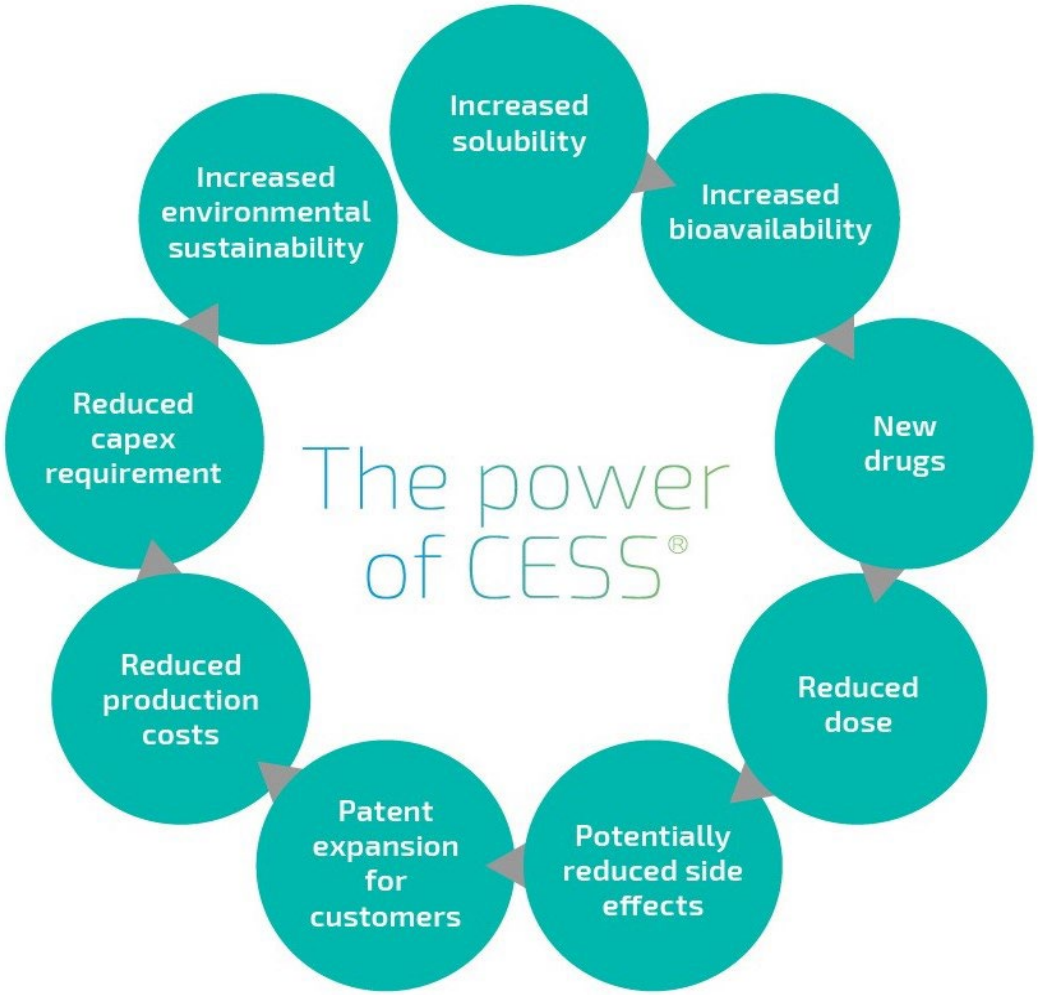
nanoform
small is powerful®

Nanoforming - the Patient- and Planet-Centric Approach From Increasing Bioavailability to Enabling Sustained Drug Delivery

BOS Basel - 4th July 2023

Small is Patient- & Planet-Centric

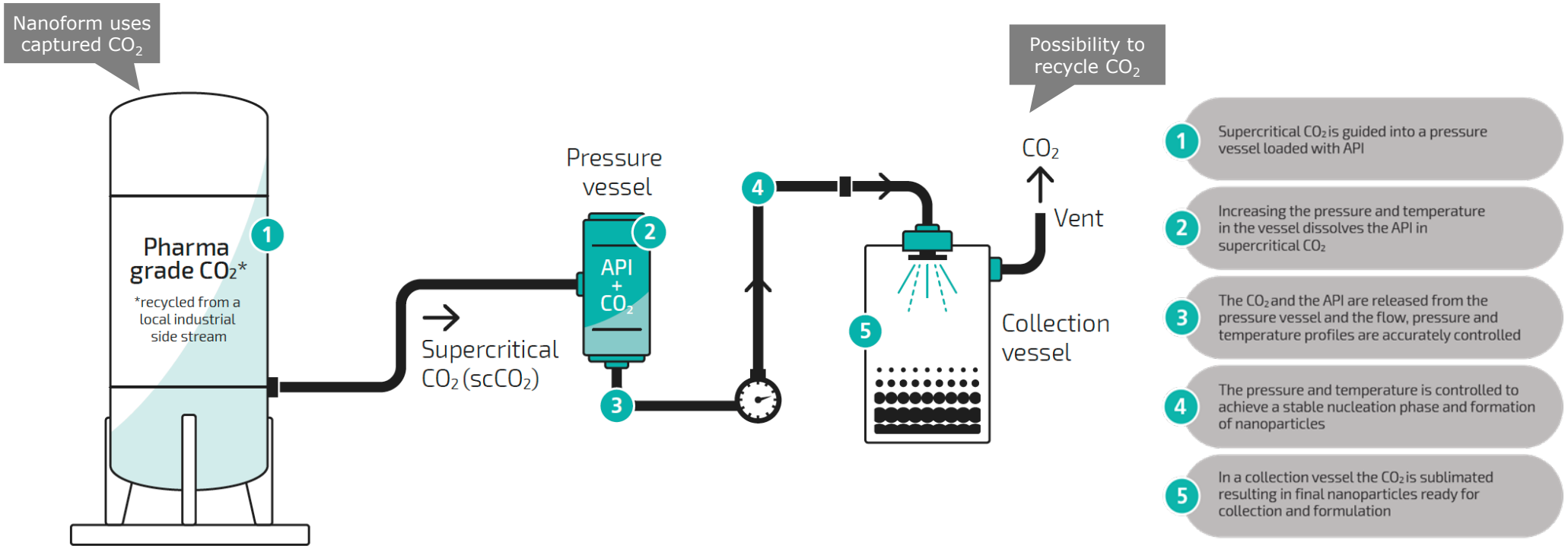


Benefits for the Planet:

- Most pharma and biotech carbon footprints (>90%) are from the supply chain
- Lower DS and DP volumes – reduced costs
- Less organic hydrocarbon solvents, polymers and excipients required as seen with ASDs
- We use recycled CO_2 as a side product from a local industry – possibility to further recycle this and become a carbon sink
- Simplified supply chain
- Opportunity to support on-shoring initiatives

Patented CESS® technology - nanoforming small molecules

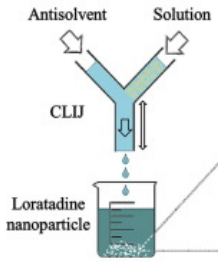
The Controlled Expansion of Supercritical Solutions - CESS®



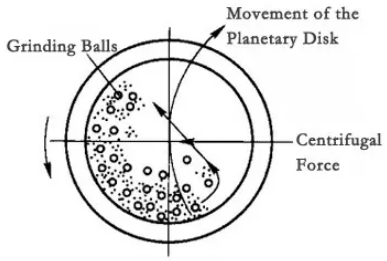
- **Nanoform's CESS® is the only 'solution-to-particle' technology that can manufacture nanoparticles without organic hydrocarbon solvents, excipients and complex production processes.**

Nanoparticle and ASD technologies

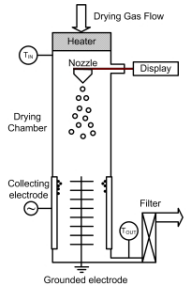
Antisolvent / microfluidics



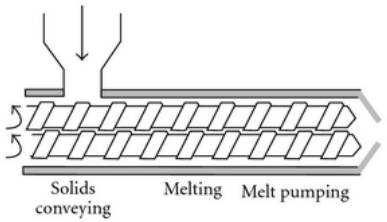
Wet milling / homogenisation



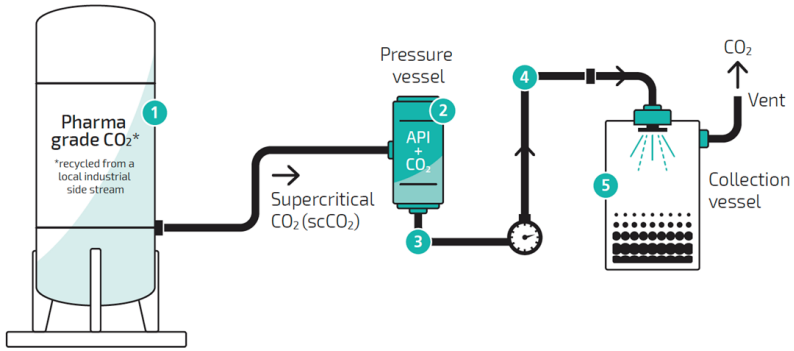
Spray drying



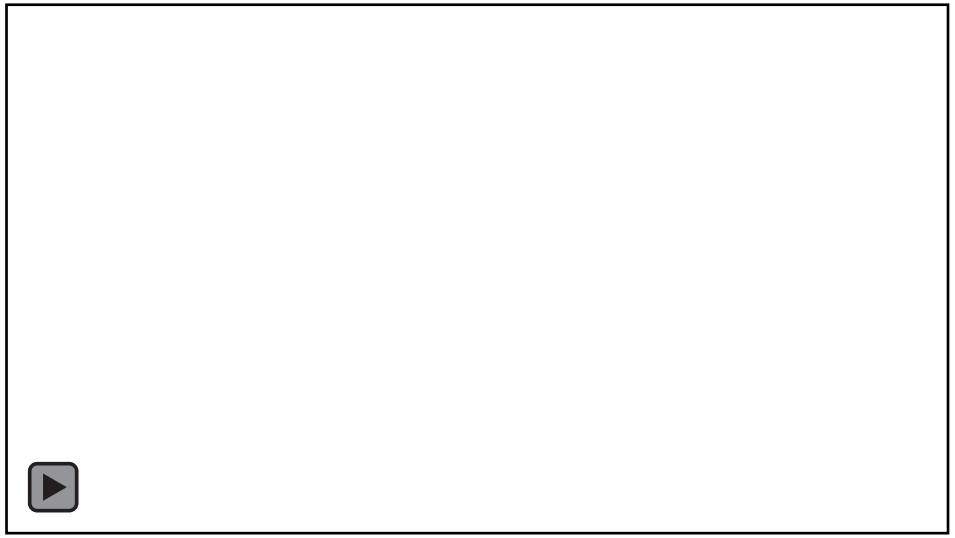
Hot melt extrusion



Nanoform's approach

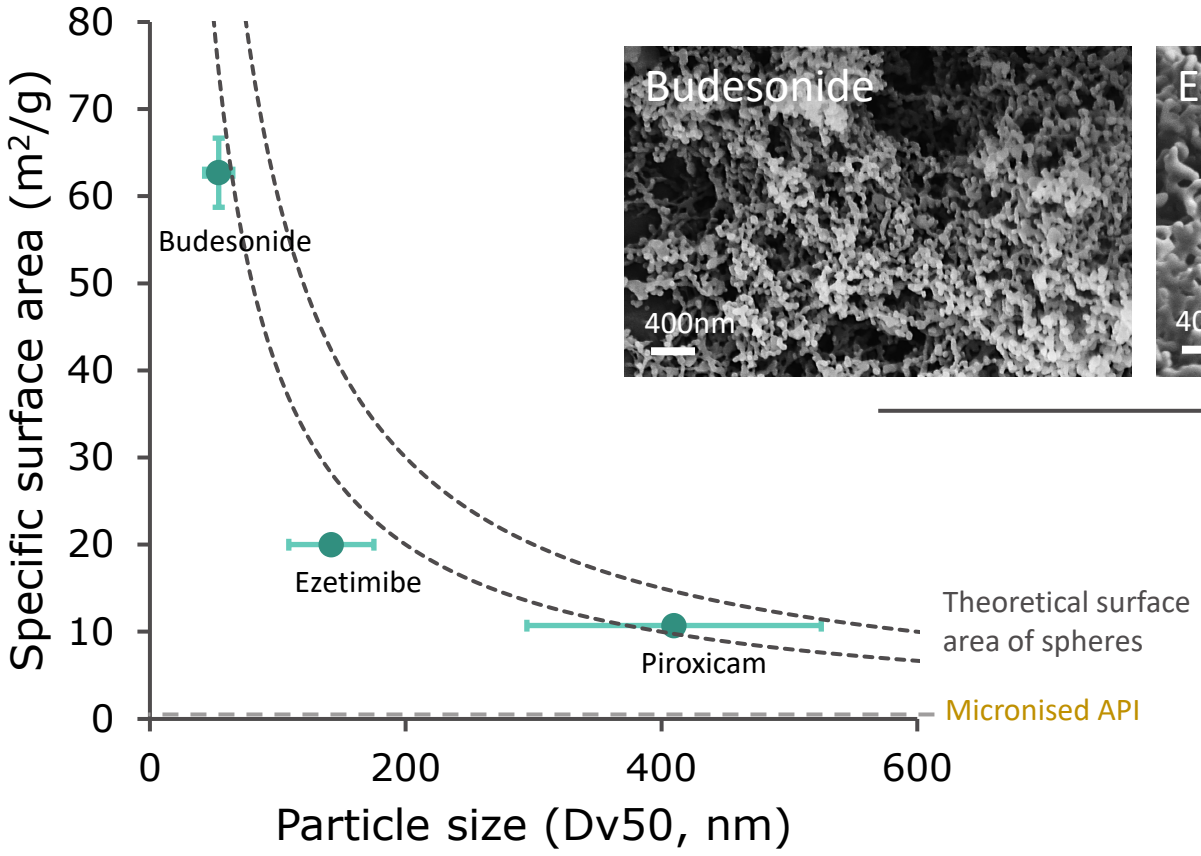


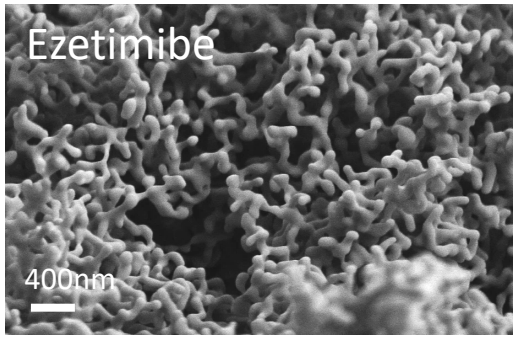
- ✓ High API loading
- ✓ No harmful solvents
- ✓ Tight particle size control
- ✓ Dry and cool process

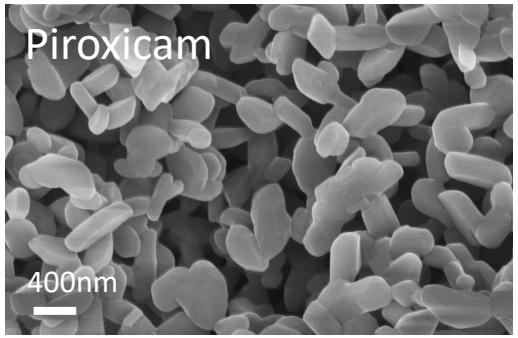


Small particle size leads to high surface area

Measured surface area (BET) and SEM particle size of nanoformed APIs





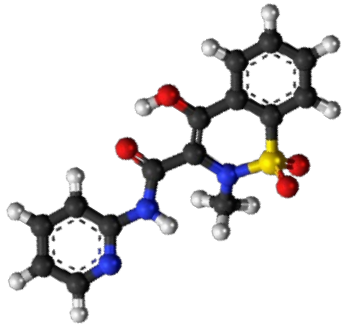


Particle size

CESS® increases the specific surface area more than 100x compared to bulk API

The CESS® Digital Twin – enhancing experimental efficiency

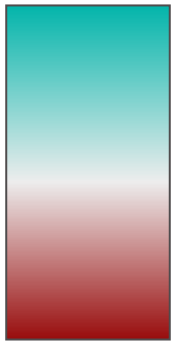
Input molecule



starmap
Illuminating the future of Pharma ®

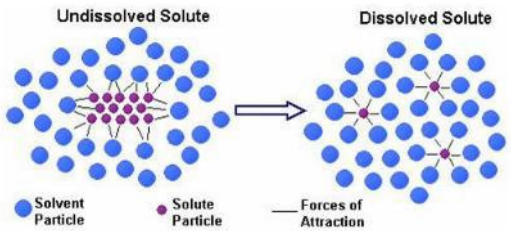
Solubility in sc-CO_2

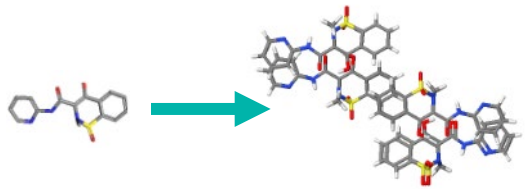
High



Low

*



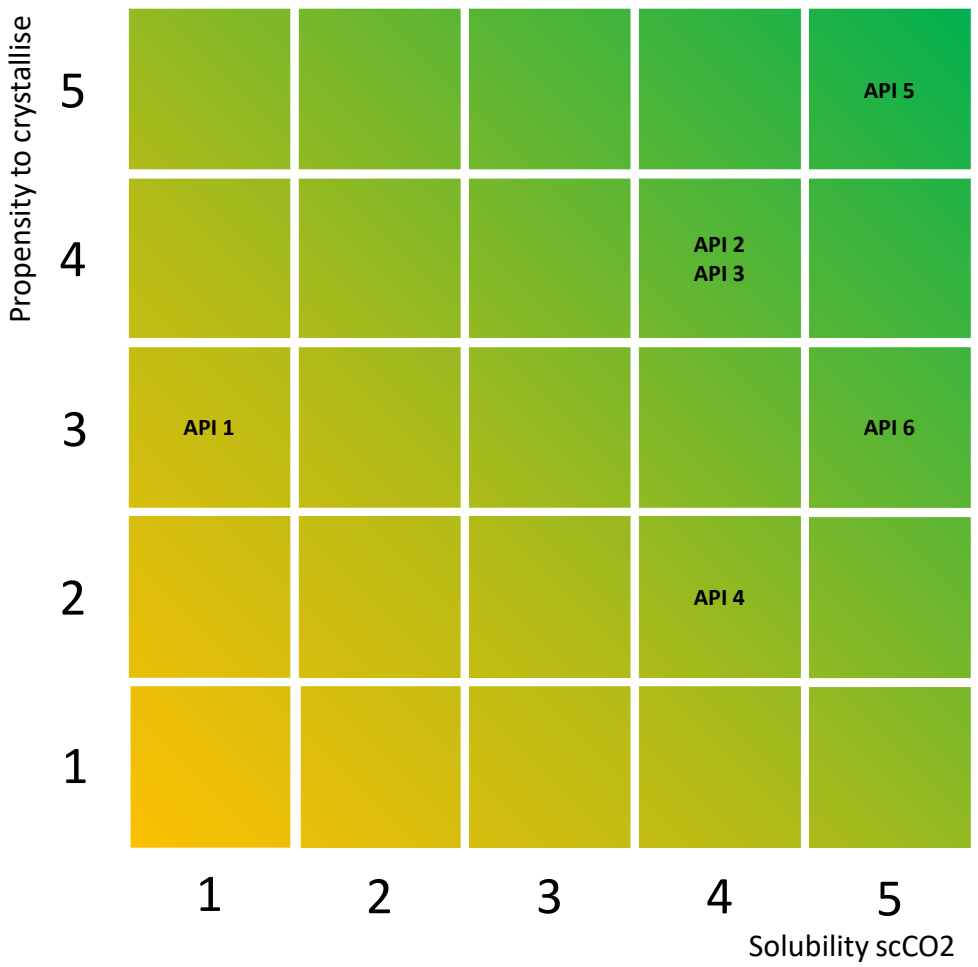


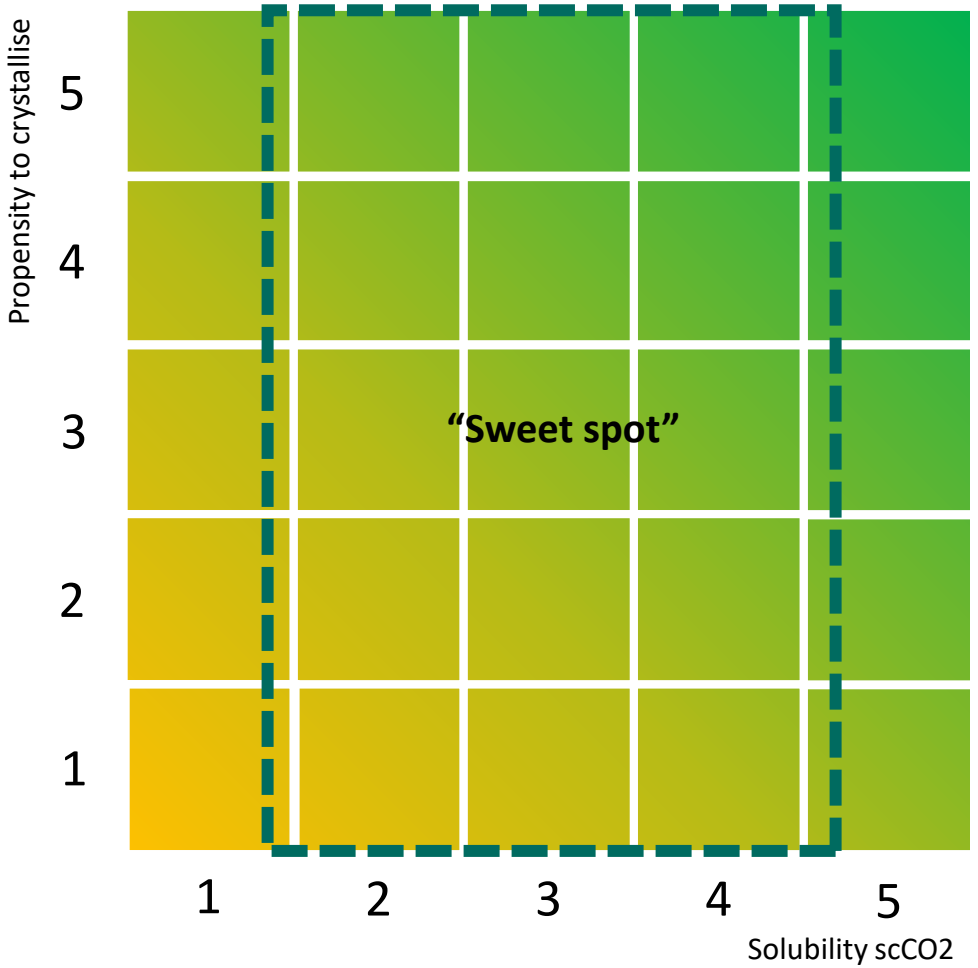
Propensity to crystallize

nanoform

* Prof. Louis Messerle, Chemistry Department, University of Iowa

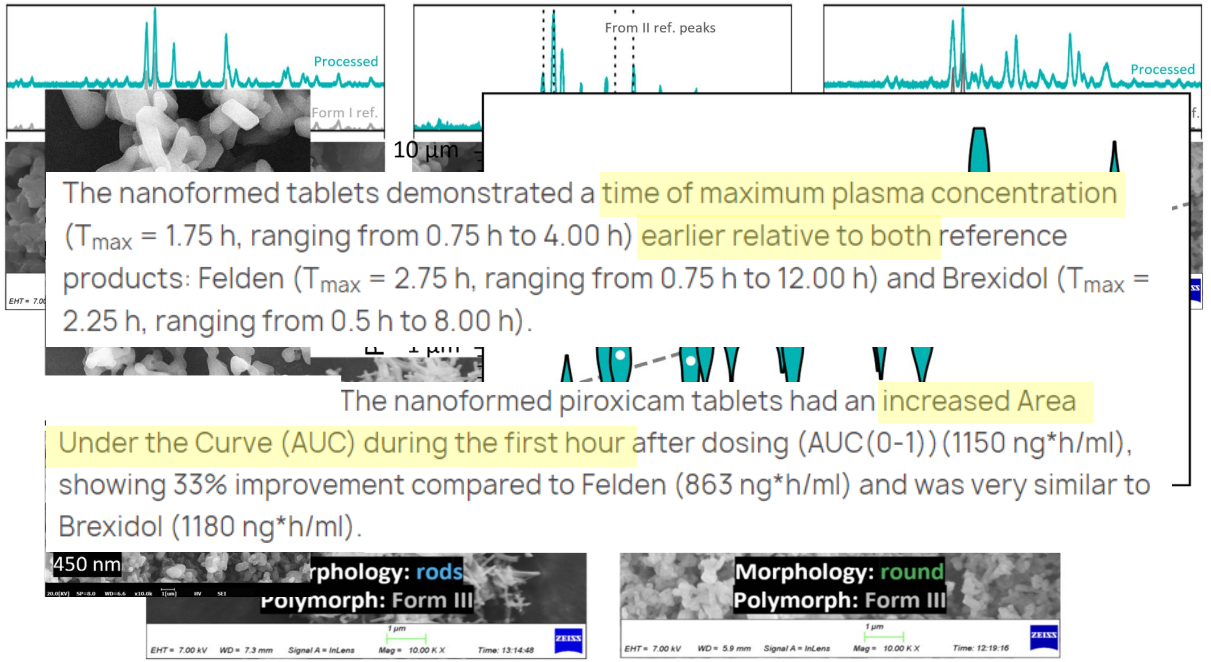
STARMAP® helps inform future experimental work…
(gives a probable coordinate)





Direct nanocrystallization using CESS®

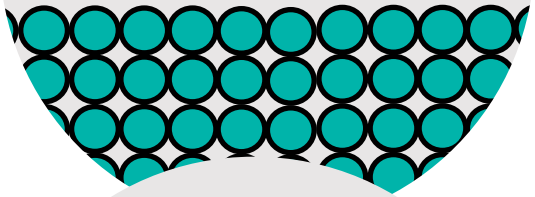
Compound	Comments
Fenofibrate	Control of PSD from 400nm to 8mm
Atovaquone	Control of polymorphic form and morphology
Piroxicam	Phase I clinical data



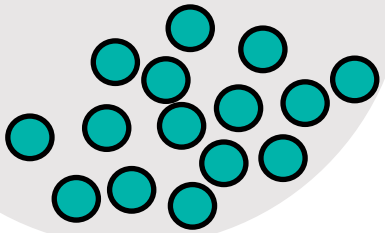
- **Direct nanocrystallization by CESS® offers control of PSD, crystalline form, morphology and improved clinical outcomes.**

Introducing an innovative green alternative to ASDs

> **Crystalline Drug:**
- Low solubility
- Stable



> **Amorphous Drug:**
- High solubility
- Unstable

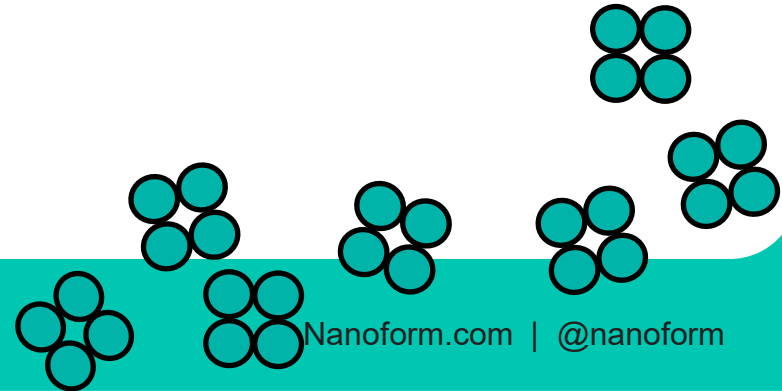


Amorphous dispersions:

- Increased solubility of the amorphous
- Typically, >50% polymer with significant volumes of undesirable solvents (spray drying)

Nanoparticle opportunities with Nanoform:

- CESS® offers the opportunity to generate crystalline nanoparticles through differing methodologies to impact patient lives
- Nanocrystalline material offering dissolution advantages without polymers



Introducing an innovative green alternative to ASDs

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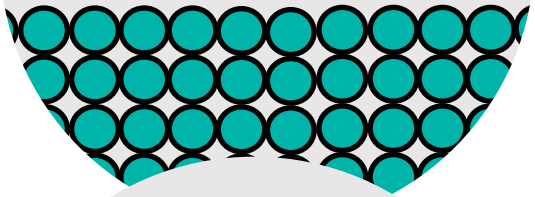

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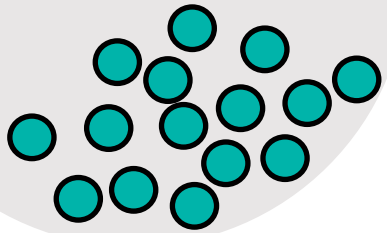

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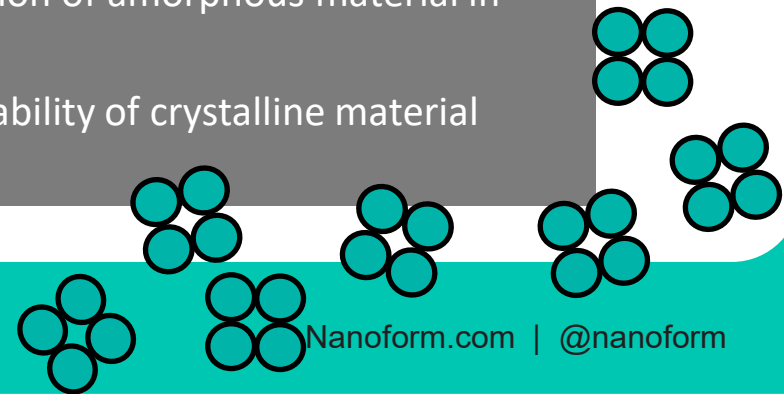
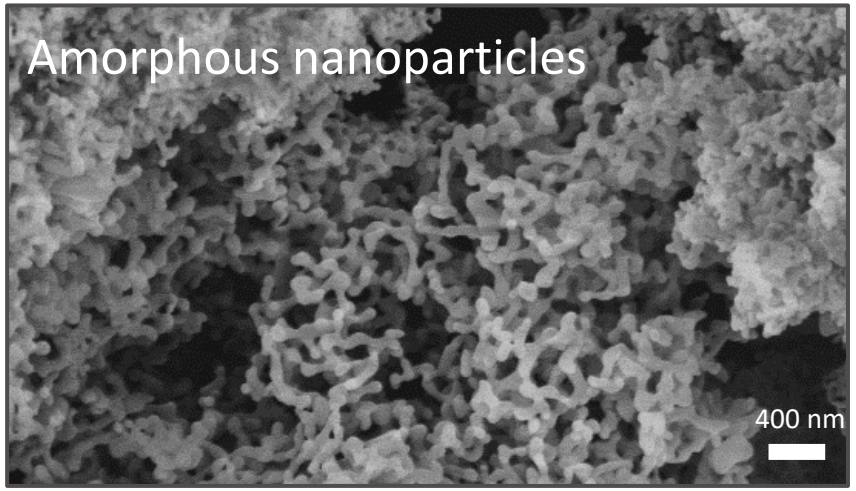
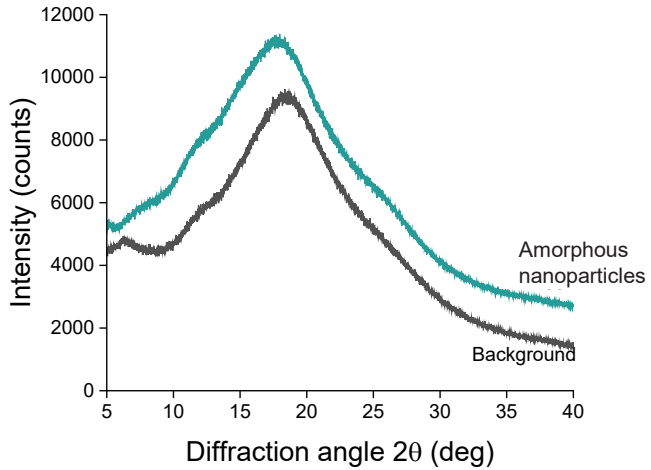
Controlled nanocrystallization of amorphous nanoparticles

- Potential to generate smaller nanoparticles through generation of amorphous material in CESS®
- Secondary crystallization: low polymer loading, increased stability of crystalline material

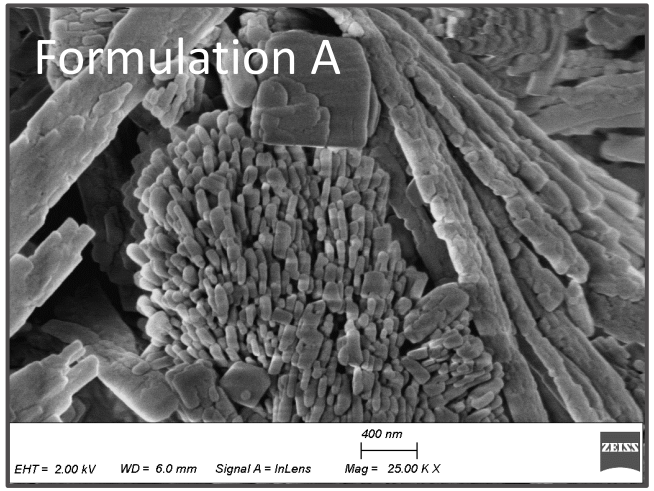


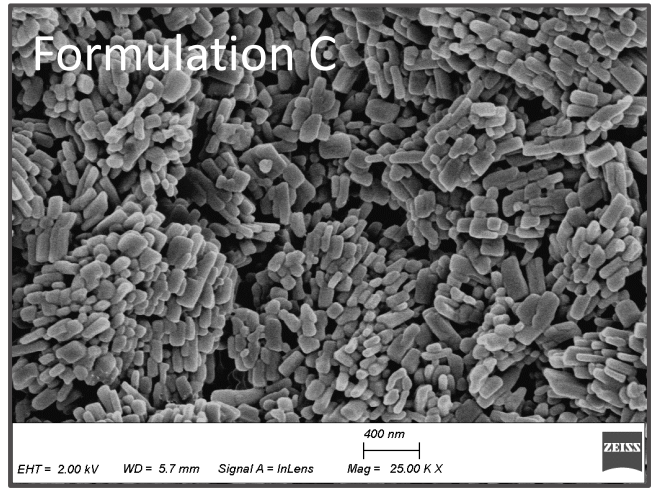
Controlled nanocrystallization, ezetimibe (Case Study 1)

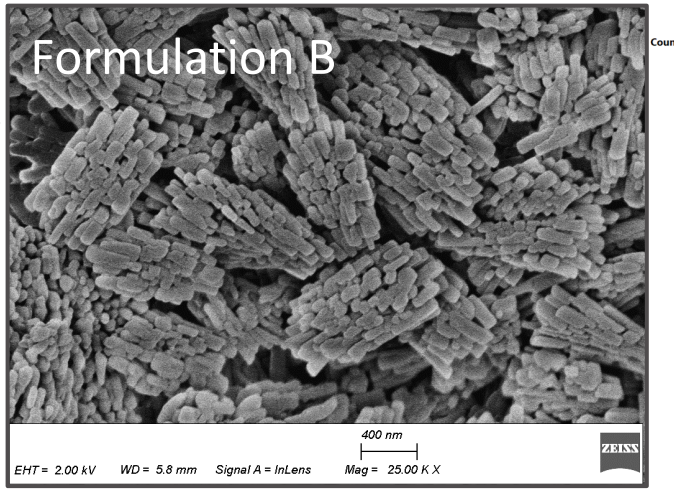


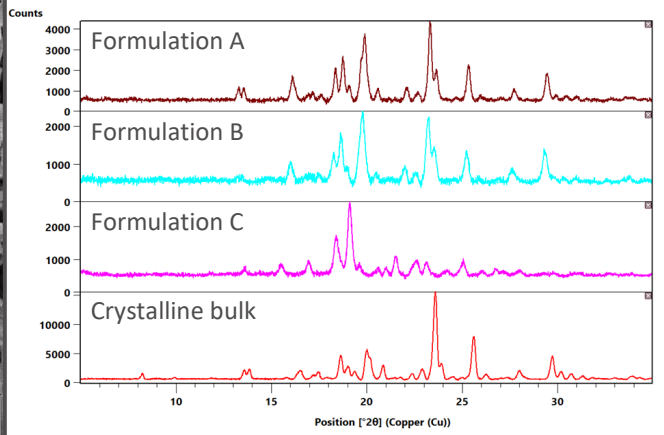


Mixing with crystallizer and polymer

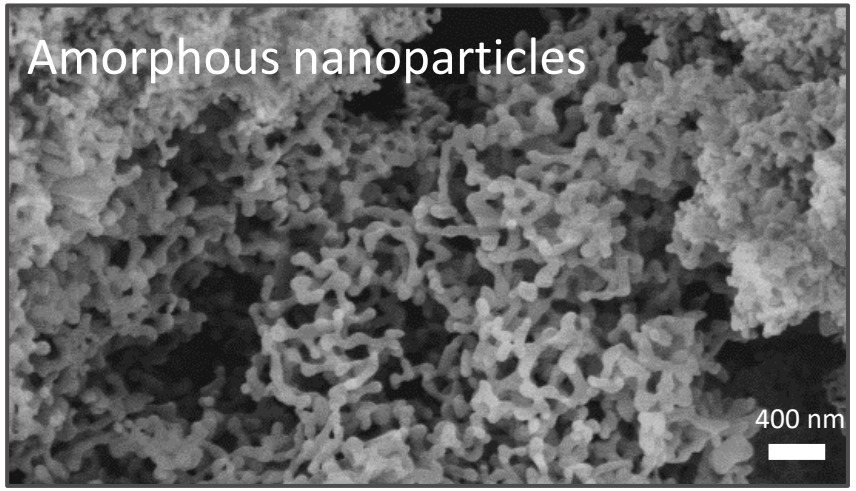


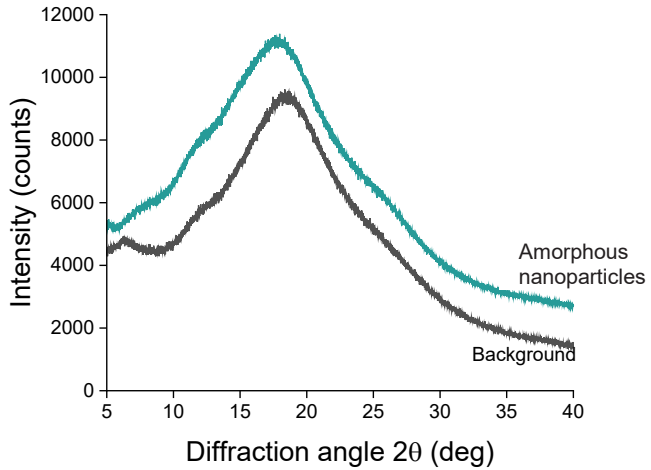






Controlled nanocrystallization, ezetimibe (Case Study 1)





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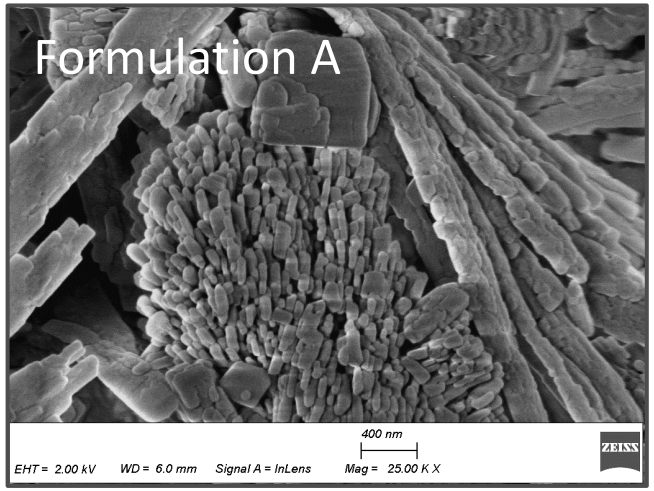
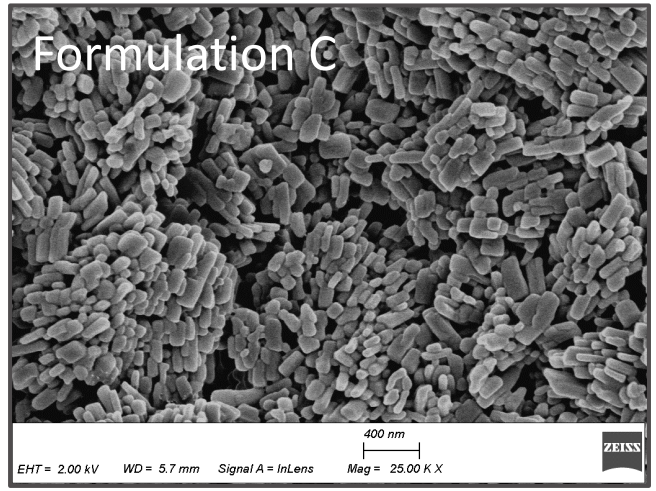
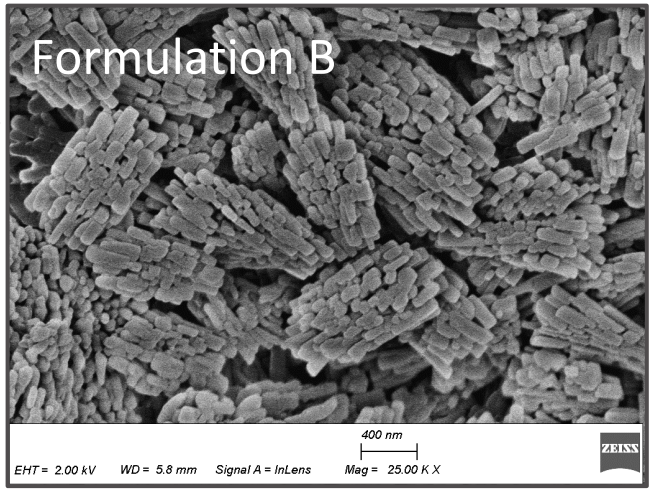
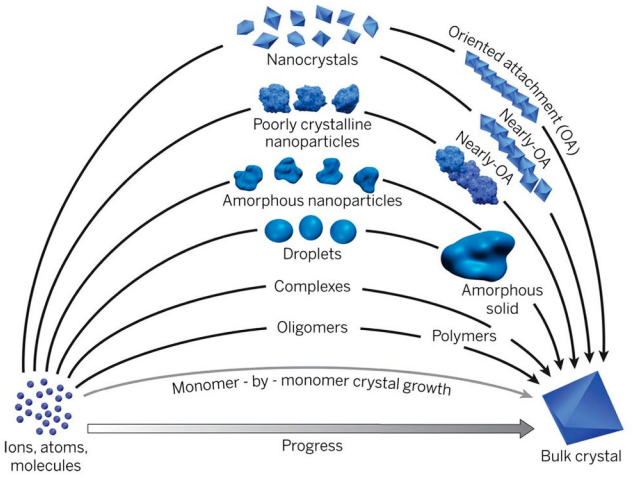




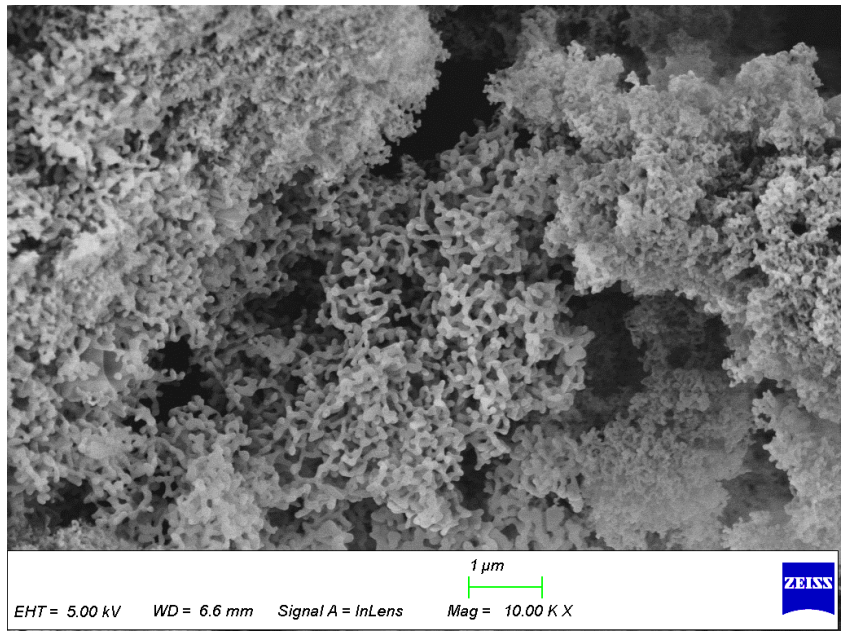




A flexible nanoforming toolbox, ezetimibe (Case Study 1)

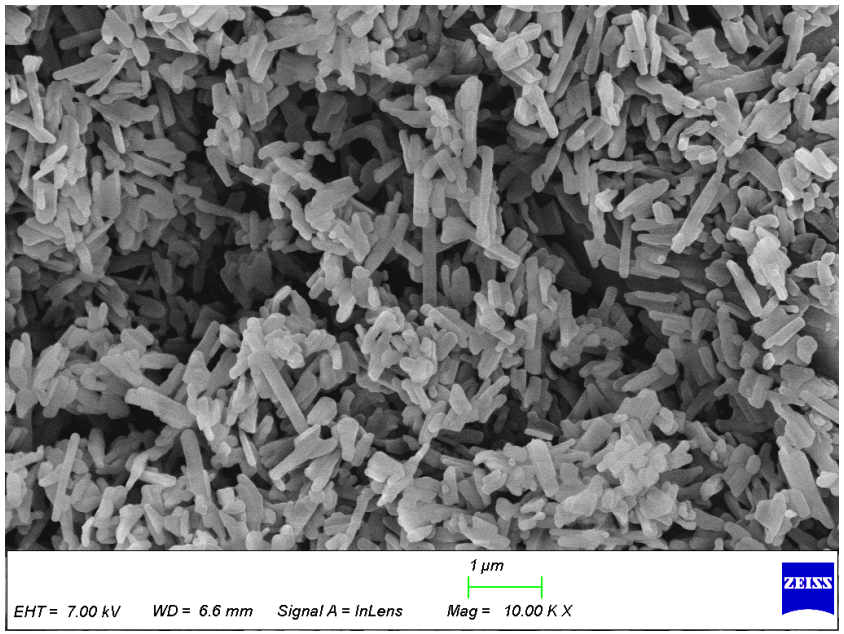
Direct Nanoparticle production via CESS® Process

Process parameters A



Smallest amorphous nanoparticles

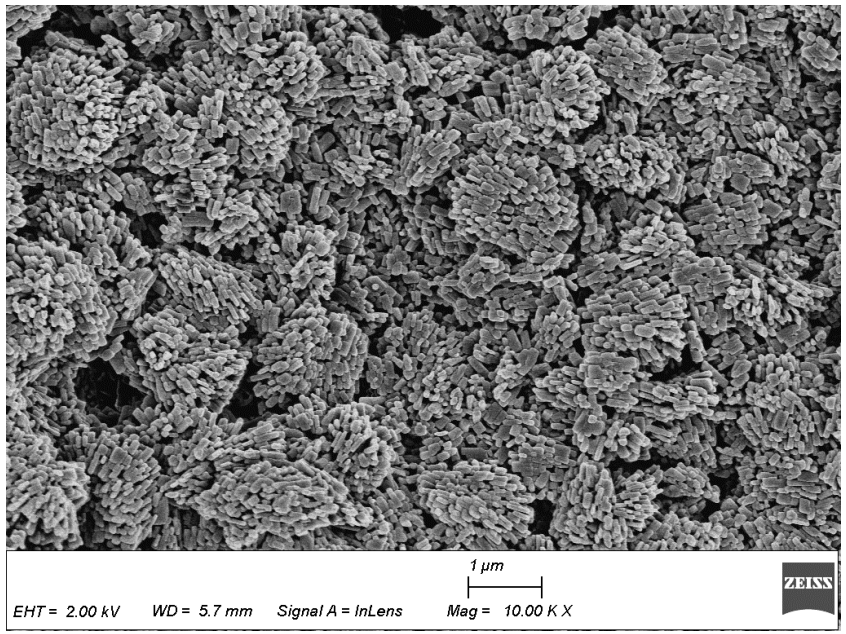
Process parameters B



Larger crystalline nanoparticles

100 % drug substance

Post-CESS®: controlled crystallization



Retaining small size and stable!

Nanocrystal drug product intermediate

Tyrosine Kinase Inhibitors (TKIs)

Anatomy of a $31B Class

Class with huge commercial potential

- 327 APIs; 78 commercial launches
- US Sales 2022 of $31.3B

SPRYCEL® dasatinib 100 mg tablets

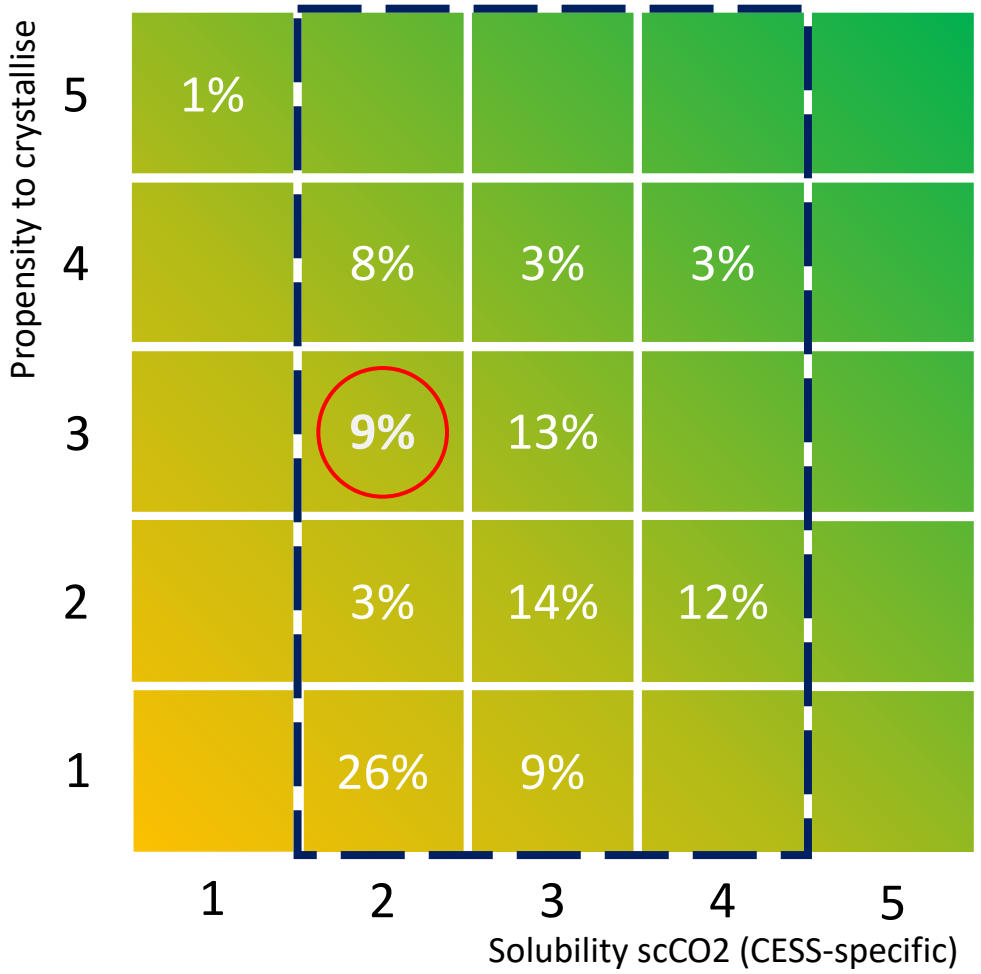
TAGRISSO® osimertinib

Characterised by solubility and bioavailability challenges

- 49% BCS Class II
- 20% BCS Class IV
- 37% with bioavailability <75%
- 55% with food effect

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

TKIs are an attractive class for Nanoforming



starmap
Illuminating the future of Pharma ®

Digital twin of our CESS process predicts many launched TKIs will perform well in our systems

Selected one "challenging molecule" for study
…Food effect
…High dose

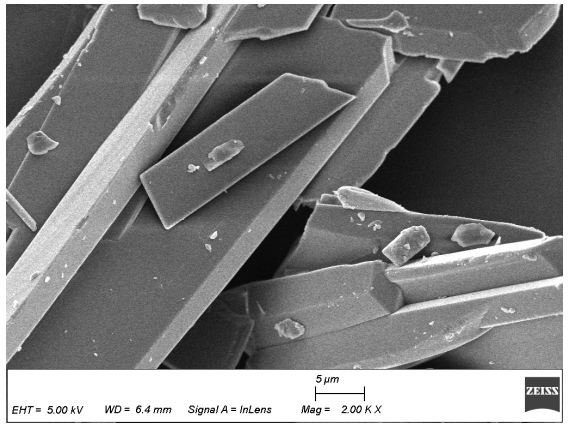
Can we develop a crystalline form of the commercial polymorph that is solubility and bioavailability-enhanced?

TKI Inhibitor: Nanocrystallization of amorphous nanoparticles

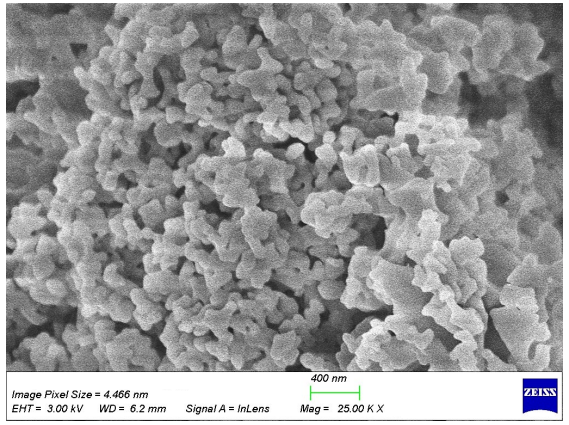
(Case Study 2)

CESS® amorphous nanoparticle production

Bulk API
~3 - 70 µm

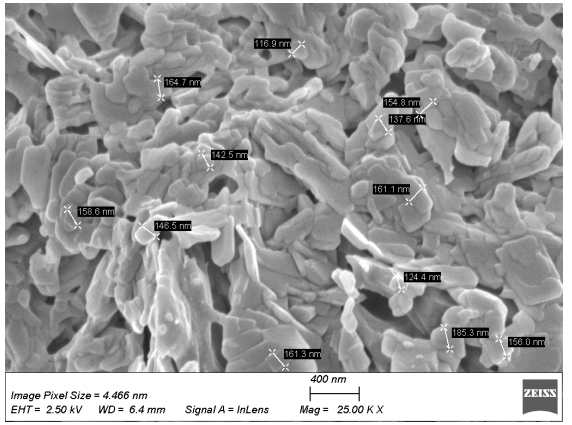


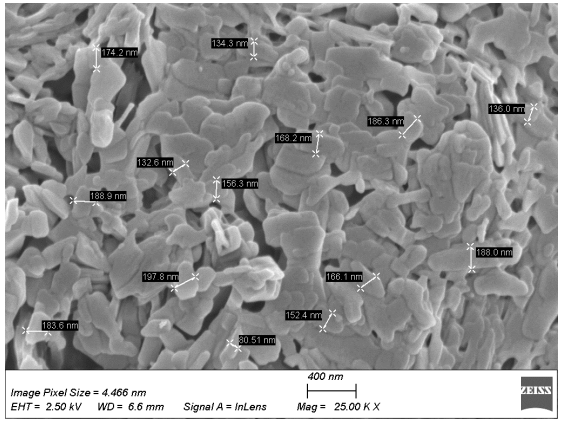
Nanoformed amorphous API
~65-300 nm

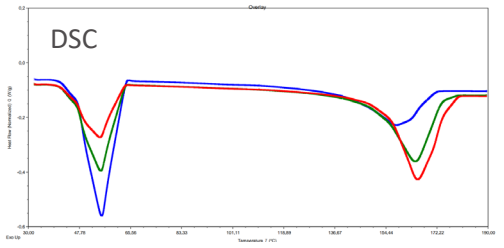


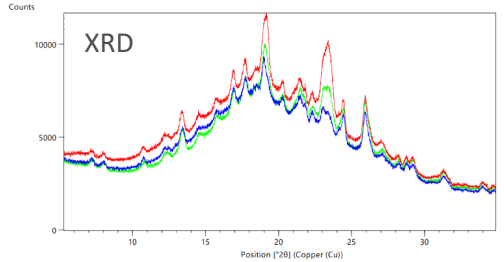
Post-CESS®: controlled nanocrystallization

Drug product intermediate nanocrystals
~70-120nm



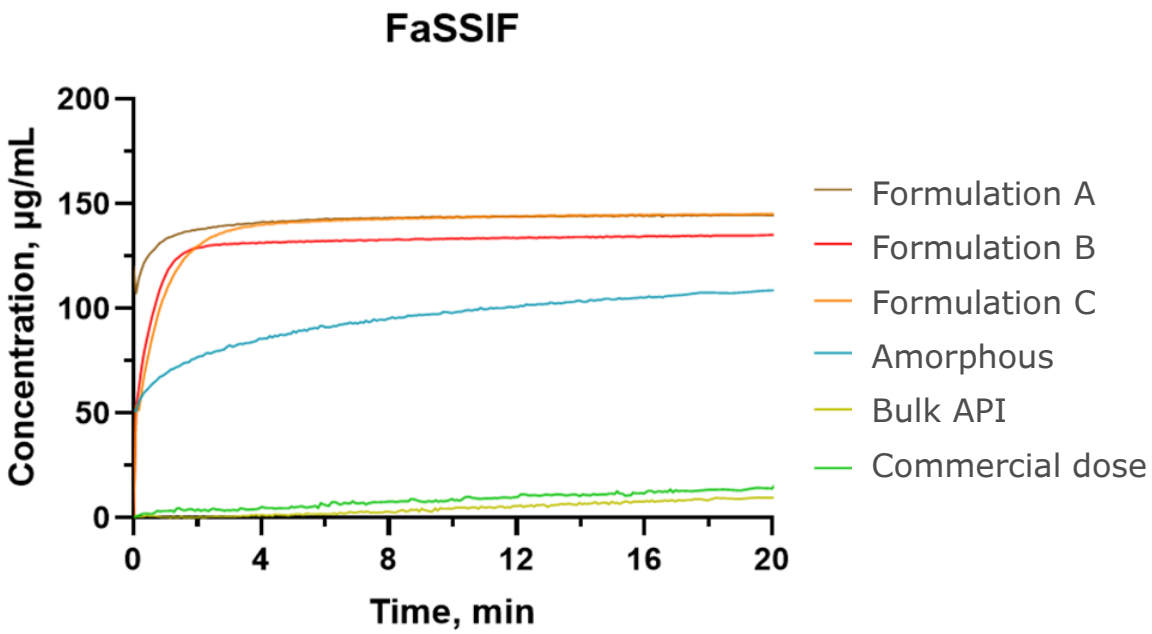






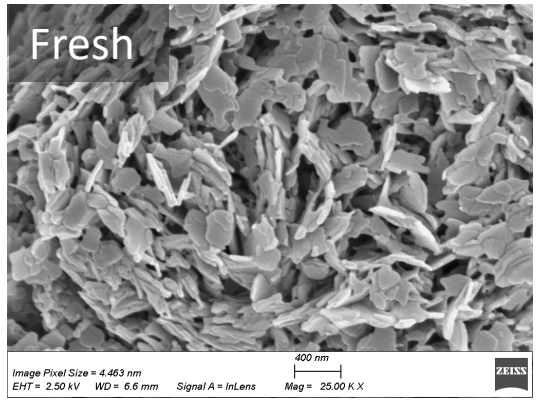
TKI Inhibitor: *in vitro* dissolution performance and stability

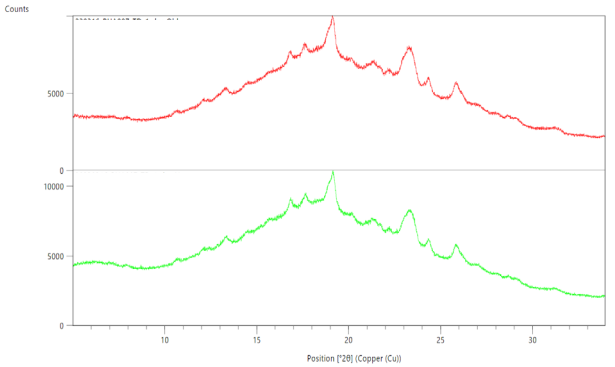
(Case Study 2)

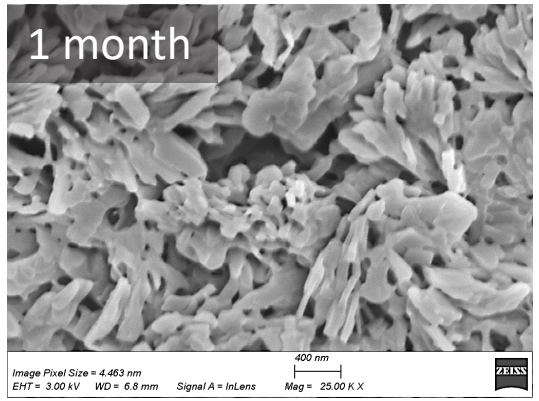


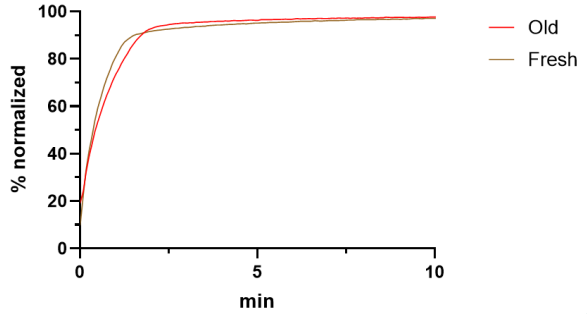
Nanocrystalline materials generated by controlled crystallization offer increased dissolution rate and higher apparent solubility than bulk API, commercial dosage and amorphous.

Stored 1 month in RT



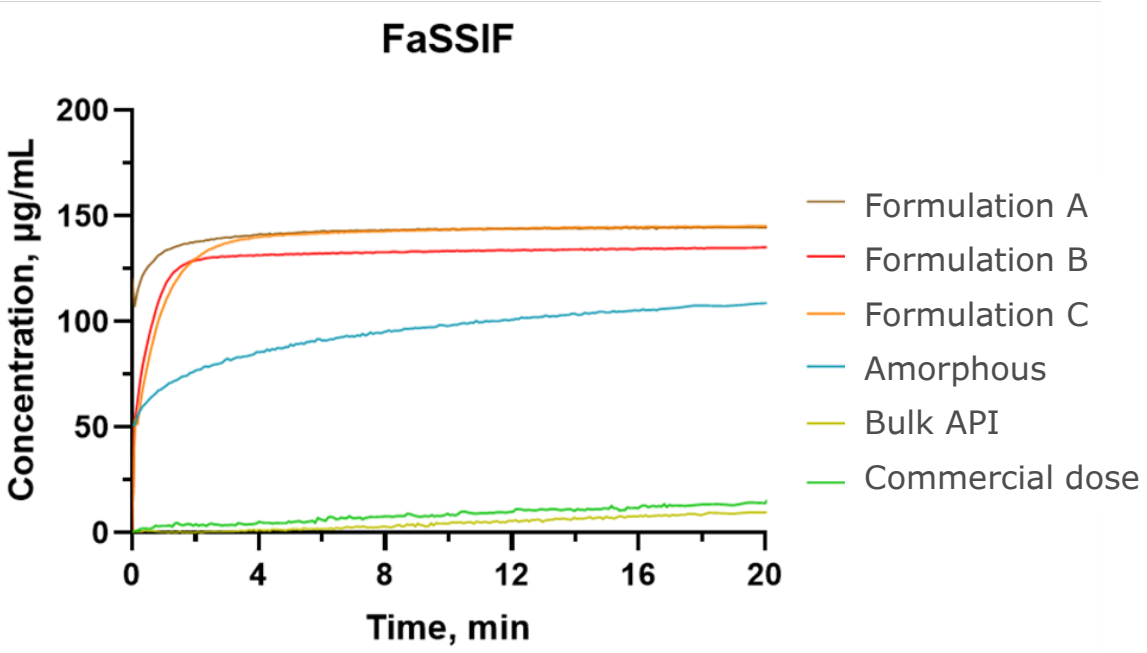


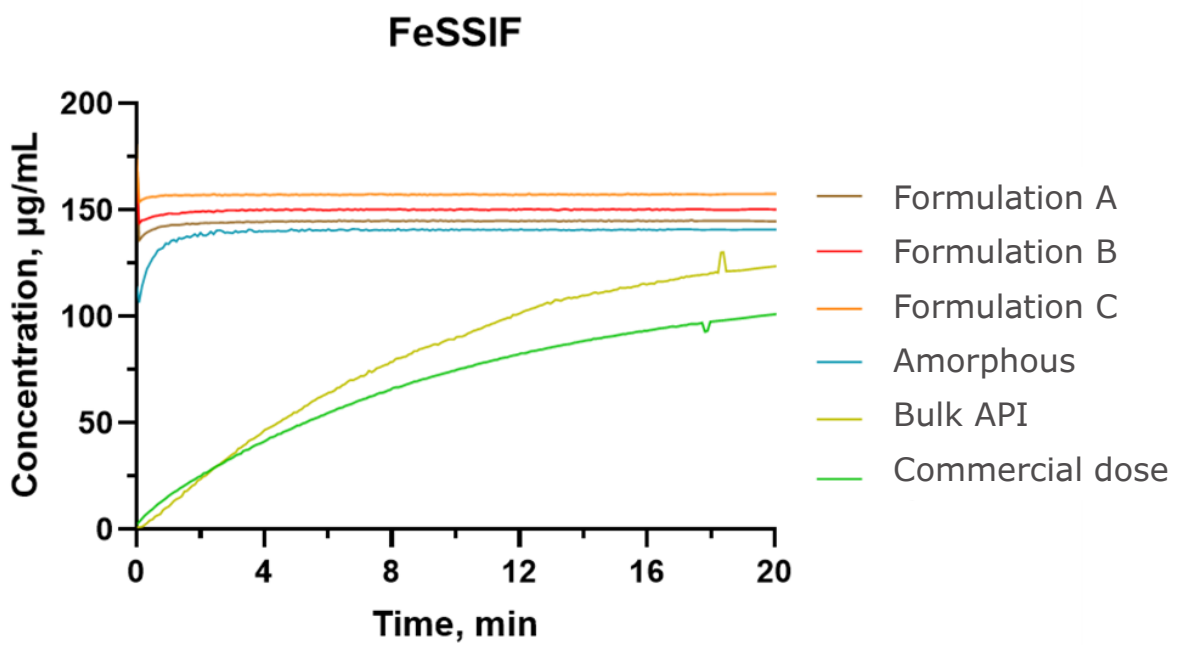




TKI Inhibitor: *in vitro* dissolution performance and stability

(Case Study 2)

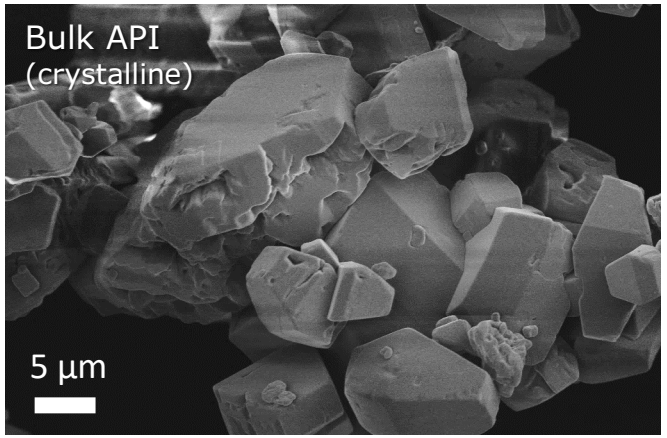


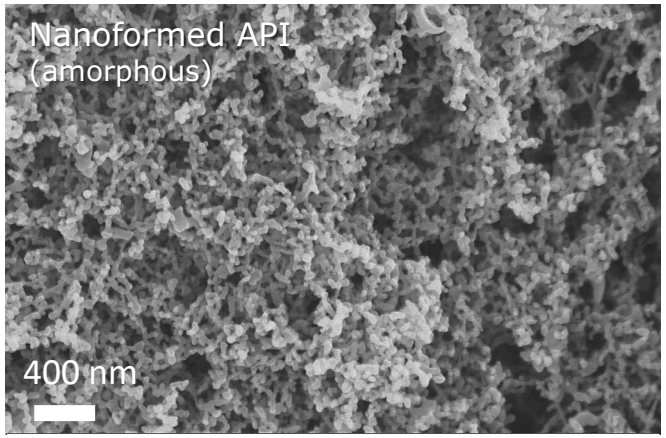


Nanocrystals may also help to reduce food effect

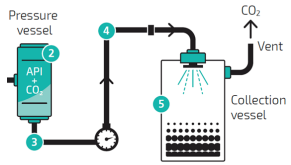
Innovative creation of small nanocrystals in Drug Product Intermediate

(Case Study 3)

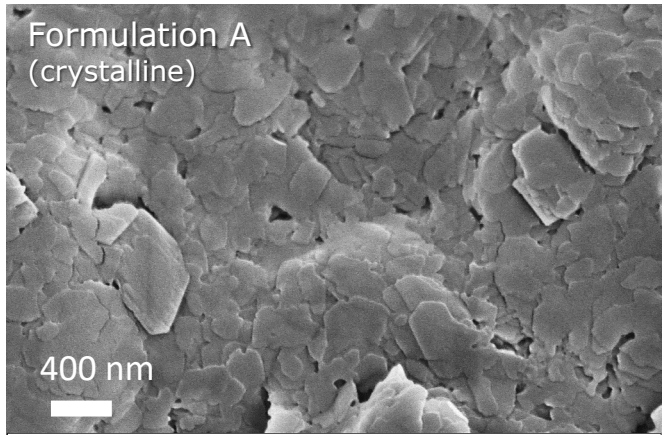


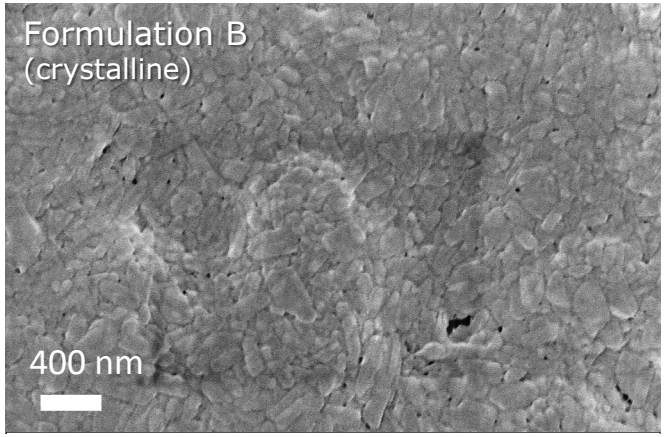


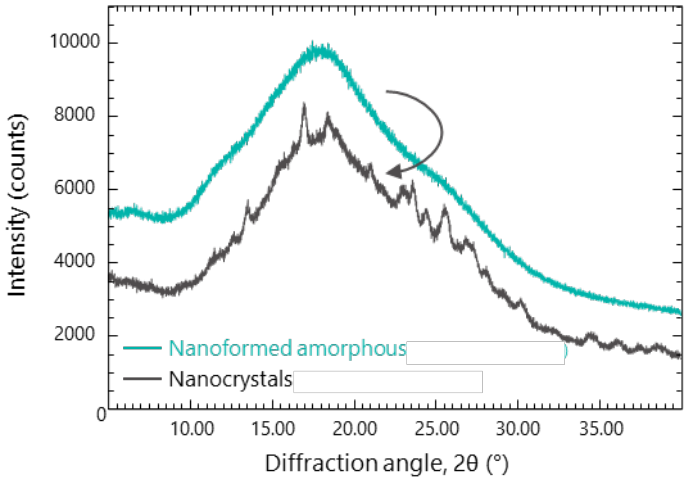
Nanoforming

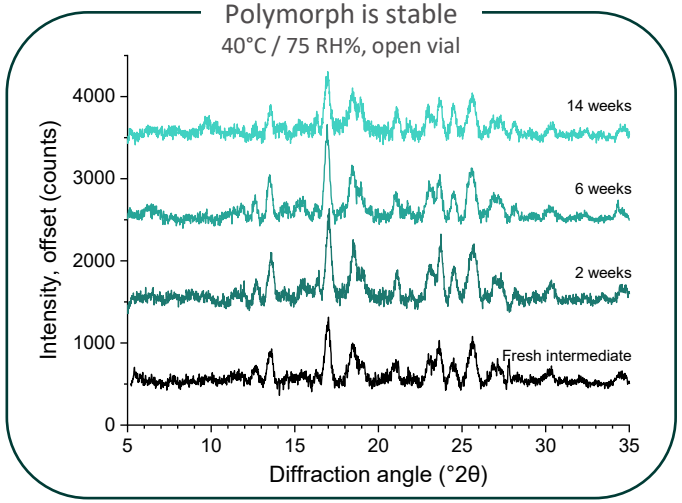


Mixing with crystallizer and polymer





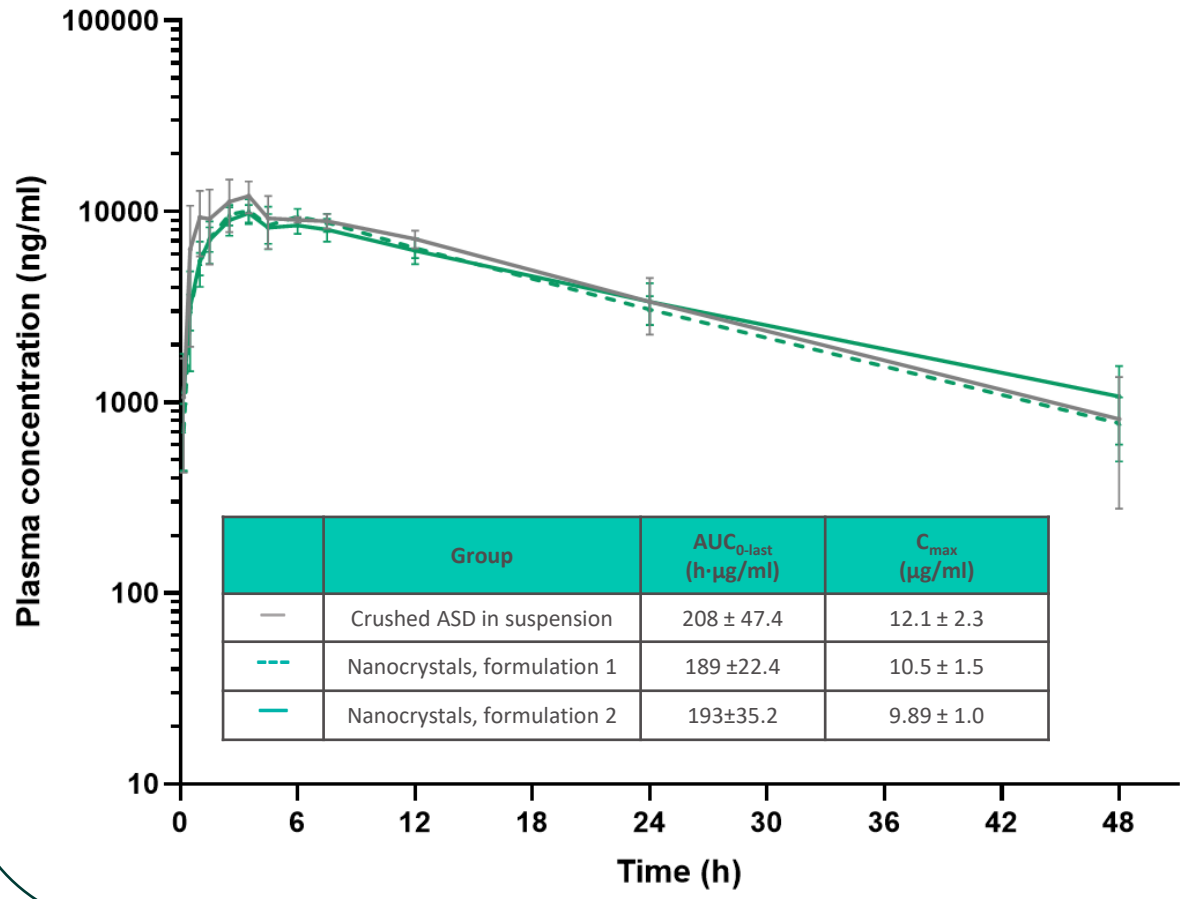




Nanoform's intermediate product matches ASD exposure *in-vivo* and is stable

(Case Study 3)

Equivalent exposure after oral administration



	Group	$AUC_{0\text{-last}}$ (h·µg/ml)	C_{max} (µg/ml)
—	Crushed ASD in suspension	208 ± 47.4	12.1 ± 2.3
---	Nanocrystals, formulation 1	189 ±22.4	10.5 ± 1.5
—	Nanocrystals, formulation 2	193±35.2	9.89 ± 1.0

Performance and stability

- **Equivalent exposure** compared to ASD product, after oral suspension administration in rodents.
- Polymorph and particle size are **stable for 14 weeks.**

Patient adherence and convenience

- Nanoform have taken a **multi tablet ASD product,** reduced it to a **single tablet, the same size as one of the original tablets, for the same combined dose** with a nanocrystalline formulation.
- Nanoform's approach improved the loading degree thus **reducing pill burden and has also enabled** FDC possibilities

The Patient- & Planet-Centric Nanoform Toolbox

- CESS® can produce tailored nanoparticles down to 50nm:
  - Direct control of crystalline *vs*. amorphous, particle size and morphology
  - Flexibility to also nanocrystallize amorphous nanoparticles with novel formulation platform

- Crystalline nanoparticles offer:
  - Increased absorption and faster onset of medications
  - Opportunities to improve on amorphous dispersions through:
    - Increased stability, lower polymer loadings, lower pill burden, no requirement for organic hydrocarbon solvents, new IP and improved patent protection for products

- Demonstrated *in-vivo* equivalence to ASDs with improved patient and planet benefits!

Small is a Powerful Ingredient in Formulations

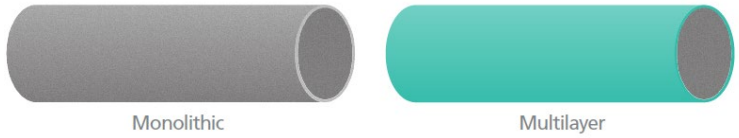
Sustained Drug Delivery

Controlling Drug Release with High-Drug Loaded System

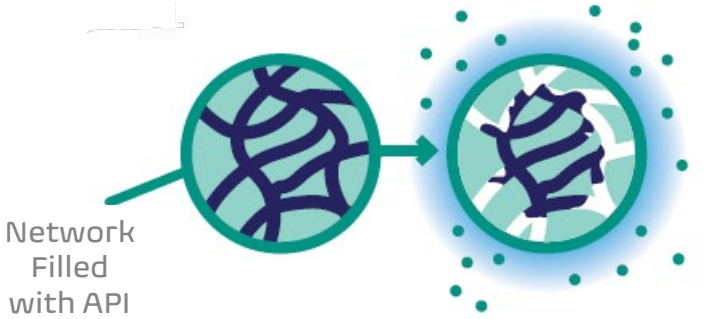
Mitigating Initial Burst Release When a Multilayer Design is Not an Option

Conventional Approach

Use of multilayer design to minimize high initial burst drug release



Drug release from high-loading EVA implants

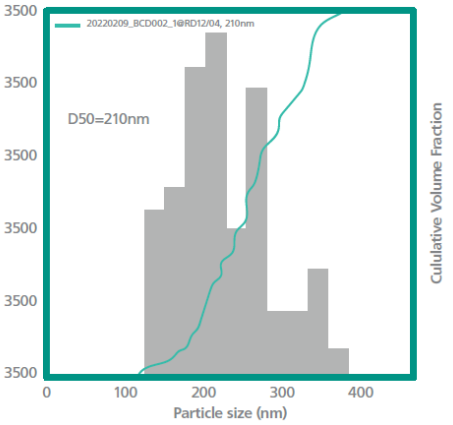


Innovative Approach

Changing the particle size of the drug impacts the network for drug release

Scanning Electron Microscopy (SEM)

Particle Size Distribution (PSD)

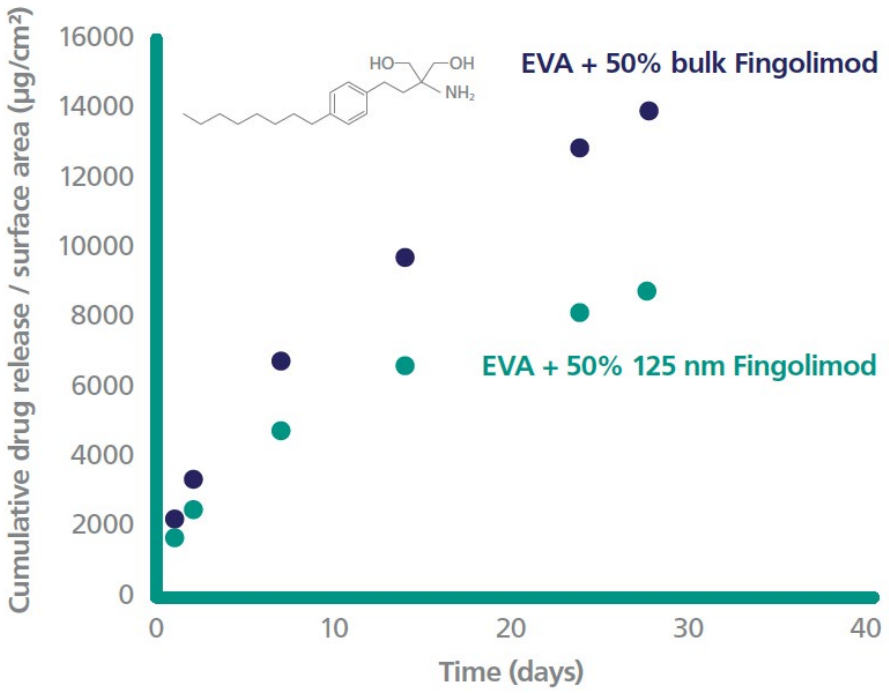


Reducing drug particle size will reduce initial burst and yield slower overall drug release

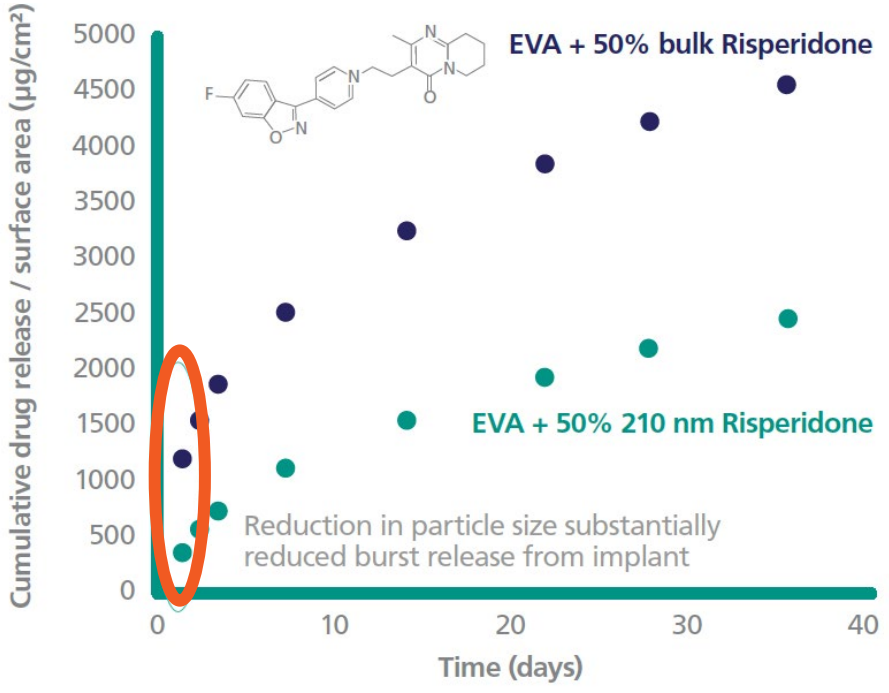
Mitigating Initial Drug Burst While Slowing Overall Drug Release

Demonstrating the Potential of CESS® and VitalDose® EVA Together

Fingolimod



Risperidone



CESS® nanoparticle engineering combined with VitalDose® EVA drug delivery can slow overall drug release as well as minimize the initial burst release associated with highly drug-loaded systems

nanoform
small is powerful®

Thank you

Please contact christian.jones@nanoform.com to discuss how ‘Small’ can be an ‘Ingredient’ in your formulation