kendall, T., Dumitrescu, D. G., Guguta, C., & Patel, S. A. (2024). Nucleation Kinetics of Ascorbic Acid in Various Aqueous Solvents. *Industrial & Engineering Chemistry Research*, *63*(6), 2812-2821.

How can solubility screening guide the crystallization processes ?

1. Solvent selection and solubility assessment

2. Crystallization process design and optimization



L-Ascorbic Acid (AA)

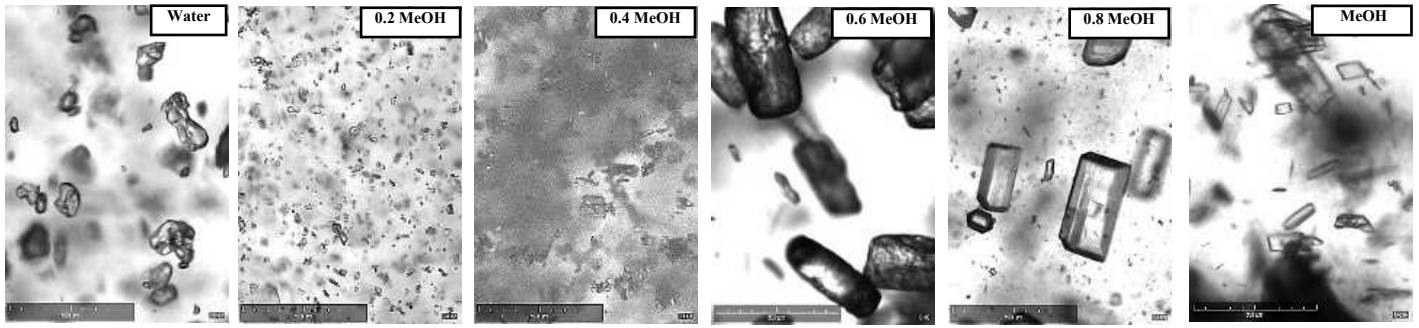
A model API with polymorphism

Solubility Screening → **Crystallization (Solvent–Antisolvent)** → **Real-Time Monitoring** (Imaging & Raman)

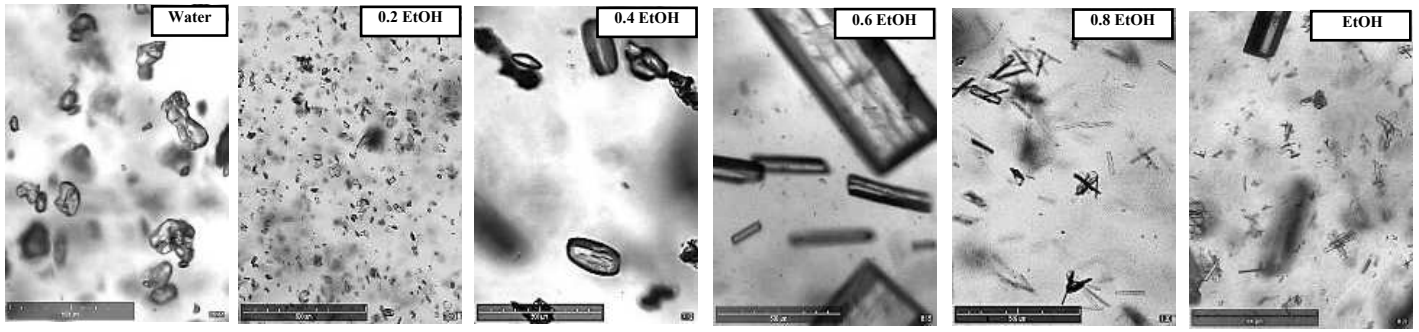
Technobis

Effect of solvent composition on crystal habit

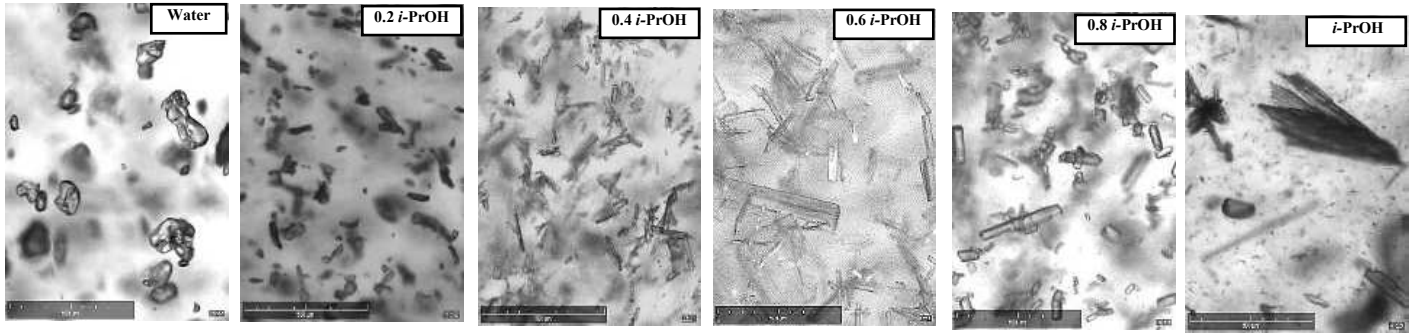
Water-Methanol



Water-Ethanol



Water-Isopropanol



- The effect of solvent composition on the crystal habit of ascorbic acid was investigated using ***Crystalline***.
- Cooling Crystallization of Ascorbic acid in different **water-alcohol (Methanol/ Ethanol/ IPA)** was performed.
- More **cubical or prism shaped** crystal were witnessed in **water**.
- With the increase in alcohol concentration more and more **lengthened crystals** were formed resulting in **rod shaped crystals** in **pure ethanol** and **cluster of needle crystal** in pure isopropanol.



Yadav, J., Dumitrescu, D. G., Kendall, T., Guguta, C., & Patel, S. A. (2022). Effect of solvent composition on solubility, thermodynamics, metastable zone width (MSZW) and crystal habit of L-ascorbic acid. *Crystals*, *12*(12), 1798.

Technobis

How do we generate reliable polymer solubility screening process? A comprehensive dataset!

1. Solvent selection and solubility assessment
2. Crystallization process design and optimization

Solvent selection goes beyond solubility; it shapes when crystals nucleate, how they grow, and ultimately, crystallization performance

Thank you for listening!



Pyrietstraat 2

1812 SC Alkmaar

crystallizationsystems.com