Marie Skłodowska-Curie Actions

LongActNow

Is bottom-up a long-acting solution?

2023 CRS Annual Meeting
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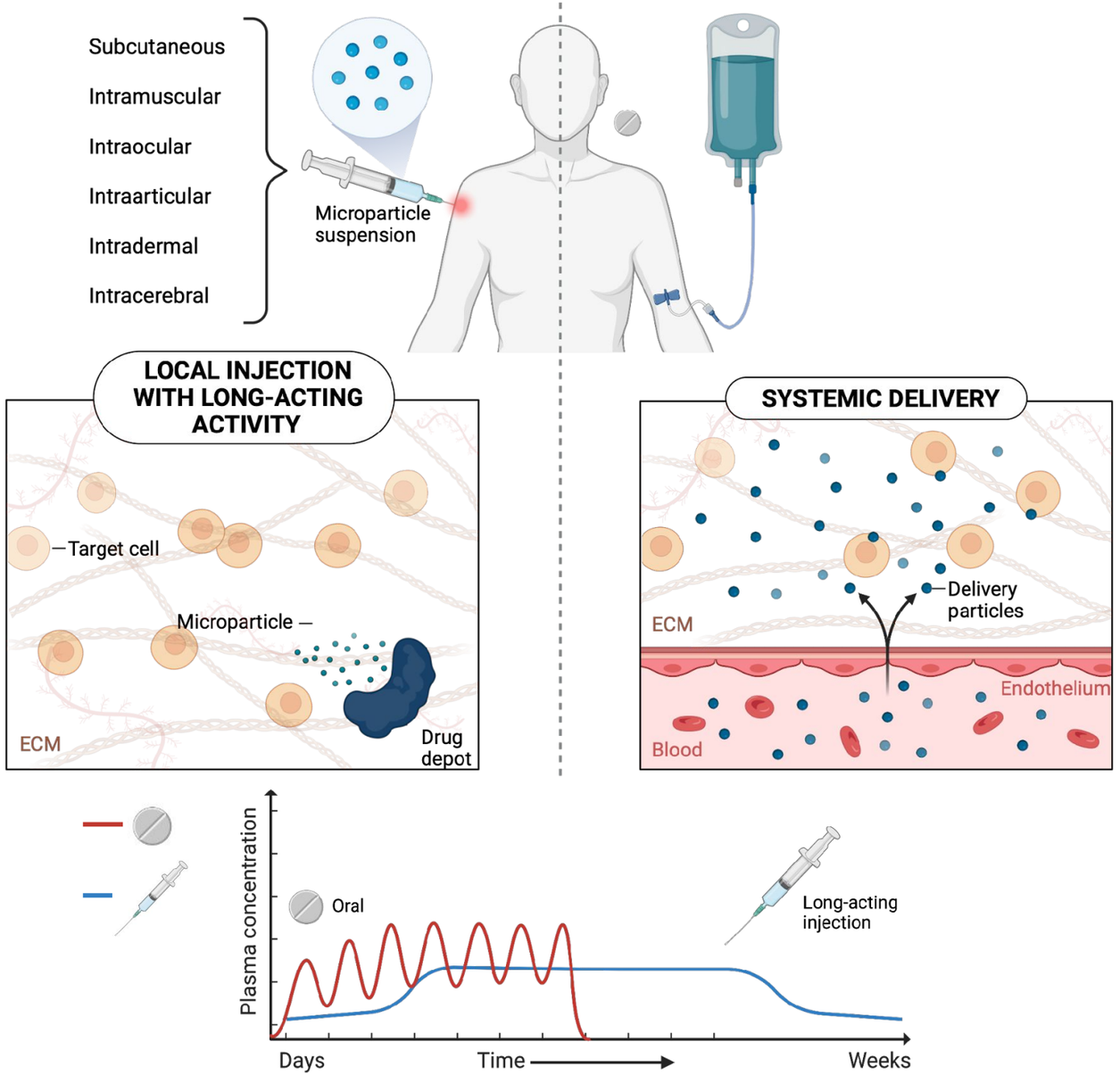
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

What are LAIs?



Project hypothesis

Experimental determination of which **excipients** work best to control nucleation, growth and stability by:

1. Milling – top-down approach
2. Liquid antisolvent precipitation – bottom-up approach

To produce long-acting injectable suspensions.

- Can we use same excipients for the different approaches?
- Are the properties of the particles produced by the different techniques similar?

- **Target particle size:** 5-10 µm

Project hypothesis

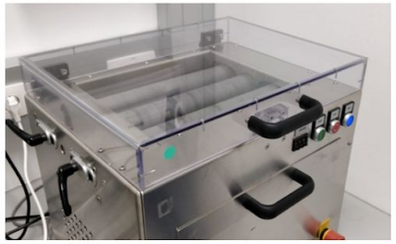
Top-down approach

Aqueous solution of excipients

Add API powder

Transfer to vial with beads

Start roller mill
Stirring rate: ~ 100 rpm

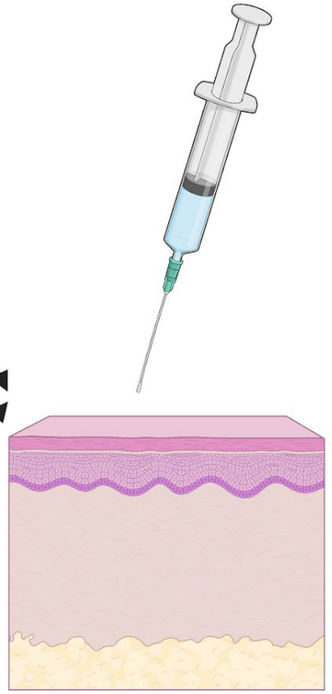


Bottom-up approach

API solution in organic solvent

Aqueous solution of excipients (+ **seeds**)

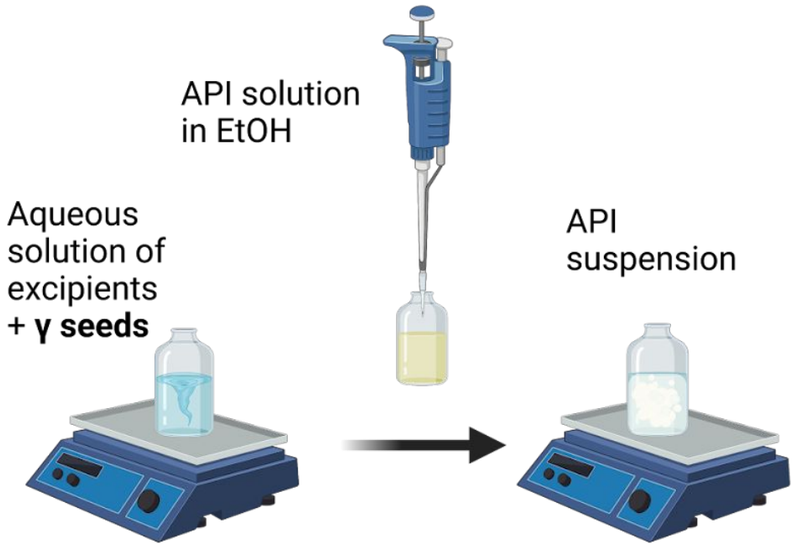
API suspension



- Control over solid-state form
- Control over particle size
- Morphology
- Dissolution
- Stability over time
- Scalability to continuous

Seeding approach schematics

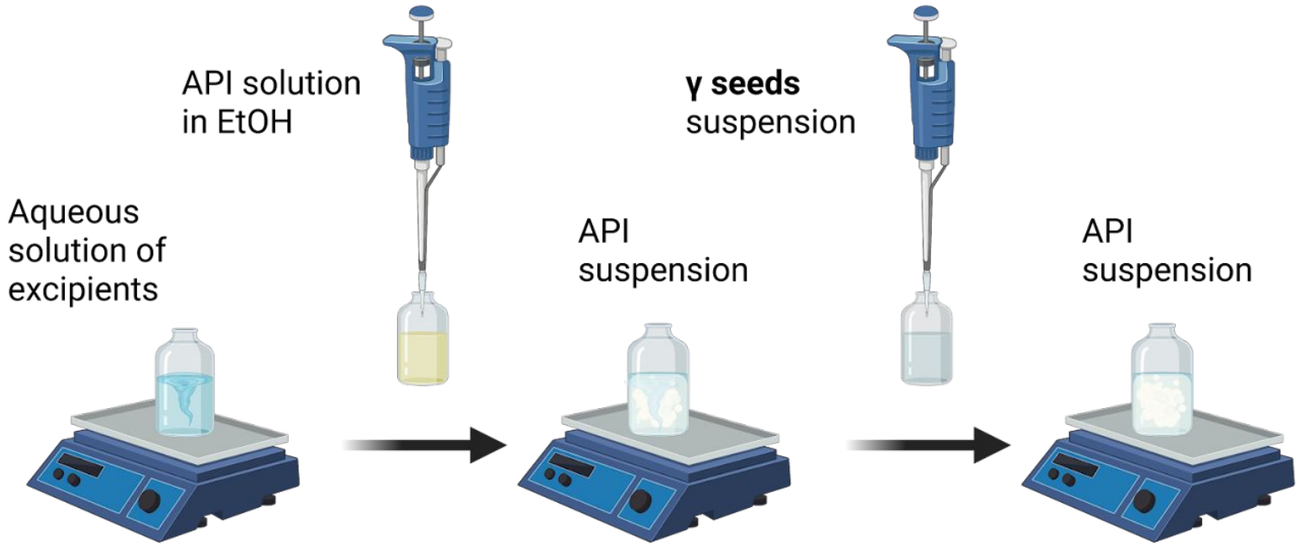
1) Seed addition before nucleation



Formulations:

- Formulation 1 - Poloxamer 407 + DOSS
- Formulation 2 - Poloxamer 407 + SLS

2) Seed addition after nucleation



Experimental conditions:

- T: 25 °C
- Mixing rate: 1200 rpm
- Solvent/antisolvent ration: 1:10
- API concentration: 10 mg/mL
- Total volume: 11 mL

Hugo Silva, M., Kumar, A., Hodnett, B. K., Tajber, L., Holm, R., & Hudson, S. P. (2022). Impact of Excipients and Seeding on the Solid-State Form Transformation of Indomethacin during Liquid Antisolvent Precipitation. *Crystal Growth & Design*, *22*(10), 6056-6069.

PSD & PXRD of indomethacin miscrosuspensions

Time point	Formulation 1 | SB			Formulation 1 | SA		
	Form by PXRD			Form by PXRD		
	1%w/v	2%w/v	4%w/v	1%w/v	2%w/v	4%w/v
4h	α	α	α	α	α	α
24h	α	α	α	α	α	α

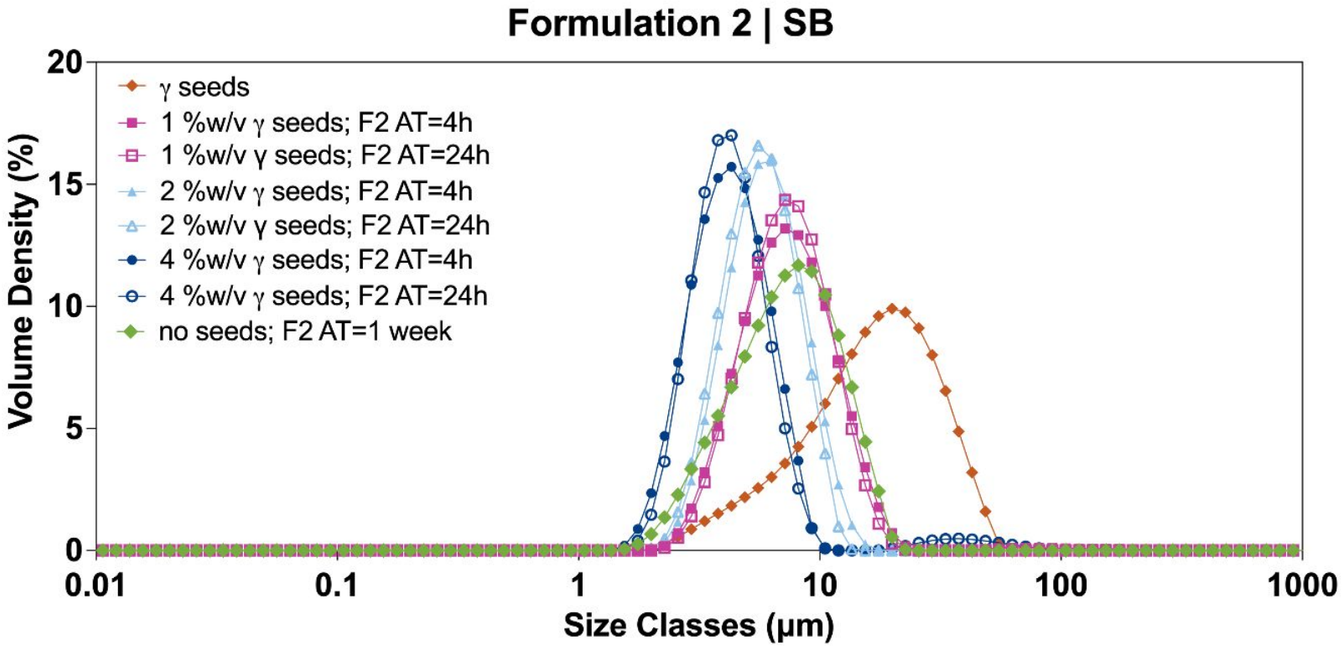
Time point	Formulation 2 | SB			Formulation 2 | SA		
	Form by PXRD			Form by PXRD		
	1%w/v	2%w/v	4%w/v	1%w/v	2%w/v	4%w/v
4h	γ	γ	γ	α	α	α
24h	γ	γ	γ	α	γ	α

SA: seeding after nucleation

SB: seeding before nucleation

γ form: stable

α form: metastable



AT: aging time

F2: formulation 2

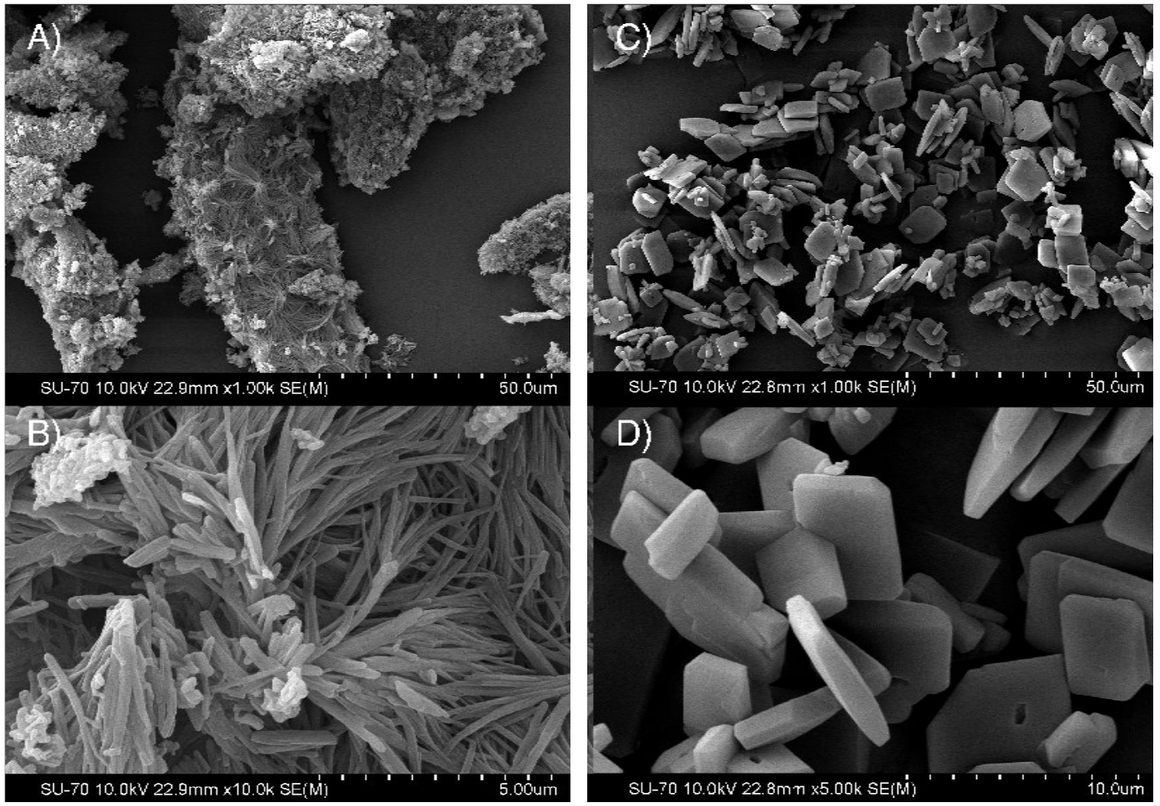
Hugo Silva, M., Kumar, A., Hodnett, B. K., Tajber, L., Holm, R., & Hudson, S. P. (2022). Impact of Excipients and Seeding on the Solid-State Form Transformation of Indomethacin during Liquid Antisolvent Precipitation. *Crystal Growth & Design*, *22*(10), 6056-6069.

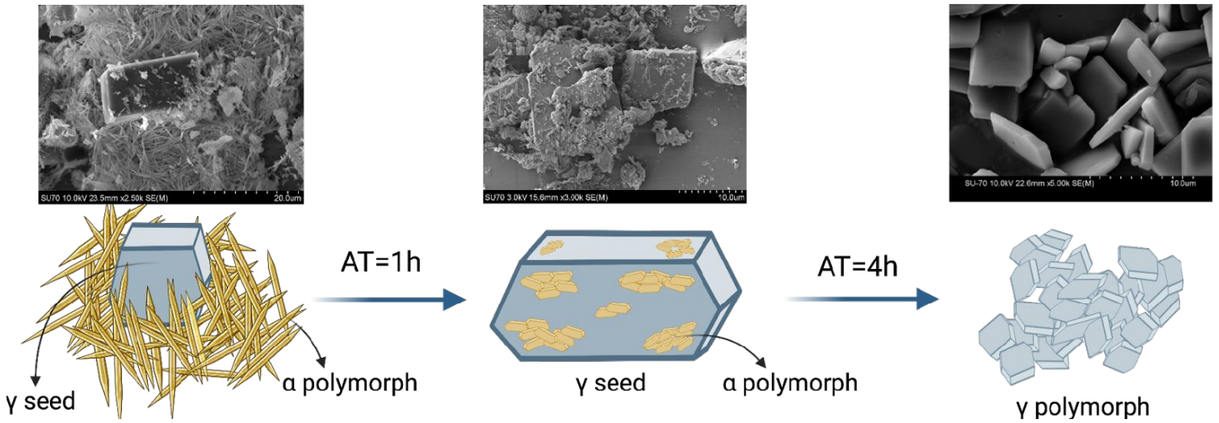
SEM of indomethacin microsuspensions

Seeding after nucleation

Formulation 1
Poloxamer 407 + DOSS

Formulation 2
Poloxamer 407 + SLS





γ form: stable

α form: metastable

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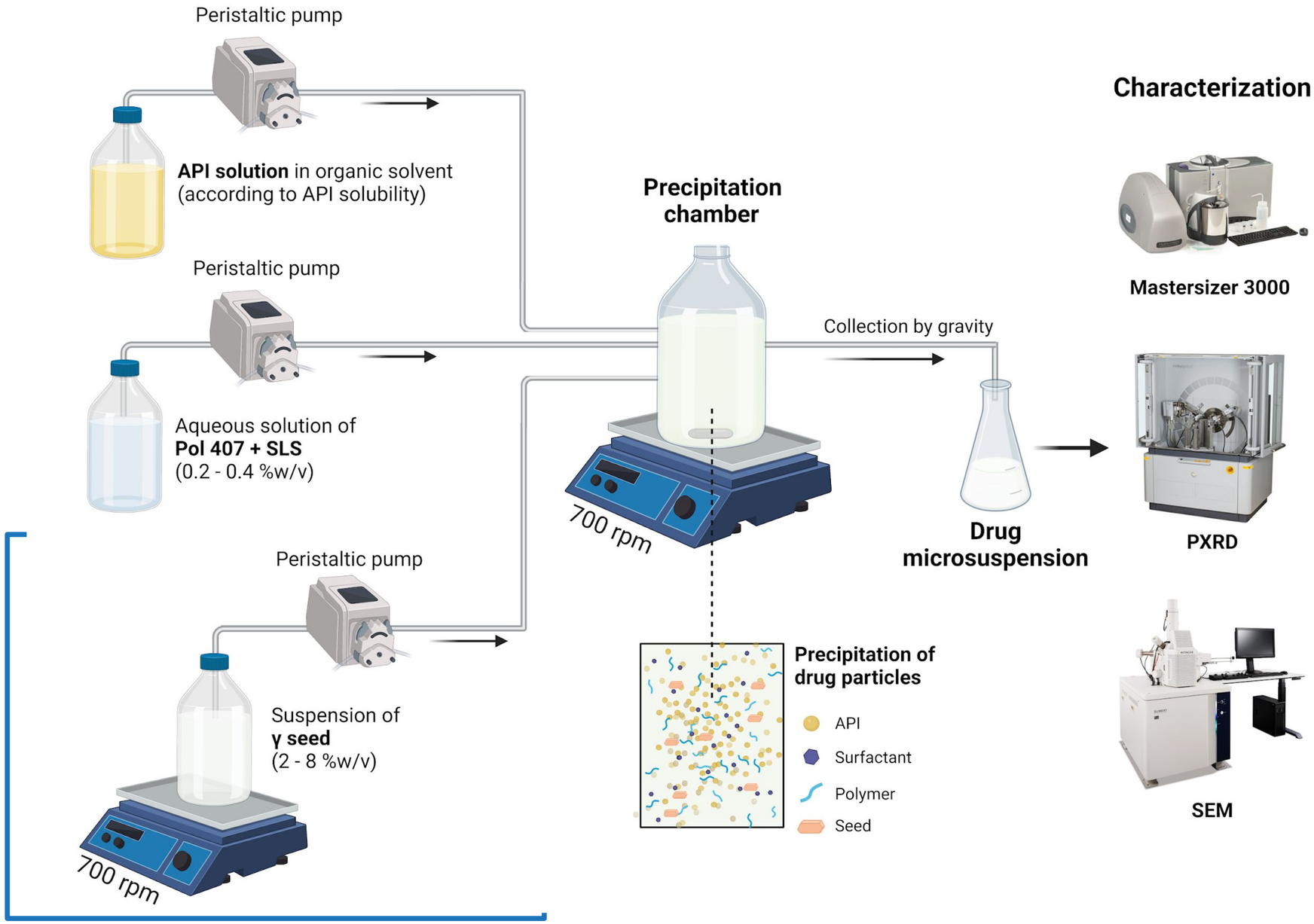
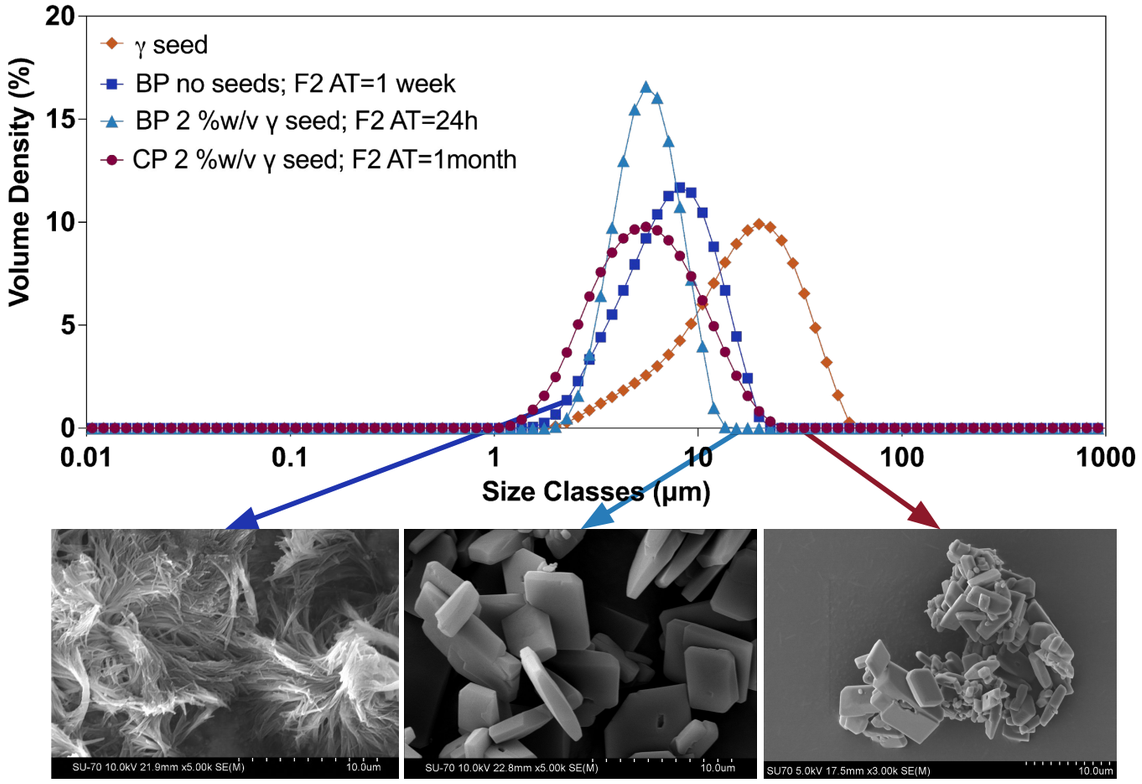
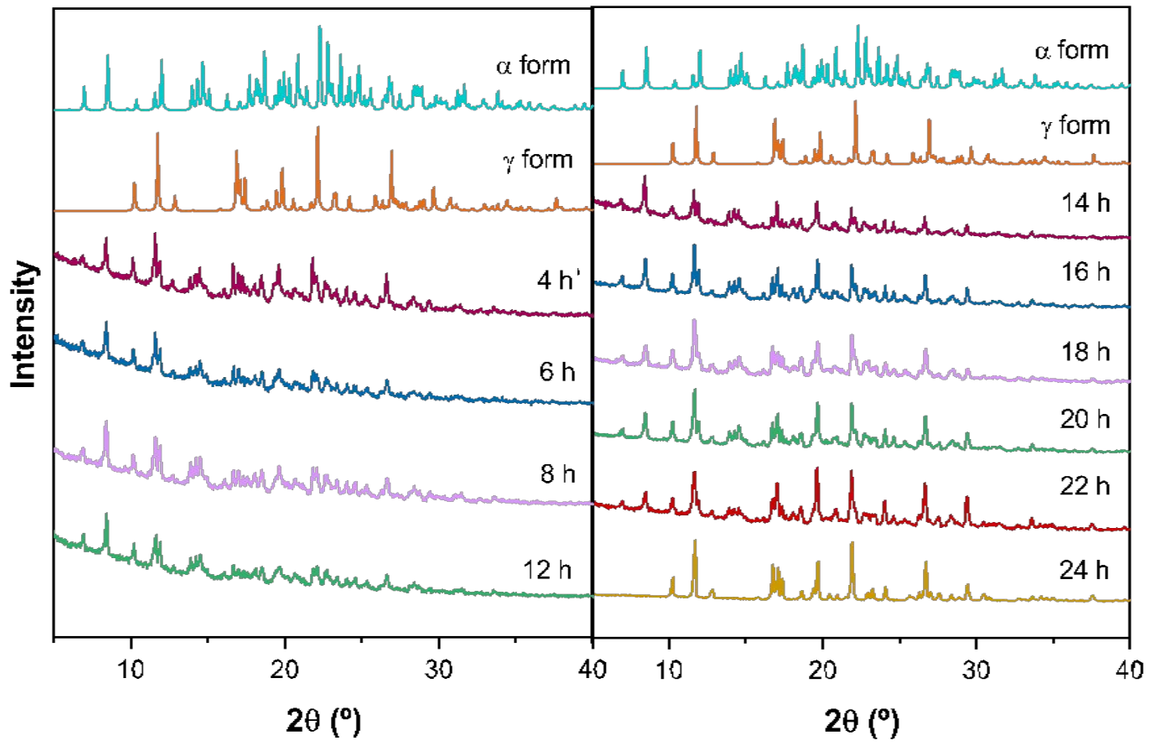
Contir[illegible] process | Seeding



PSD, SEM & PXRD indomethacin microsuspension

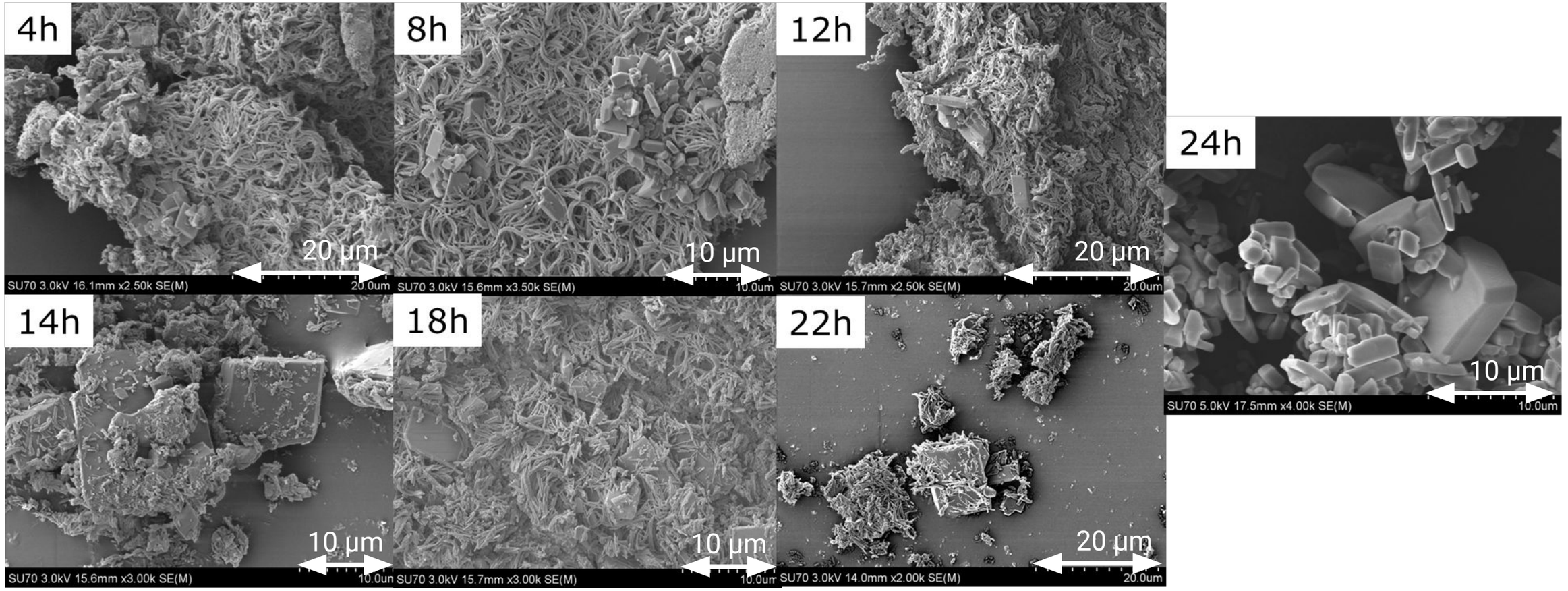




γ form: stable

α form: metastable

SEM observations of solid-state form evolution



Controlling the solid-state form outcome in continuous mode

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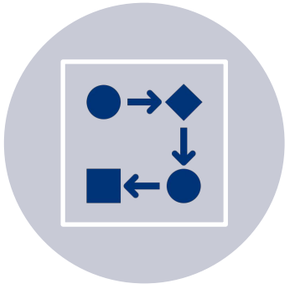


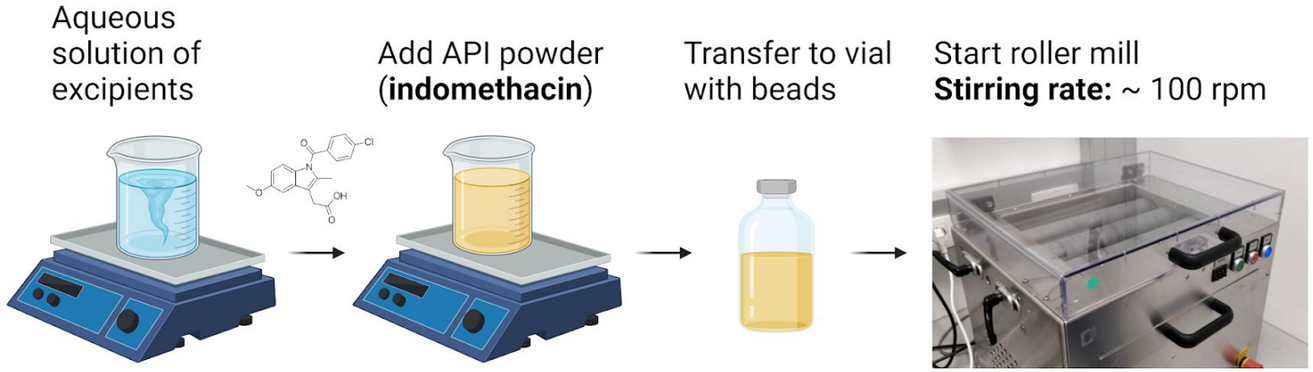
Longer period of time for solid-state form transformation

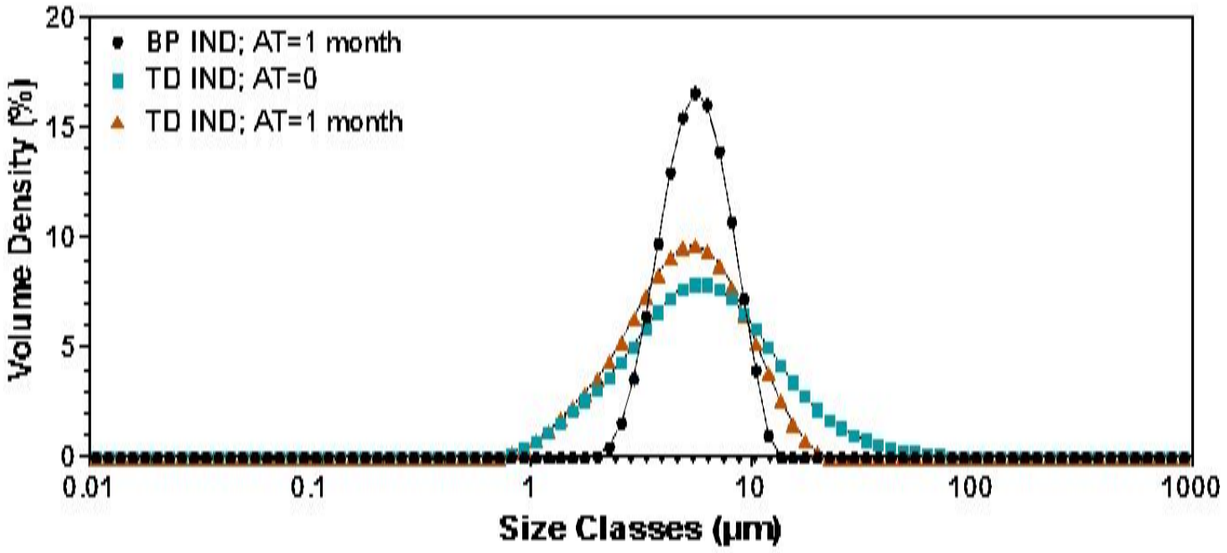
Challenge in getting aimed PSD

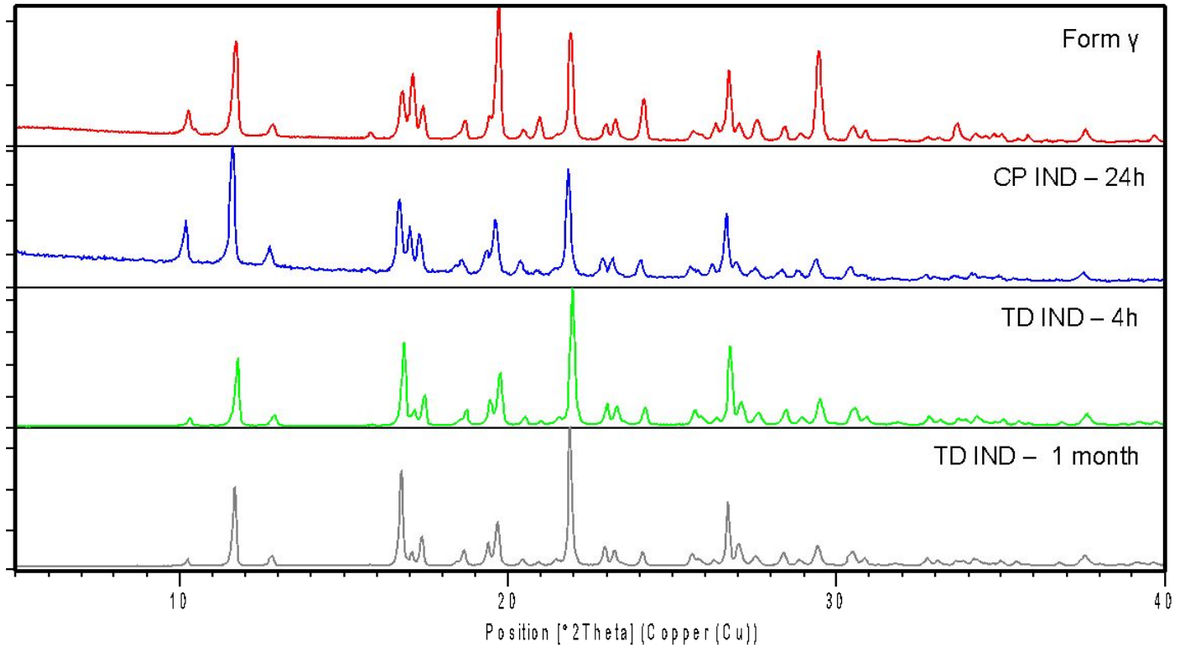
Producing seeds with consistent PSD

Optimization of flow rate and mixing conditions

Wet media milling microsuspensions





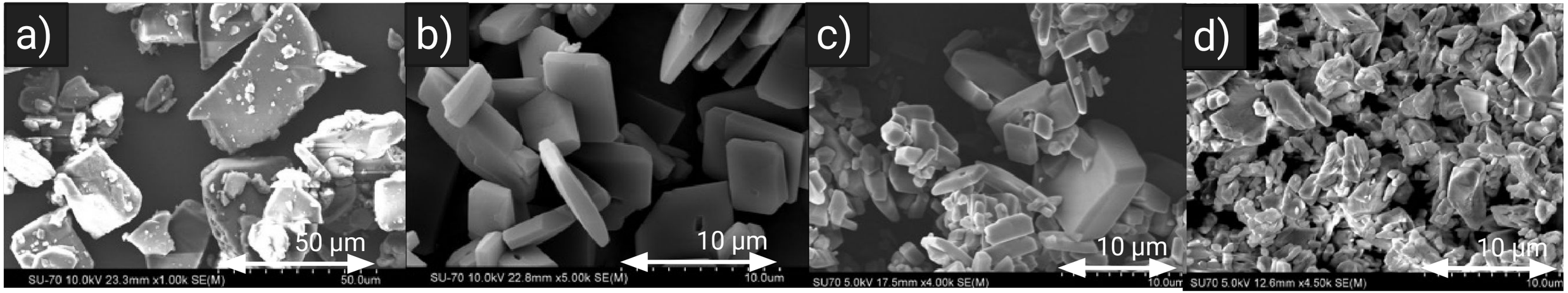


IND: indomethacin *CP: continuous process liquid antisolvent precipitation*

BP: batch-process *TD: top-down (wet media milling)*

AT: aging time

Comparison production methods



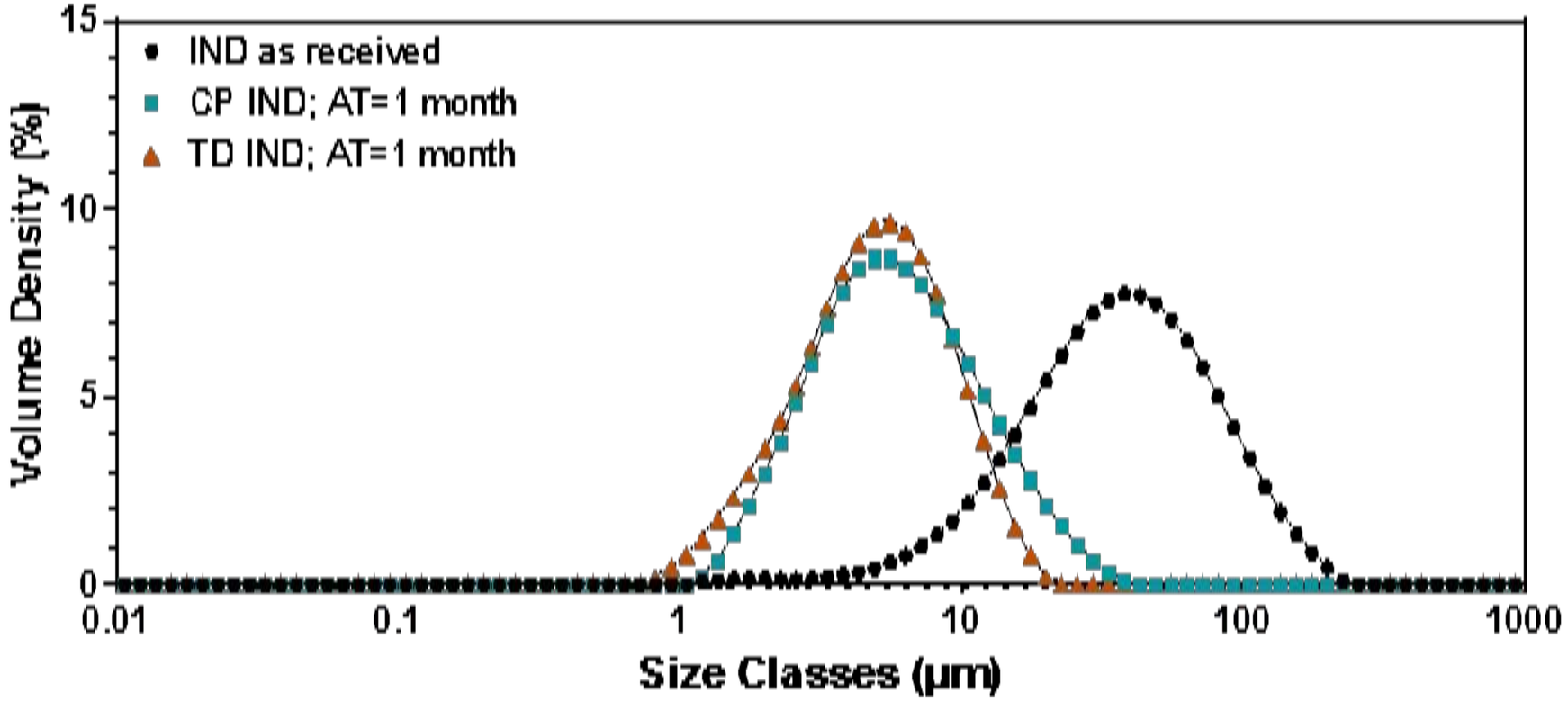
As received

Batch mode
LAS precipitation

Continuous mode
LAS precipitation

Continuous mode
Wet media milling

Comparison PSD of the formulations produced



IND: indomethacin

CP: continuous process liquid antisolvent precipitation

TD: top-down (wet media milling)

Comparison dissolution profile of the formulations produced

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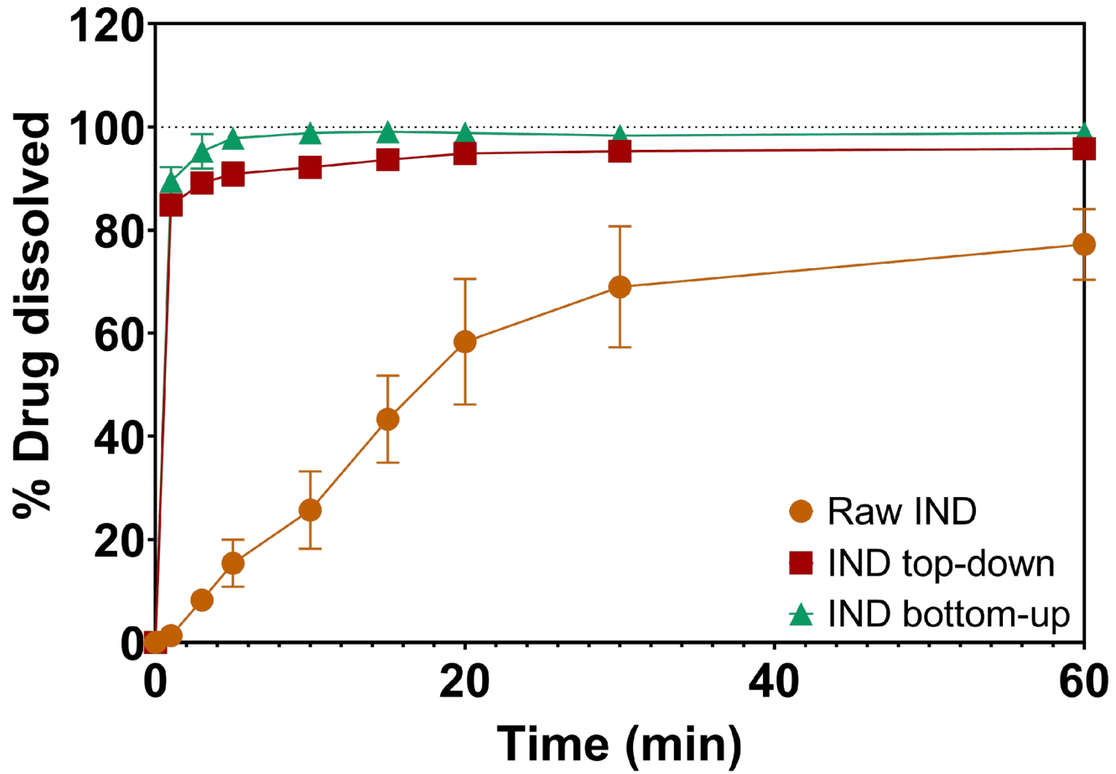
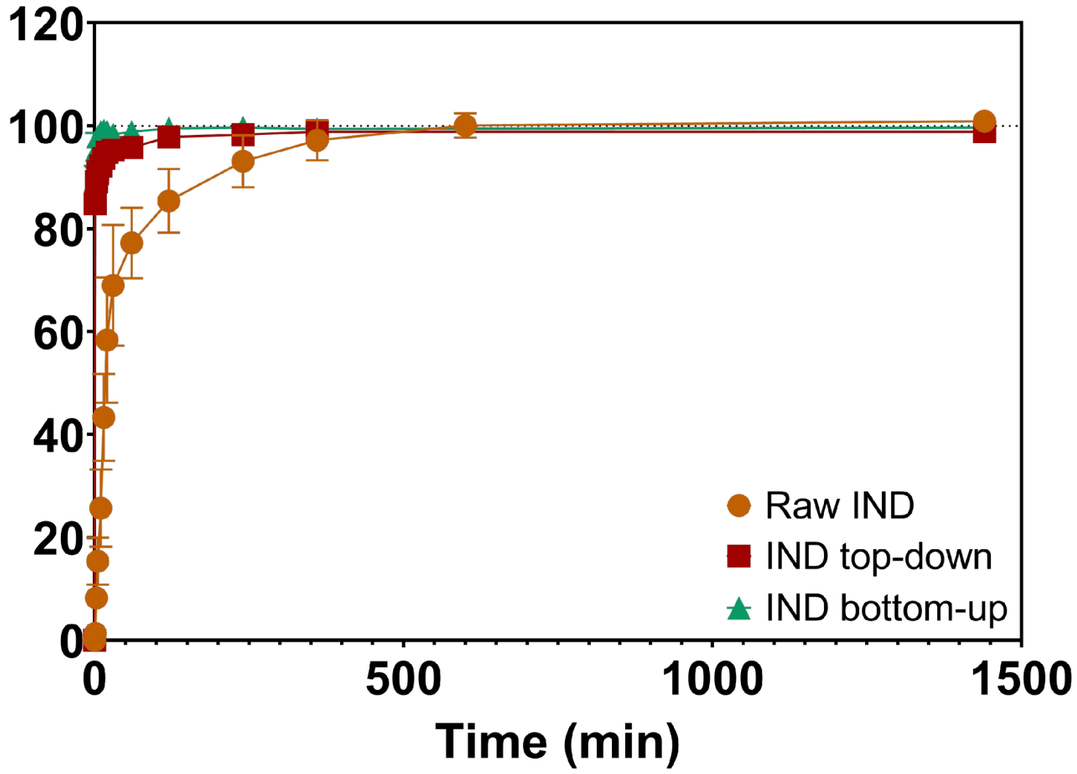
First 60 minutes



After 24 hours



Media: PBS pH 7.4
Temperature: 37 °C
Agitation: 150 rpm

Volume dissolution: 500 mL
API concentration: 5 mg/L
Sink conditions

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Comparison techniques

	Wet media milling	BP LAS precipitation	CP LAS precipitation
Particle production	✔	✔	✔
Desired solid-state form and PSD	✔	✔	✔
Control over solid-state form and PSD	✔	✔	✔
Excipient selection for particle suspension	✔	✔	✔
Design stable particle suspension	✔	✔	✔
Scalability of the method	-	✔	-
Control over release kinetics	-	-	-

Conclusions

To produce long-acting injectable suspensions.

- Can we use same excipients for the different approaches?
- Are the properties of the particles produced by the different techniques similar?

- Production of similar stable API suspensions by top-down and bottom-up approaches in continuous mode is feasible
  - Challenges remain including
    - solvent removal and
    - API loading per unit volume
  - Barriers remain to switching from industrially accepted top-down approaches to alternative bottom-up approaches include
    - Cost savings still unclear
    - Regulatory considerations
    - Industrial experience, ‘in house know-how’
    - Not clear if any change in in vivo efficacy by using new bottom-up approach

- Selection and addition of excipients is API and approach dependent

Acknowledgements

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Marta Bergillos Ruiz

Peuli Ghosh

Parenterals & Liquids group – J&J

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Thank you
for your time today

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