Sonocrystallisation - Application of Ultrasound Energy to Control Nucleation of Crystallisation by Syrris

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Background

Syrris creates automated products for research and development chemists and is a world leader in flow chemistry, microreactor and automation technology.

Syrris products are used in a wide variety of applications and laboratories including process, discovery, crystallization, process safety, scale-up and many more.

Syrris products include the innovative range of fully automated batch reactor products (Atlas), which includes the Atlas Reaction Calorimeter (for Heat Flow Calorimetry and Power Compensation Calorimetry) and the flow chemistry systems (FRX, Asia and Africa). Syrris also offers the Medstere software for suggesting novel bioisosteres to lead compounds.

Introduction

Sonocrystallisation is the application of ultrasound energy to control the nucleation of a crystallisation process. Applying Ultrasound to crystallization results in:

- Nucleation at the lowest level of supersaturation where the crystallization overcomes the tendency of the compound to re-dissolve in the solution
- Narrowing of the metastable zone width
- Narrow particle size distribution
- Decrease in the level of undercooling necessary to achieve crystallization (hence avoiding crash crystallisation)
- Highly repeatable and predictable crystallization
- Polymorph control

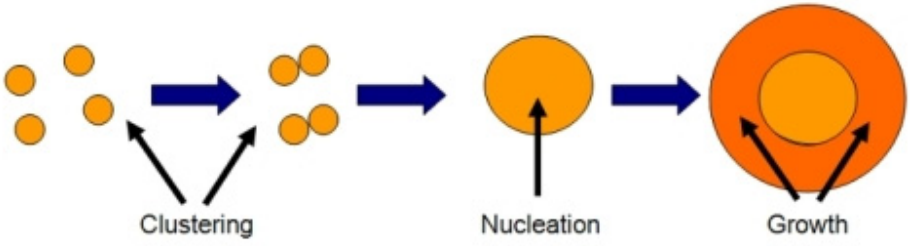
The Atlas Sonolab System offers narrow particle size distribution and polymorph control

Crystallization - Two Major Events

Crystallization consists of two major events:

Nucleation: Solute molecules gather into clusters and reach a critical size to constitute nuclei

Crystal growth: Subsequent growth of the nuclei

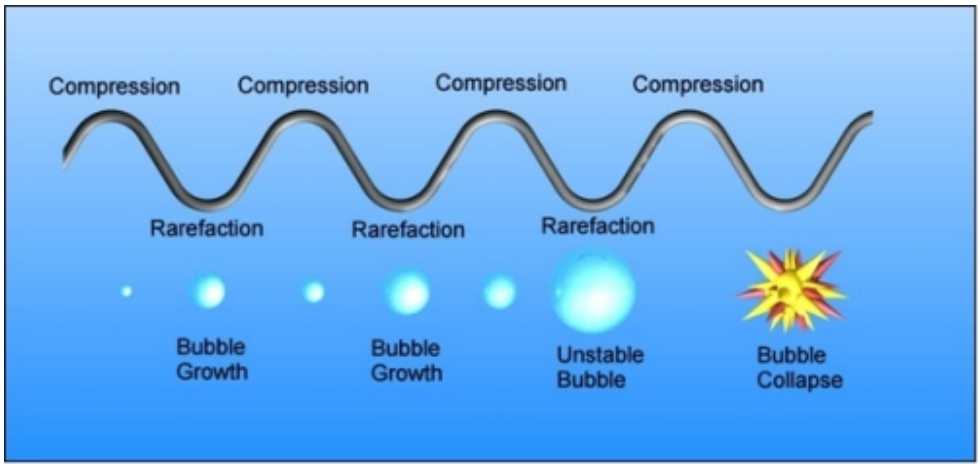


Depending on conditions, either nucleation or growth may be predominant over the other this results in crystals with different shapes and sizes.

- Classically, Nucleation is random, and resultant crystallization processes are uncontrolled, leading to poorly performing API, and drug formulations

How Does Sonocrystallisation Work?

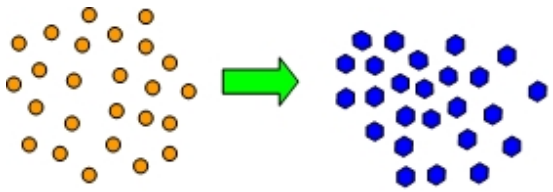
The ultrasound energy creates sequential compression then expansion. Over several cycles a bubble forms and grows then collapses. The collapse of the bubble provides energy to encourage the nucleation process at the earliest possible point in time. This results in highly repeatable and predictable crystallization.



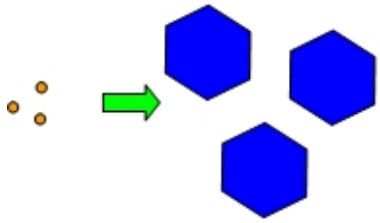
Particle Size Control

It is possible to control the size and number of particles produced by the timing of the application of the ultrasound to the supersauurated solution. Three examples are given below:

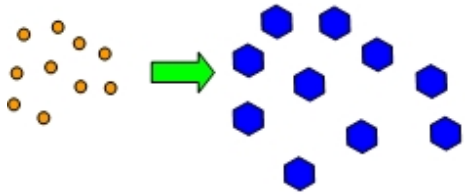
1. Continuous ultrasound produces many nuclei resulting in small crystals



2. Initial ultrasound only produces finite nuclei which can be grown into large crystals



3. Pulsed ultrasound gives tailored crystal size



Polymorph Control

Ultrasound can induce crystallization over a range of supersaturation conditions and therefore potentially access a range of different physical forms.

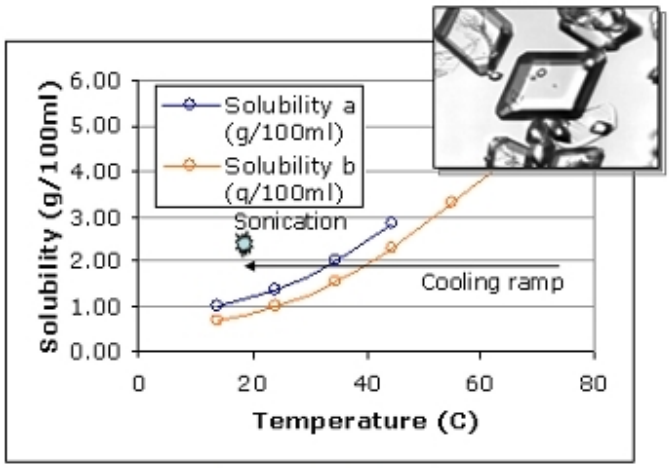
Low supersaturation: Tends to yield thermodynamic polymorph (most likely to produce a single polymorph)

High supersaturation: Tends to yield kinetic polymorph (if a stable kinetic polymorph is accessible)

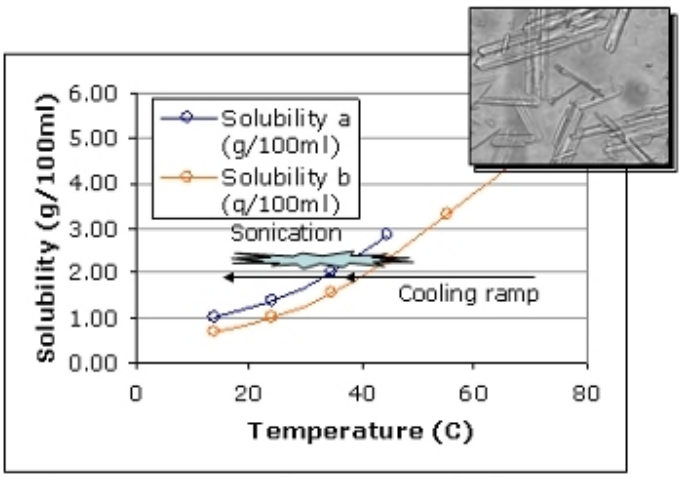
The key advantage to polymorph studies using Sonocrystallisation is reproducibility.

Polymorph control example:

- L-glutamic acid has two polymorphic forms: alpha & beta
- Meta-stable alpha-form: produced under kinetic control
- The metastable alpha form is difficult to obtain
- Use power ultrasound to reproducibly prepare the alpha or beta form



With sonication < 18°C the a form can be prepared



With sonication during cooling the ß form can be prepared

Source: Syrris.

For more information on this source please visit Syrris

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