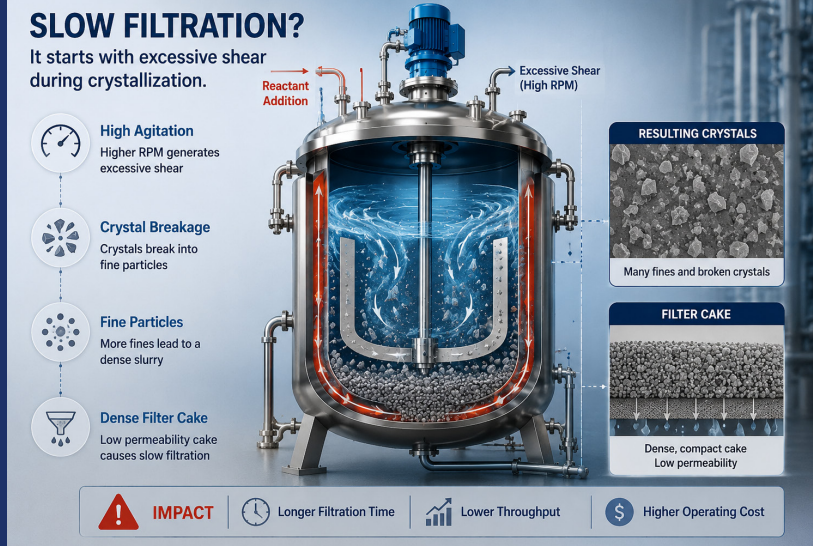


Introduction

- Reactive crystallization is one of the most critical operations in pharmaceutical manufacturing, where **hydrodynamic conditions directly influence crystal size, morphology, and downstream filtration performance**. Even when crystallization is completed successfully, excessive agitation can generate high shear forces that promote crystal breakage and the formation of fine particles, leading to poor filterability.
- Traditional process optimization often relies on changing agitator speed and addition time through repeated plant trials. However, without understanding the underlying hydrodynamic mechanisms—such as shear rate and particle collision energy—it is difficult to predict their impact on crystal growth, crystal breakage, and downstream filtration performance.
- This case study demonstrates how VisiMix was used to analyze shear rate and particle collision energy, identify the root cause of slow filtration, and establish an optimized scale-up strategy for a 1.6 kL commercial reactor, reducing filtration time from 7.5 hours to less than 2 hours.



The Process Challenge

Reactive crystallization was carried out in a **500 L reactor** equipped with an Anchor agitator and four baffles at a **356 L working volume**. During the process, 320 L of water was initially charged into the reactor, followed by the gradual addition of 36 L of reaction mass containing 32 L of DMAc and 8 Kg of suspended solids, where crystallization occurred immediately upon mixing.

Although crystallization was successfully completed under different operating conditions, filtration performance varied significantly. At **65 RPM with a 70-minute addition time**, filtration required approximately **7.5 hours**, whereas operating at **25 RPM with a 260-minute addition time** reduced filtration to approximately 2.35 hours. This indicated that hydrodynamic conditions during crystallization had a major influence on crystal morphology and filter cake permeability.

Objective

The objective of this study was to identify the root cause of slow filtration during reactive crystallization and develop a reliable hydrodynamic scale-up strategy using VisiMix for a **1.6 kL commercial reactor (30 kg batch size)**.

The study aimed to:

- Determine the influence of agitation intensity on crystal growth and breakage.
- Evaluate the combined effect of agitator speed and reaction mass addition time on crystal filterability.
- Match the critical hydrodynamic conditions of the successful pilot trial during scale-up.
- Establish the optimum operating conditions to achieve faster filtration and improved process performance.

VisiMix Simulation Approach

To identify the root cause of slow filtration, the reactive crystallization process was first modeled in **VisiMix** using the actual configuration of the **500 L pilot reactor**. Two operating conditions were simulated—**65 RPM with a 70-minute reaction mass addition** and **25 RPM with a 260-minute addition**—to understand how agitation intensity and addition strategy influenced crystal growth, crystal breakage, and filterability.

Once the favourable hydrodynamic conditions were established, the same methodology was applied to the **1.6 kL commercial reactor**. By matching the critical parameters, particularly turbulent shear rate and particle collision energy, VisiMix determined the equivalent operating speed required to achieve reliable commercial-scale performance.

TANK WITH ELLIPTICAL BOTTOM		FLAT BAFFLE-2	
Inside diameter	800 mm	Number	4
Total tank height	1061 mm	Width	75 mm
Total volume	500 l	Length	800 mm
Level of media	774.9 mm	Dist. from bottom	170 mm
Volume of media	356 l	Dist. from wall	10 mm
		Angle to radius (fi)	0 deg

ANCHOR	
Tip diameter (D)	600 mm
Number of blades	1
Height of blade	400 mm
Width of blade	42 mm
Rotational speed	25 Rpm
Motor power	3 hp

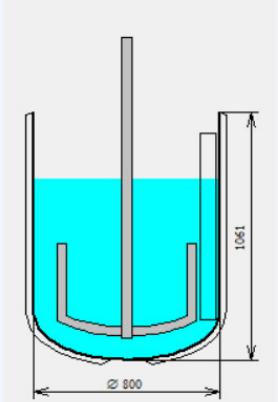


Figure: VisiMix model of the 500 L pilot-scale reactor

TANK WITH ELLIPTICAL BOTTOM		FLAT BAFFLE-2	
Inside diameter	1200 mm	Number	4
Total tank height	1515 mm	Width	100 mm
Total volume	1600 l	Length	1200 mm
Level of media	600 mm	Dist. from bottom	250 mm
Volume of media	565.5 l	Dist. from wall	25 mm
		Angle to radius (fi)	0 deg

ANCHOR	
Tip diameter (D)	900 mm
Number of blades	1
Height of blade	600 mm
Width of blade	63 mm
Rotational speed	21 Rpm
Motor power	7.5 hp

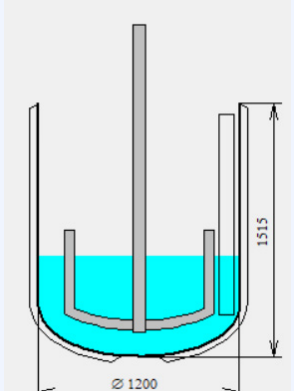


Figure: VisiMix simulation model of the 1.6 kL commercial reactor

The VisiMix simulations generated the key hydrodynamic parameters governing reactive crystallization, including **turbulent shear rate**, **maximum particle collision energy**, **mixing power**, and **energy dissipation**. These engineering parameters were used to compare the 65 RPM and 25 RPM operating conditions and subsequently establish the equivalent operating speed for the 1.6 kL commercial reactor through hydrodynamic similarity.

Simulation Results

The VisiMix simulations quantitatively compared the hydrodynamic conditions generated in the 500 L pilot reactor and the 1.6 kL commercial reactor. The key engineering parameters presented below were used to identify the root cause of crystal breakage and establish the optimum operating speed for reliable commercial scale-up.

KEY SCALING UP PARAMETERS	500 L		1.6 KL
	65 RPM	25 RPM	21 RPM
Mixing power, W	126	7.19	29.2
Turbulent shear rate near the impeller blade, 1/s	14100	3360	3350
Maximum energy of particle collisions, J	4.92E-13	7.29E-14	7.27E-14
Energy dissipation - maximum value, W/kg	128	7.29	7.27

The simulation results revealed that operating at **65 RPM** generated significantly higher **turbulent shear** and **particle collision energy** than the **25 RPM** condition. These elevated hydrodynamic stresses increased crystal attrition, producing a larger proportion of fine particles that formed a **dense, low-permeability filter cake**, resulting in prolonged filtration.

In contrast, operating at **25 RPM** created a milder hydrodynamic environment that promoted larger, well-defined crystals. Combined with the **260-minute reaction mass addition**, the process provided sufficient time for controlled crystal growth, producing a **more porous filter cake** and substantially improving filtration performance.

For commercial scale-up, VisiMix identified **21 RPM** as the equivalent operating speed for the **1.6 kL reactor** by closely matching the turbulent shear rate and particle collision energy of the successful **25 RPM** pilot trial. The optimized process was implemented together with a **minimum 4-hour reaction mass addition**, ensuring both hydrodynamic similarity and favourable crystal growth conditions.

Key Observations

- **Higher agitation accelerated crystal attrition:** At **65 RPM**, VisiMix predicted the highest turbulent shear rate (**14,100 s⁻¹**) and particle collision energy, creating an aggressive hydrodynamic environment that increased crystal breakage and the generation of fine particles.
- **Lower shear created favourable crystal growth conditions:** Reducing the agitation speed to **25 RPM** lowered the shear rate to approximately **3,360 s⁻¹**, providing a milder mixing environment that promoted the formation of larger, well-defined crystals with improved crystal morphology.
- **Gradual reaction mass addition improved filterability:** Extending the **reaction mass addition from 70 minutes to 260 minutes** provided sufficient time for controlled crystal growth, resulting in a **more porous filter cake** that enabled easier liquid drainage and significantly faster filtration.
- **Hydrodynamic similarity enabled successful scale-up:** By matching the **turbulent shear rate** and **particle collision energy** of the optimized **25 RPM** pilot trial, VisiMix identified **21 RPM** as the equivalent operating speed for the **1.6 kL commercial reactor**, ensuring consistent crystallization performance during commercial implementation.

The optimized operating strategy of **21 RPM** combined with a **minimum 4-hour reaction mass addition** reduced filtration time from **7.5 hours to less than 2 hours**, demonstrating the value of hydrodynamic scale-up using VisiMix.

Conclusion

- This collaborative study demonstrated how VisiMix transformed reactive crystallization from a trial-and-error process into a scientifically optimized scale-up methodology. By identifying turbulent shear rate and particle collision energy as the key hydrodynamic parameters influencing crystal breakage, the optimum operating conditions were established with confidence.
- The optimized strategy—**21 RPM** combined with a **minimum 4-hour reaction mass addition**—successfully reproduced the favourable crystallization environment of the pilot trial in the **1.6 kL commercial reactor** (30 kg batch). As a result, filtration time was reduced from **7.5 hours to less than 2 hours**, delivering improved crystal quality, enhanced filterability, and a reliable commercial-scale process.

VisiMix enables confident crystallization scale-up by matching critical hydrodynamic conditions, reducing plant trials, and improving commercial process reliability.

Start Your Free Trial of VisiMix Today

Want to model your own process and avoid costly mistakes?

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