



Slovak Society of Chemical Engineering  
Institute of Chemical and Environmental Engineering  
Slovak University of Technology in Bratislava

## PROCEEDINGS

51<sup>st</sup> International Conference of the Slovak Society of Chemical Engineering SSCHE 2025

Hotel DRUŽBA  
Jasná, Demänovská Dolina, Slovakia  
May 27 - 30, 2025

Editors: Assoc. Prof. Mário Mihaľ

ISBN: 978-80-8208-158-2, EAN: 9788082081582

Published by the Faculty of Chemical and Food Technology Slovak Technical University in Bratislava in Slovak Chemistry Library for the Institute of Chemical and Environmental Engineering; Radlinského 9, 812 37 Bratislava, 2024

Hládek, F., Nagy, O., Smrcka, D., Štěpánek, F.: Development and Optimization of a Continuous Liquid Antisolvent Precipitation Device for Nanocrystalline Formulations, Editors: Mihaľ, M., In *51st International Conference of the Slovak Society of Chemical Engineering SSCHE 2025*, Jasná, Demänovská Dolina, Slovakia, 2025.

## Development and Optimization of a Continuous Liquid Antisolvent Precipitation Device for Nanocrystalline Formulations

Filip Hládek<sup>1,2</sup>, Oliver Nagy<sup>1,2</sup>, David Smrčka<sup>2</sup>, František Štěpánek<sup>1</sup>,

*1. University of Chemistry and Technology, Prague, Department of Chemical Engineering,  
Technická 5, Praha 166 28, Czech Republic*

*2. Zentiva, k.s., U Kabelovny 130, 102 00 Praha 10, Czech Republic*

*e-mail: hladekf@vscht.cz*

**Key words:** Antisolvent precipitation, Nanocrystals, Continuous processing, High-throughput screening, Optimization, API solubility

The increasing number of poorly water-soluble active pharmaceutical ingredients (APIs) presents significant formulation challenges in early-stage drug development, particularly regarding dissolution rates and bioavailability. Conventional practices that utilise dimethylsulfoxide (DMSO) for preclinical studies often lead to formulation problems during the clinical phases, highlighting the need for robust, scalable, and direct formulation methods.

This study presents a continuous liquid antisolvent precipitation device (CLAP) designed and optimized for high-throughput production of nanocrystalline API formulations. The CLAP device utilises precise control of solvent and antisolvent streams to produce stable nanocrystals with enhanced solubility and bioavailability. A modular design that incorporates interchangeable mixing chambers, HPLC grade pumps, and automated parameter control was implemented to facilitate rapid experimentation and scalability.

Extensive parametric studies investigated the influence of critical factors such as solvent-to-antisolvent flow ratios, API concentrations, stabiliser types, and mixer geometries on particle size distribution (PSD). Optimal configurations demonstrated the capability to consistently yield nanoparticles below 200 nm with narrow PSDs. Computational fluid dynamics (CFD) modelling and nucleation studies further enhanced understanding of the mixing and nucleation dynamics, guiding mixer design improvements toward achieving minimal particle growth after nucleation.

The developed system provides a platform for early-stage drug screening, reducing the risk of formulation-related development hurdles and accelerating translation from laboratory to clinical application.

## Development and Optimization of a Continuous Liquid Antisolvent Precipitation Device for Nanocrystalline Formulations

Filip Hládek<sup>1,2</sup>, Oliver Nagy<sup>1,2</sup>, David Smrčka<sup>2</sup>, František Štěpánek<sup>1</sup>,

1. *University of Chemistry and Technology, Prague, Department of Chemical Engineering, Technická 5, Praha 166 28, Czech Republic*

2. *Zentiva, k.s., U Kabelovny 130, 102 00 Praha 10, Czech Republic*

*e-mail: hladekf@vscht.cz*

**Key words:** Antisolvent precipitation, Nanocrystals, Continuous processing, High-throughput screening, Optimization, API solubility

### Abstract

The increasing number of poorly water-soluble active pharmaceutical ingredients (APIs) presents significant formulation challenges in early-stage drug development, particularly regarding dissolution rates and bioavailability. Conventional practices that utilise dimethylsulfoxide (DMSO) for preclinical studies often lead to formulation problems during the clinical phases, highlighting the need for robust, scalable, and direct formulation methods.

This study presents a continuous liquid antisolvent precipitation device (CLAP) designed and optimized for high-throughput production of nanocrystalline API formulations. The CLAP device utilises precise control of solvent and antisolvent streams to produce stable nanocrystals with enhanced solubility and bioavailability. A modular design that incorporates interchangeable mixing chambers, HPLC grade pumps, and automated parameter control was implemented to facilitate rapid experimentation and scalability.

Extensive parametric studies investigated the influence of critical factors such as solvent-to-antisolvent flow ratios, API concentrations, stabiliser types, and mixer geometries on particle size distribution (PSD). Optimal configurations demonstrated the capability to consistently yield nanoparticles below 200 nm with narrow PSDs. Computational fluid dynamics (CFD) modelling and nucleation studies further enhanced understanding of the mixing and nucleation dynamics, guiding mixer design improvements toward achieving minimal particle growth after nucleation.

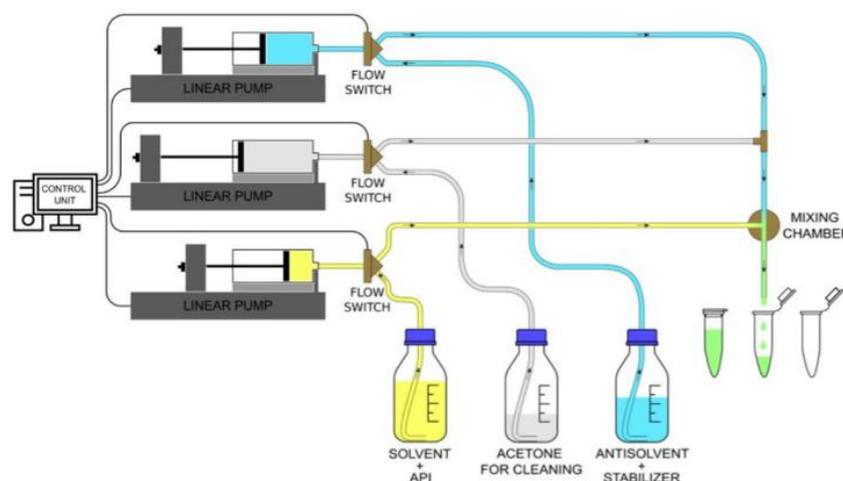
The developed system provides a platform for early-stage drug screening, reducing the risk of formulation-related development hurdles and accelerating translation from laboratory to clinical application.

## Introduction

With the increasing proportion of active pharmaceutical ingredients (APIs) exhibiting poor aqueous solubility, efficient formulation methods are essential for enhancing dissolution rates and bioavailability. Traditional preclinical testing methods employing dimethylsulfoxide (DMSO) frequently lead to later stage formulation challenges, thus requiring robust, scalable, and direct formulation techniques suitable from preclinical through clinical phases. Continuous liquid antisolvent precipitation (CLAP) offers significant potential as a scalable approach for nanocrystalline formulations, ensuring consistent bioavailability of API without the need for reformulation during clinical development.

## Materials and Methods

The CLAP system comprises modular components designed for rapid experimentation and flexibility, HPLC grade pumps for solvent and antisolvent flow control, interchangeable mixing chambers, and automated process control systems. The device's modularity facilitates the rapid assessment of various processing parameters, such as solvent-to-antisolvent ratios, API concentrations, stabiliser types, and mixer geometries.



*Figure 1: Simplified schematic of the CLAP device*

A systematic parametric study was performed utilising dynamic light scattering (DLS) and optical microscopy to evaluate particle size distributions (PSD) and morphology. Computational fluid dynamics (CFD) modelling and nucleation modelling were performed to optimize mixing conditions and minimise particle growth post-nucleation, thus enhancing overall process efficiency and product quality.

## Results and Discussion

The experimental studies revealed clear dependencies between the processing parameters and the resulting PSD and colloidal stability. Higher antisolvent fractions accelerated supersaturation, increasing nucleation rates, but requiring careful control to prevent uncontrolled particle growth. Enhanced mixing intensities achieved through optimised total flow rates and confined impinging jet mixers significantly reduced particle aggregation and size, producing nanoparticles consistently below 200 nm.

CFD modelling highlighted critical aspects of mixing dynamics within the precipitation device, illustrating that high-energy mixing zones are essential to achieve minimal particle sizes. The nucleation modelling further provided insights into the solubility and supersaturation kinetics, enabling refined predictions for optimal process parameters and conditions for controlled nucleation.

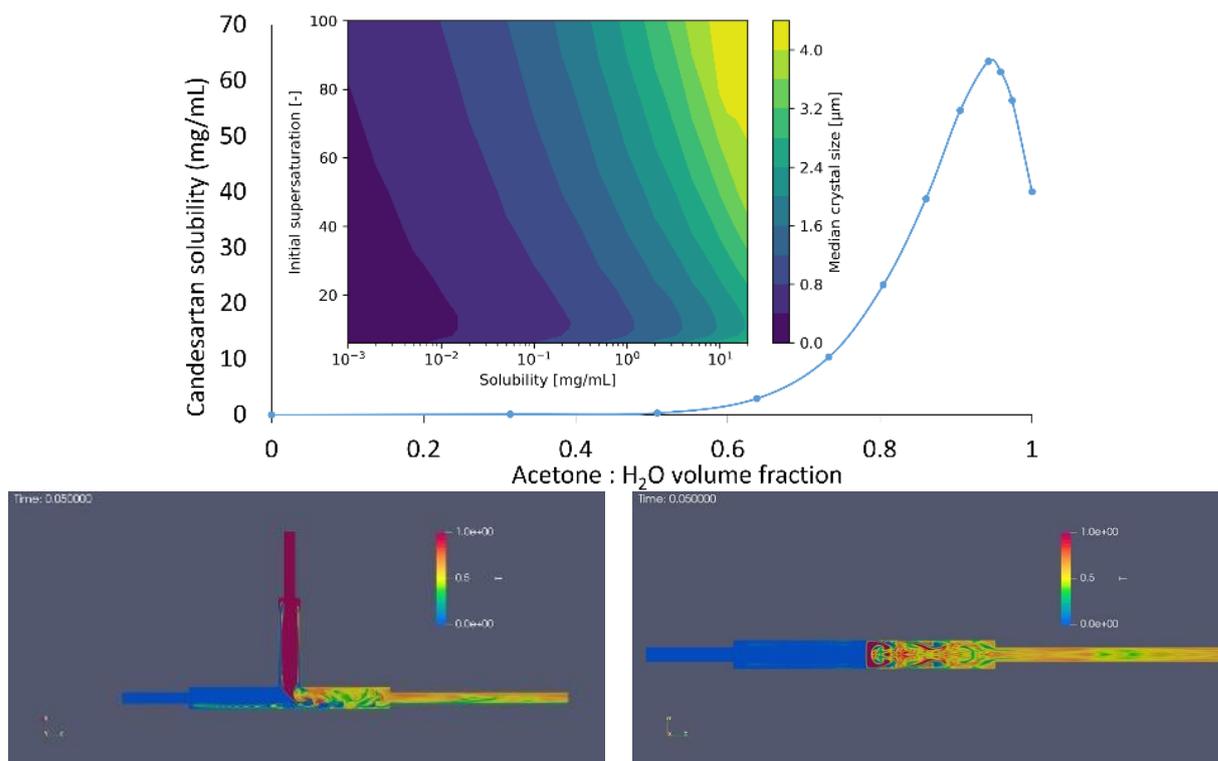


Figure 2: Nucleation modelling (dependence of resulting PSD on API solubility & supersaturation, top), and CFD modelling of a simple T-shaped mixing chamber (bottom)

Improvements to the device, such as ongoing development of potential inline analytical tools for real-time monitoring and automated cleaning protocols, are expected to further enhance performance and throughput.

## **Conclusion**

The developed CLAP device demonstrates robust capabilities for producing nanocrystalline APIs with improved solubility and bioavailability. Extensive parametric studies, supported by computational modelling, provided a thorough understanding of the process dynamics, enabling optimisation of the formulation parameters. The modularity and scalability promise significant streamlining of early-stage pharmaceutical development, reducing the risks associated with formulation challenges and expediting the transition from laboratory experimentation to clinical applications.