Factors Affecting CNC Organogel Formation and Their Effects on Pharmaceutical Crystallization

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TAPPI

Current challenges in oral dosage forms

- Tablets are the most common form of small molecule drug delivery

(Active pharmaceutical ingredient – API)

Oral drug delivery

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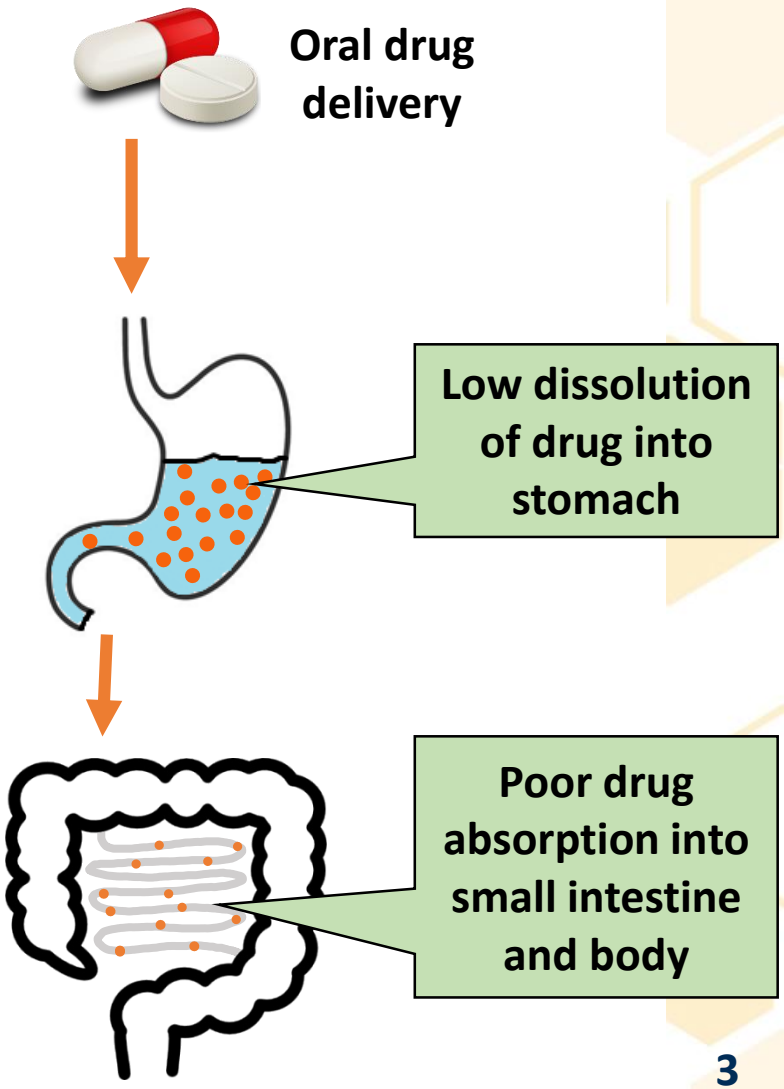

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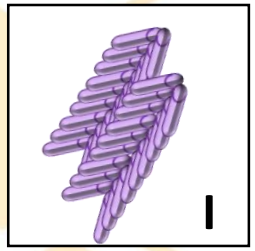

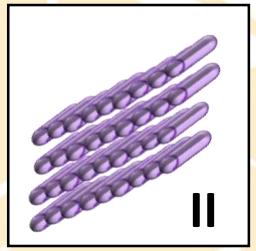

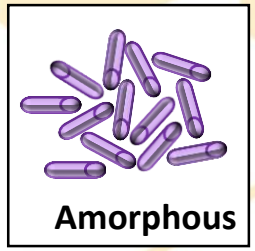

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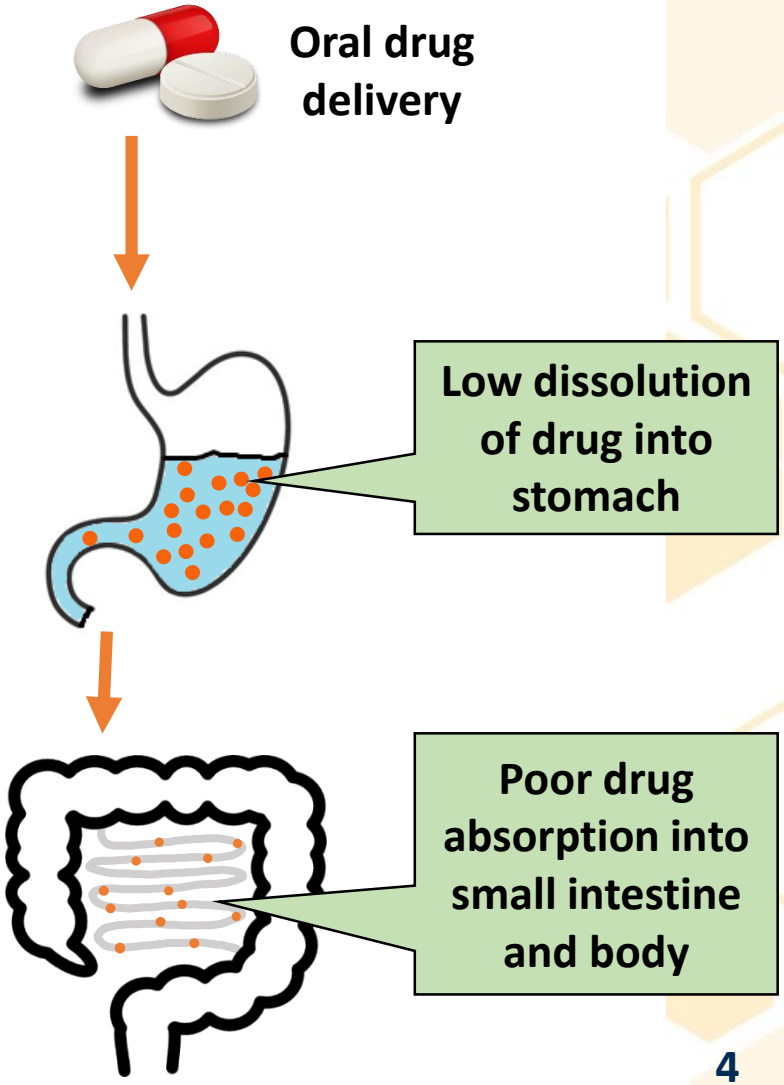

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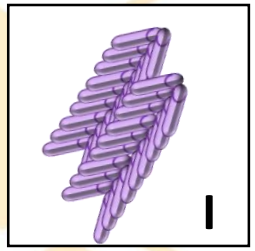

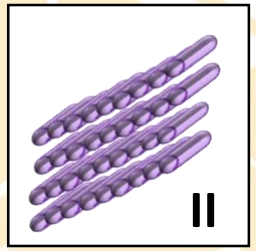

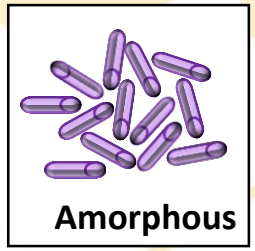

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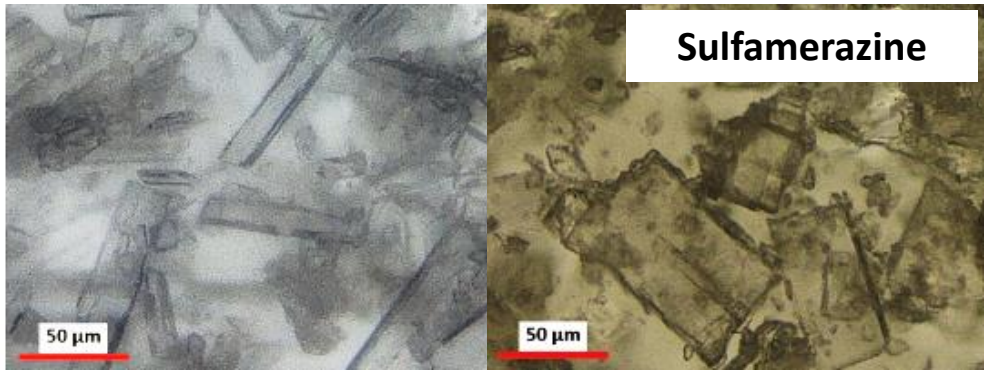
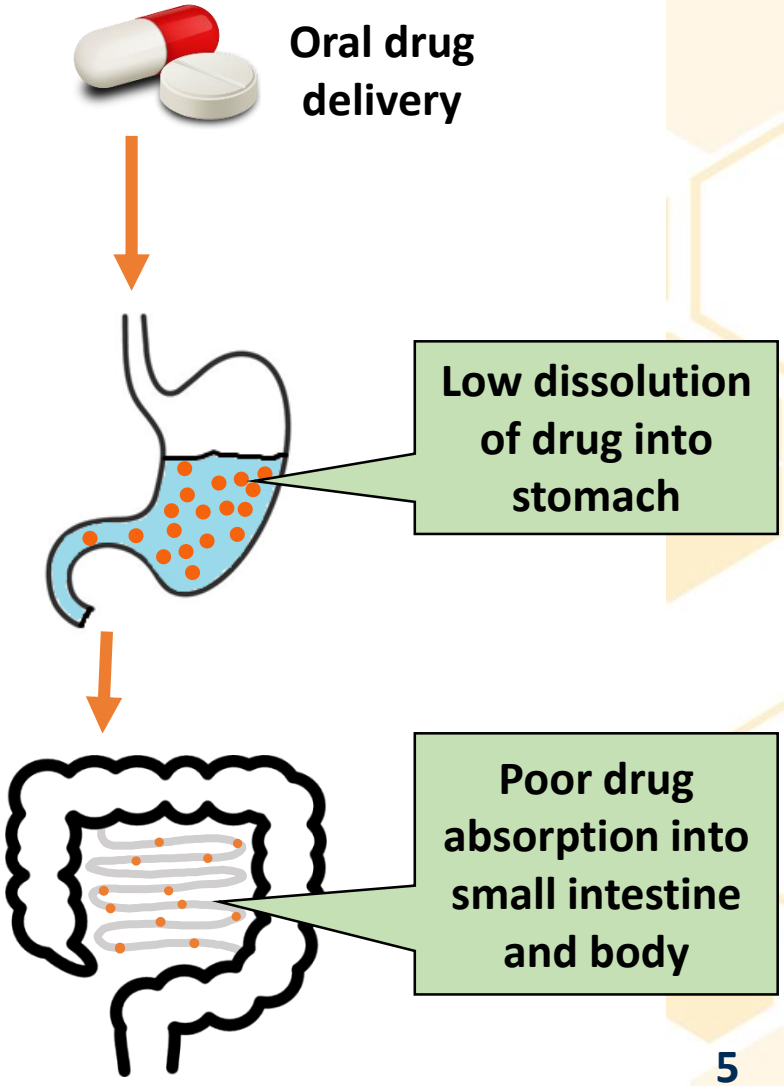
- Low aqueous solubility of drugs
- APIs are prone to polymorphism
- Crystal shape and size differences



Banerjee et al., J. Mat. Chem. B 2018

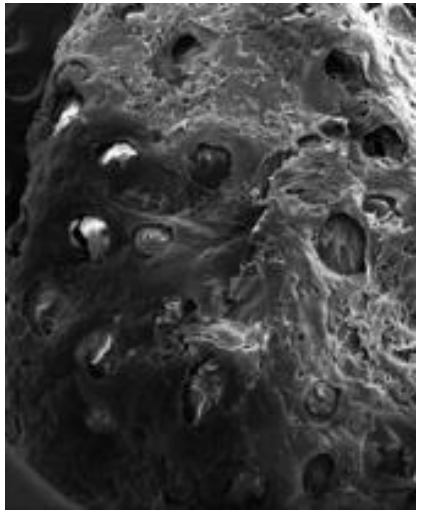


Production methods for higher solubility API polymorphs

- Heterogeneous crystallization on a substrate
- Homogeneous crystallization in confined pores

Surfaces can be used to promote desired polymorph nucleation

Chadwick, K., et al. Cryst. Growth Des., 2012



Confinement in pores enables control over crystal size and shape

Ling and Chadwick, OPR&D 2017

Nanocellulose for API control

- Advantages
  - Biodegradable with low toxicity
  - High strength and stiffness
  - Large surface area with hydroxyls
  - MCC already used in pharmaceutical industry

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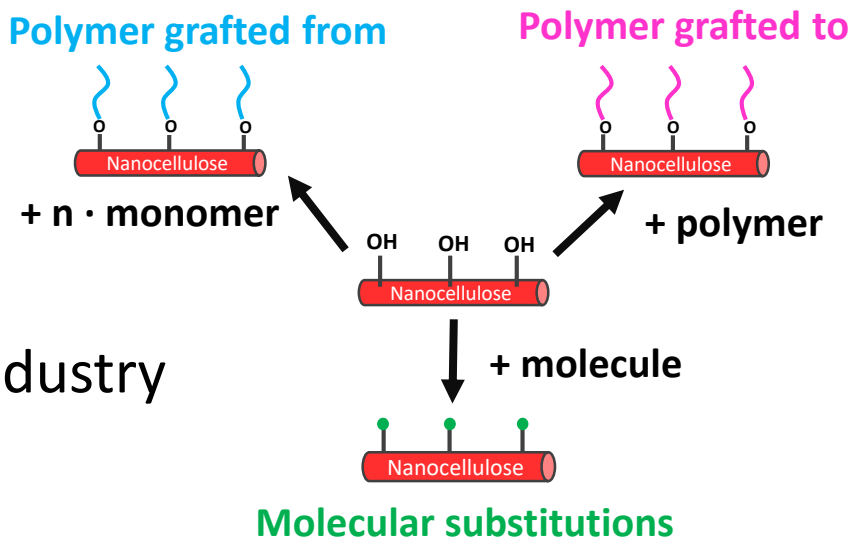

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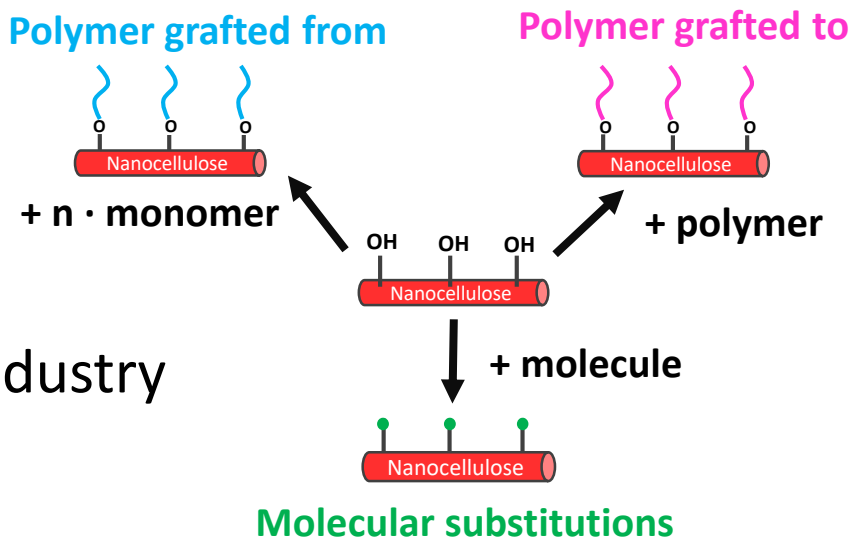
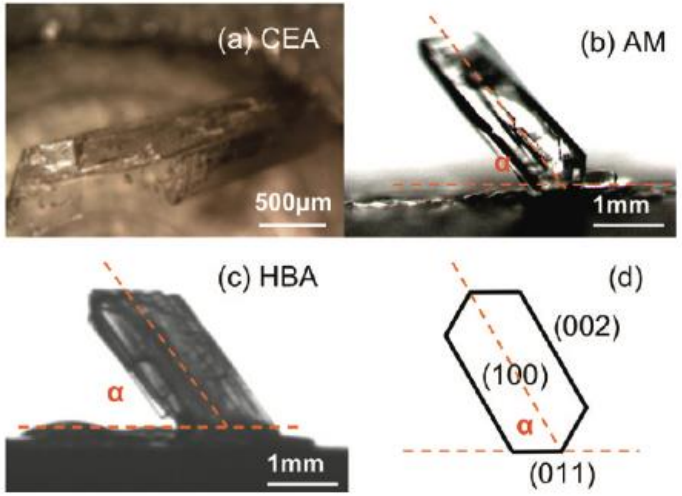
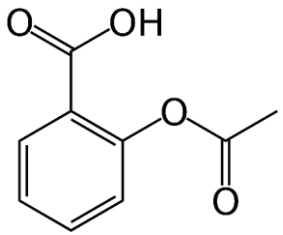




*Diao et al., Langmuir 2011

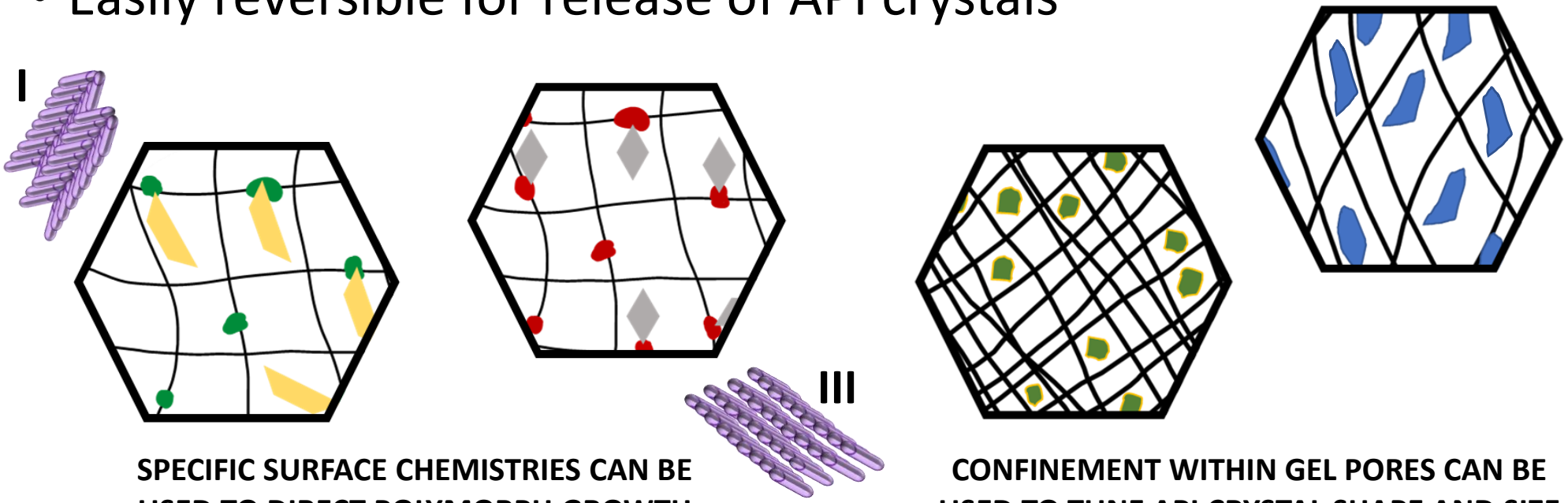
Aspirin



Crystal growth and polymorph have been shown to be dependent on surface chemistry

CNC gels as crystallization media

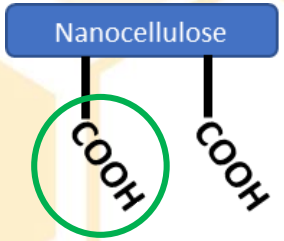
- Control over surface chemistry
- Control over pore size for confinement
- Localization of APIs in favorable environment
- Easily reversible for release of API crystals



SPECIFIC SURFACE CHEMISTRIES CAN BE USED TO DIRECT POLYMORPH GROWTH

CONFINEMENT WITHIN GEL PORES CAN BE USED TO TUNE API CRYSTAL SHAPE AND SIZE

Surface modifications to CNCs



- **Step 1: TEMPO Oxidation**
  - Carboxylic acid groups (green circle)

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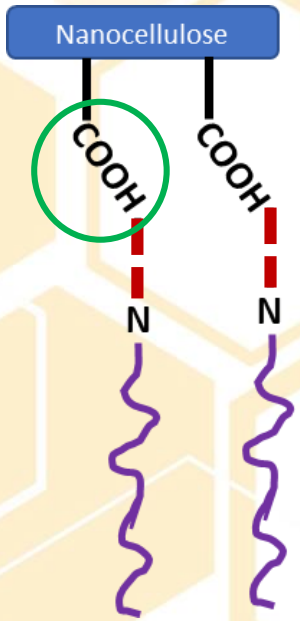
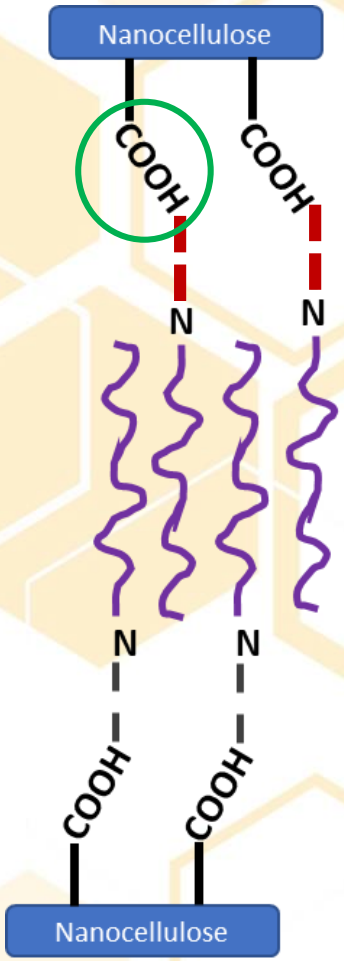


- **Step 1: TEMPO Oxidation**
  - Carboxylic acid groups (green circle)
- **Step 2: Amine attachments**
  - Add long chain amine – octadecylamine

  - Hydrogen bonding (red line) between carboxyl and amine groups

Organogel formation with modified CNCs



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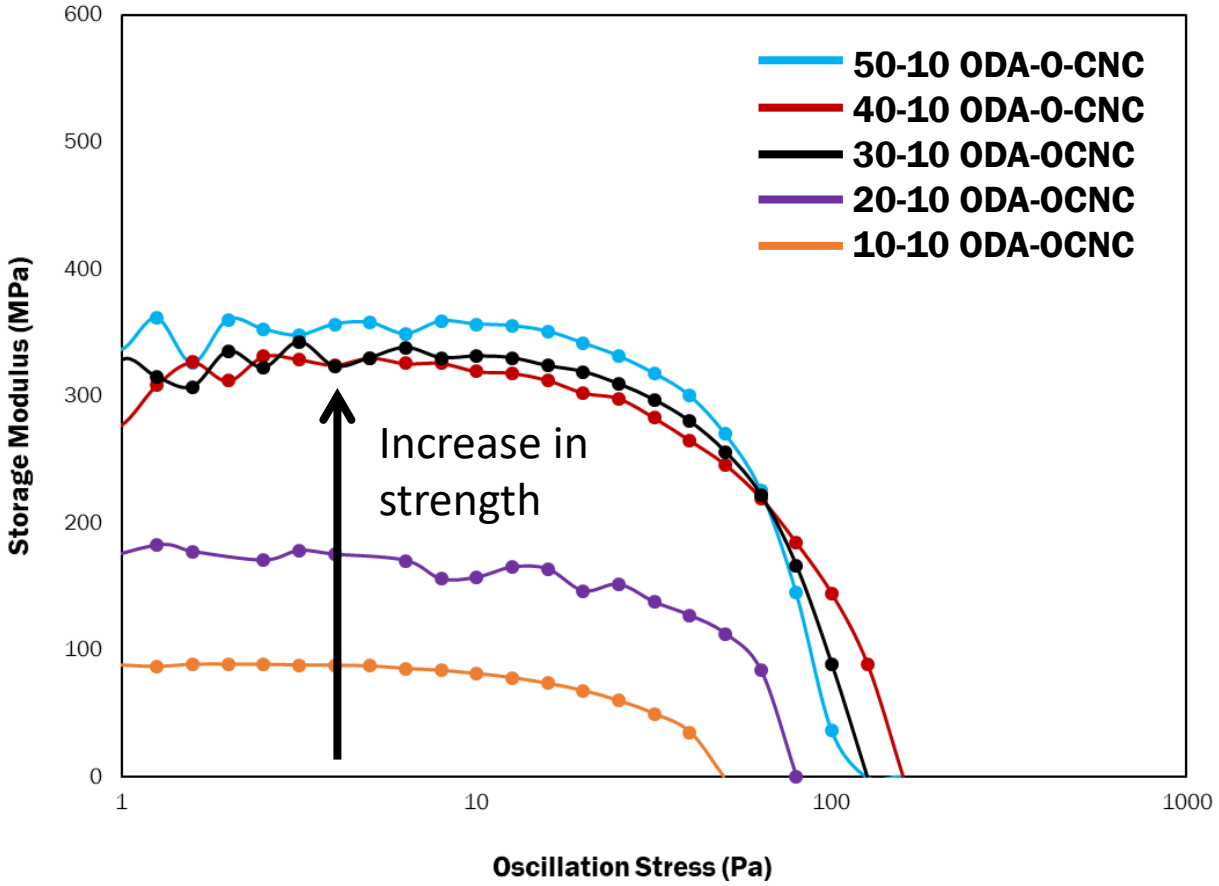
  - Hydrogen bonding (red line) between carboxyl and amine groups
- **Organogel network formation**
  - Dispersion in organic solvent
  - Heating and cooling
  - Rearrangement of solvophobic alkyl chains (purple)

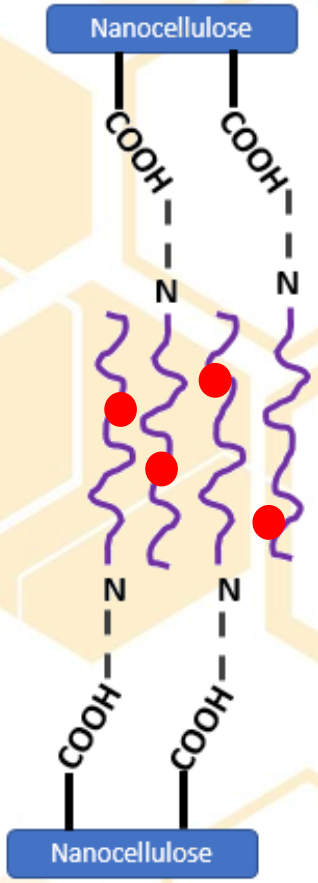
Determining factors affecting CNC organogel formation



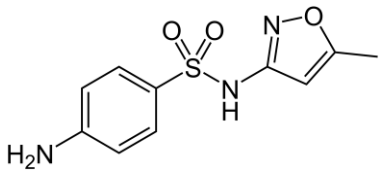
- Strong gel for stable crystallization support
- Strength of gel increases as ratio of ODA to O-CNC is increased.
- Peak reached 3:1 ratio of ODA to O-CNC

Banerjee et al., J. Mat. Chem. B 2018

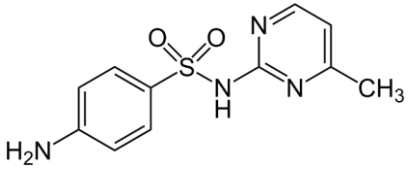
Crystallize APIs in CNC organogels



- Mix drug with O-CNCs and ODA prior to heating and cooling for gelation



Sulfamethoxazole (SMX)



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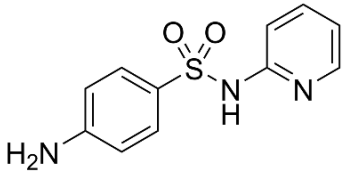

Sulfapyridine (SP)

Banerjee et al., J. Mat. Chem. B 2018

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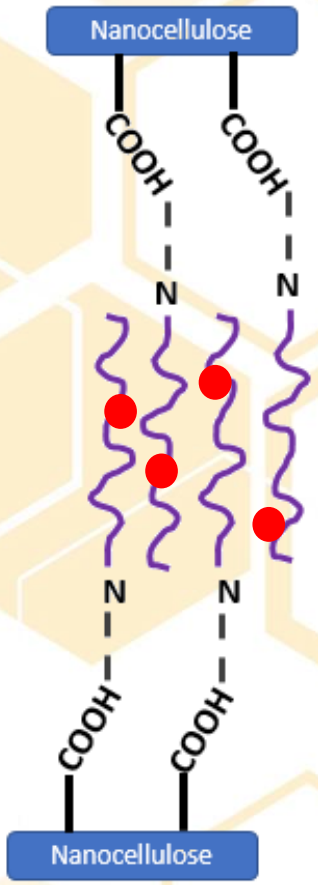
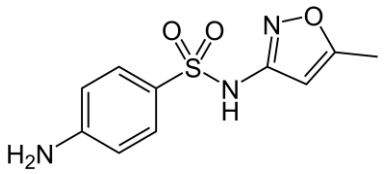


- Mix drug with O-CNCs and ODA prior to heating and cooling for gelation
- Drug localizes in alkyl chain because of hydrophobic interactions



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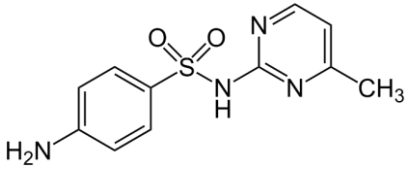

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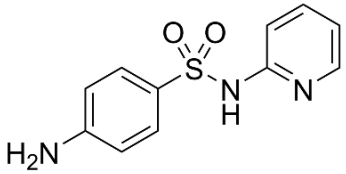

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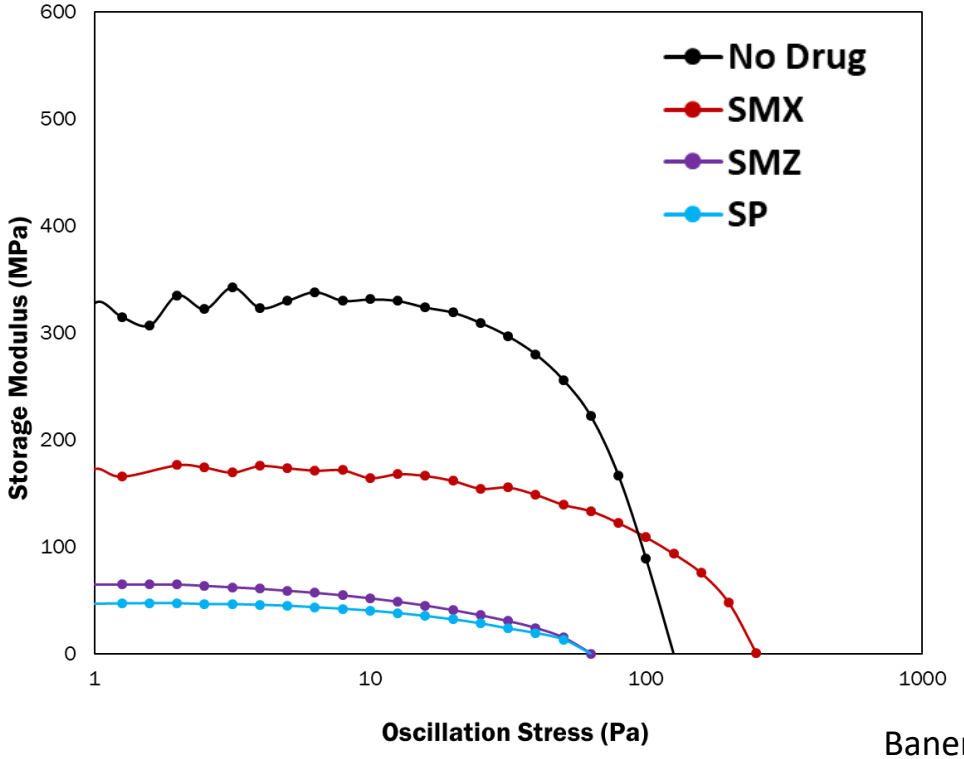
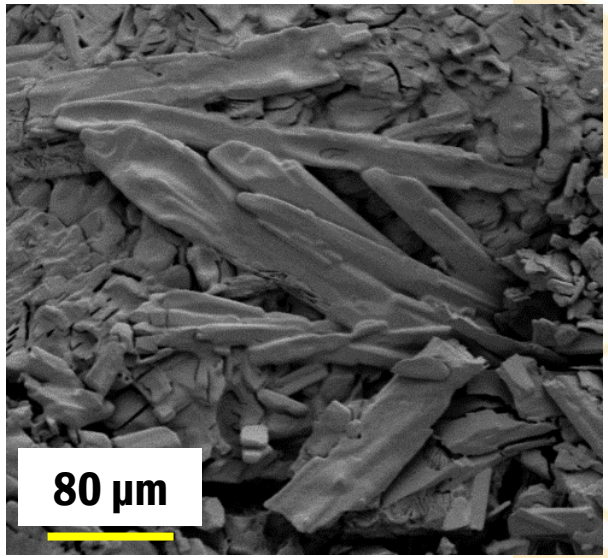
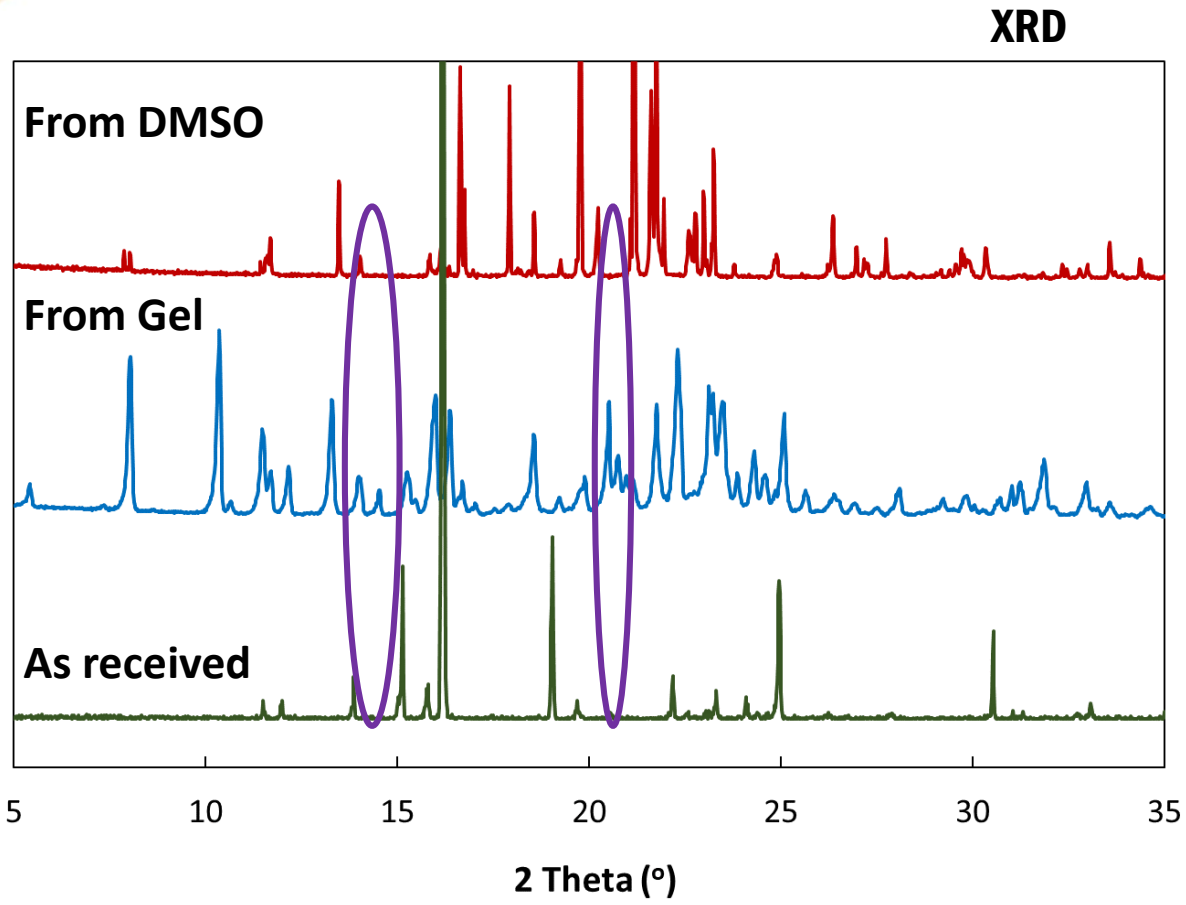




Banerjee et al., J. Mat. Chem. B 2018

Sulfapyridine recovered as a mixture of polymorphs

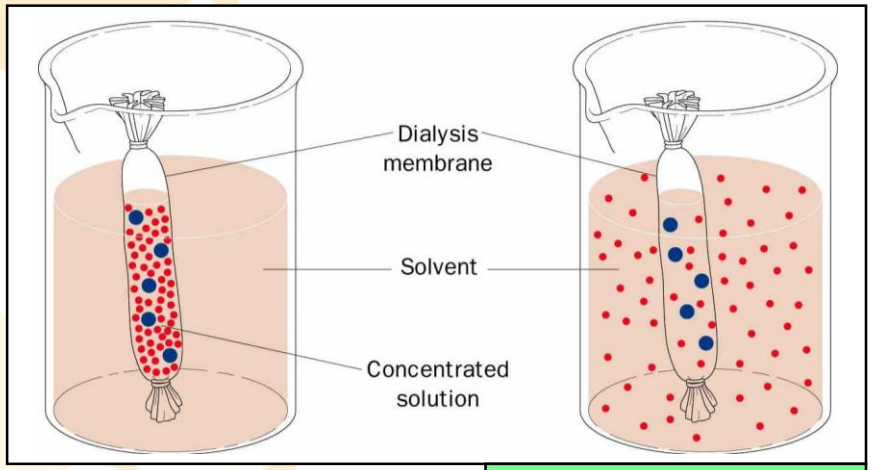


SP was recovered as forms III, IV, and V.
As-received is form III.

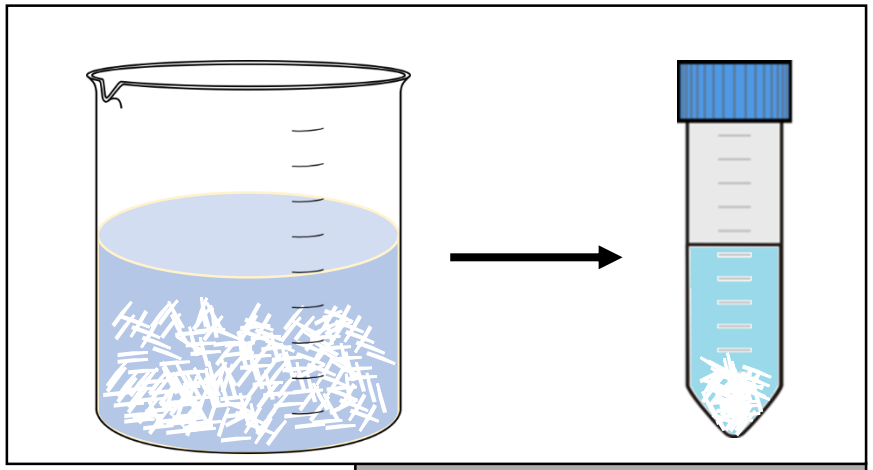
- Mixtures could be due to a combination of crystallization methods
- Heterogeneous crystallization on gel surfaces
- Homogeneous crystallization from confinement within gel pores
- Could also be due to heterogeneities in CNCs

CNC is a natural material with different processing depending on the source

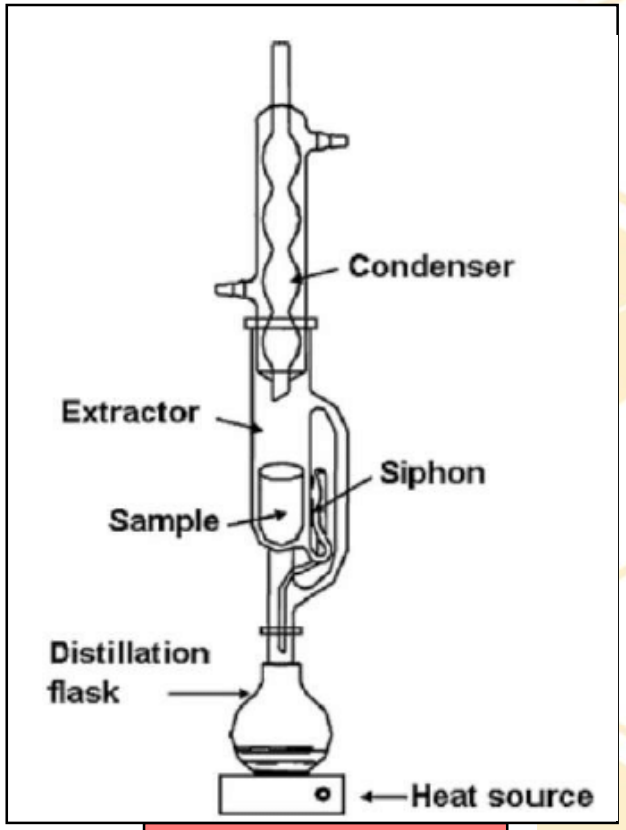
- Three different CNC sources
  - CD - Charged spray dried
  - CS - Charged slurry
  - US – Uncharged slurry
- Post treatments used to purify CNCs



Dialysis

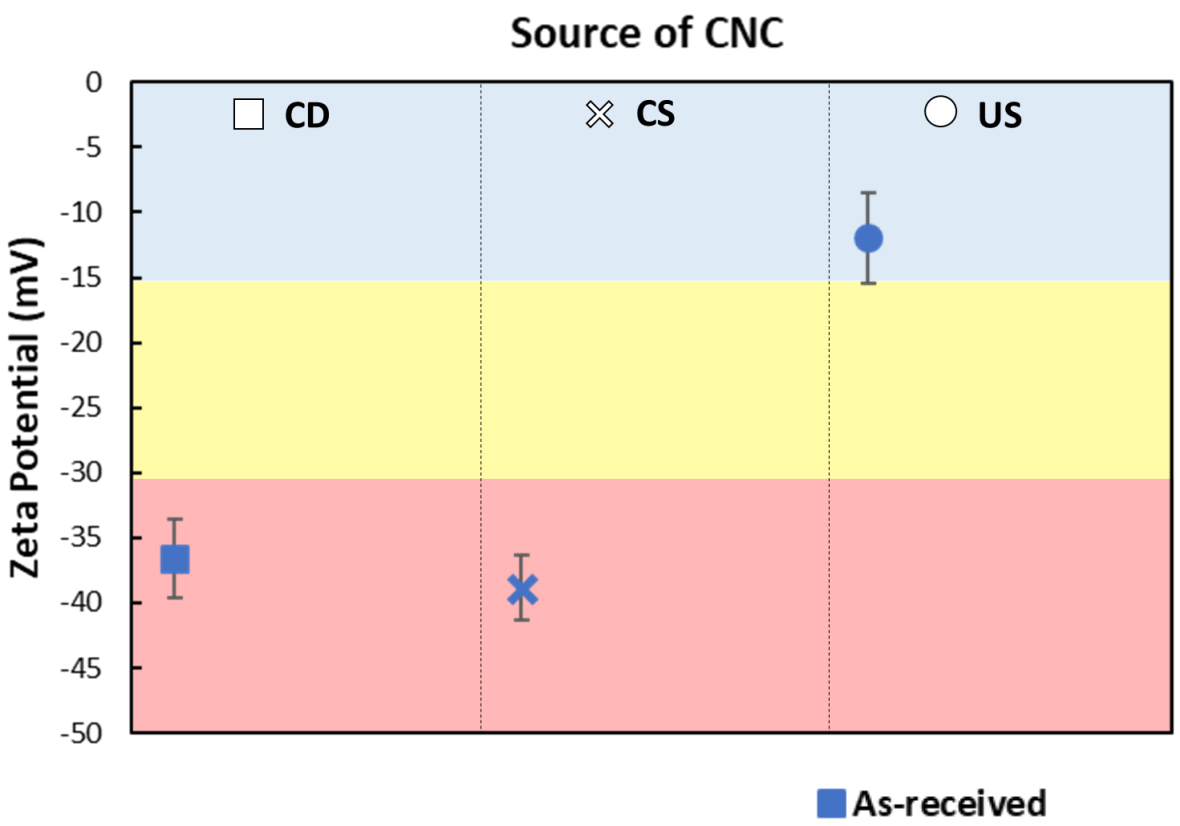


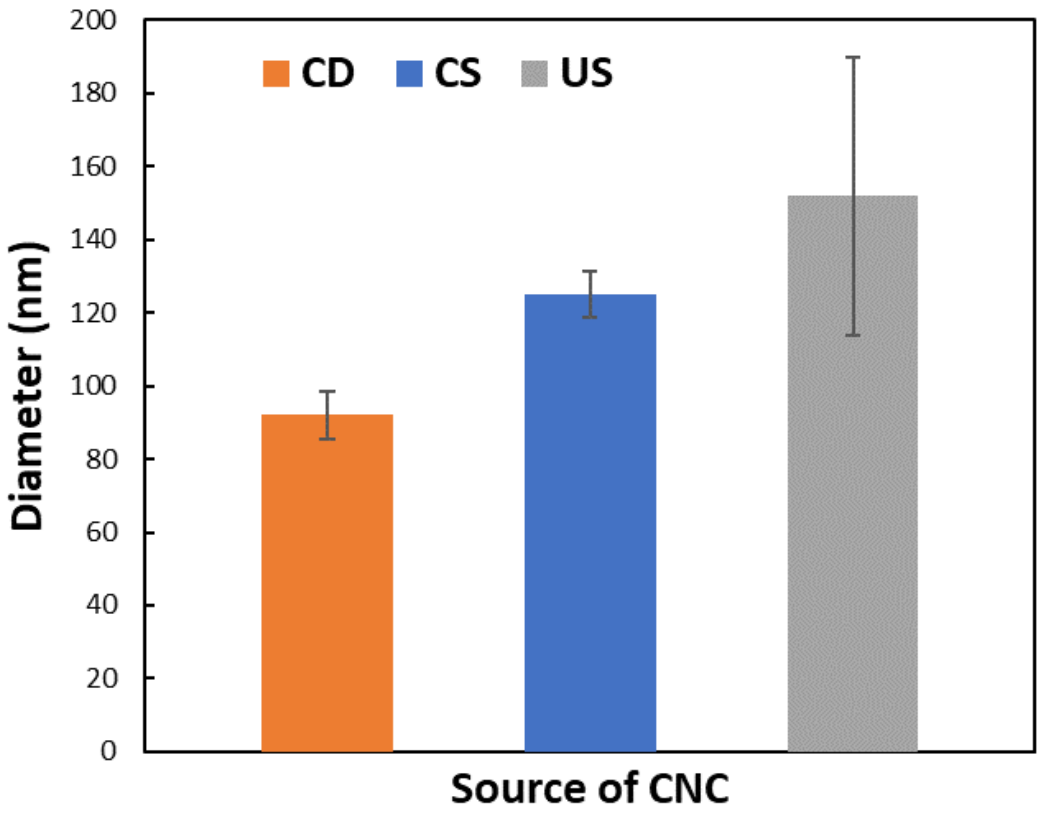
Acetone Washing



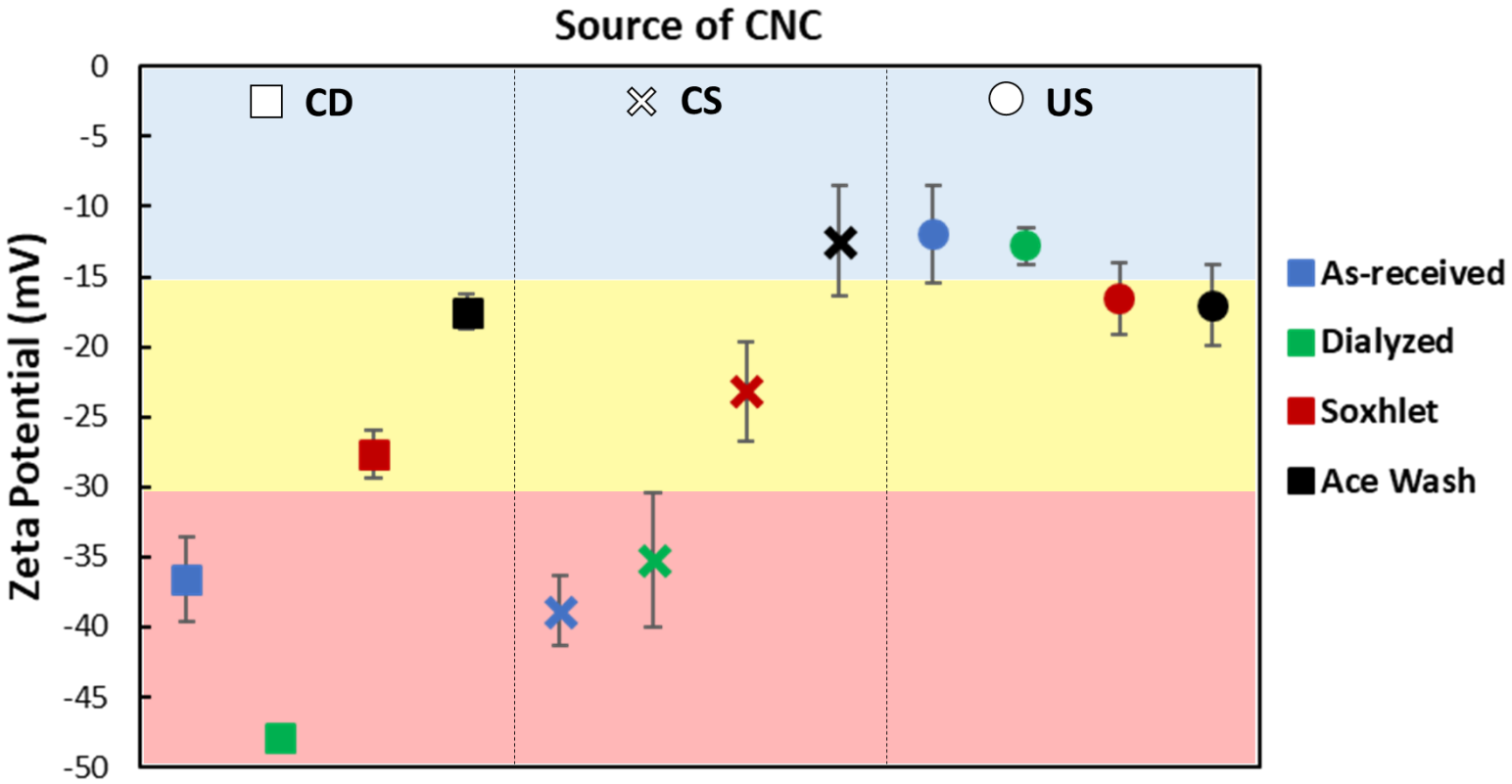
Soxhlet

Sulfate ester groups on as received charged CNCs provide colloidal stability





Zeta potential decreased by acetone washing and Soxhlet with ethanol



For CD and CS

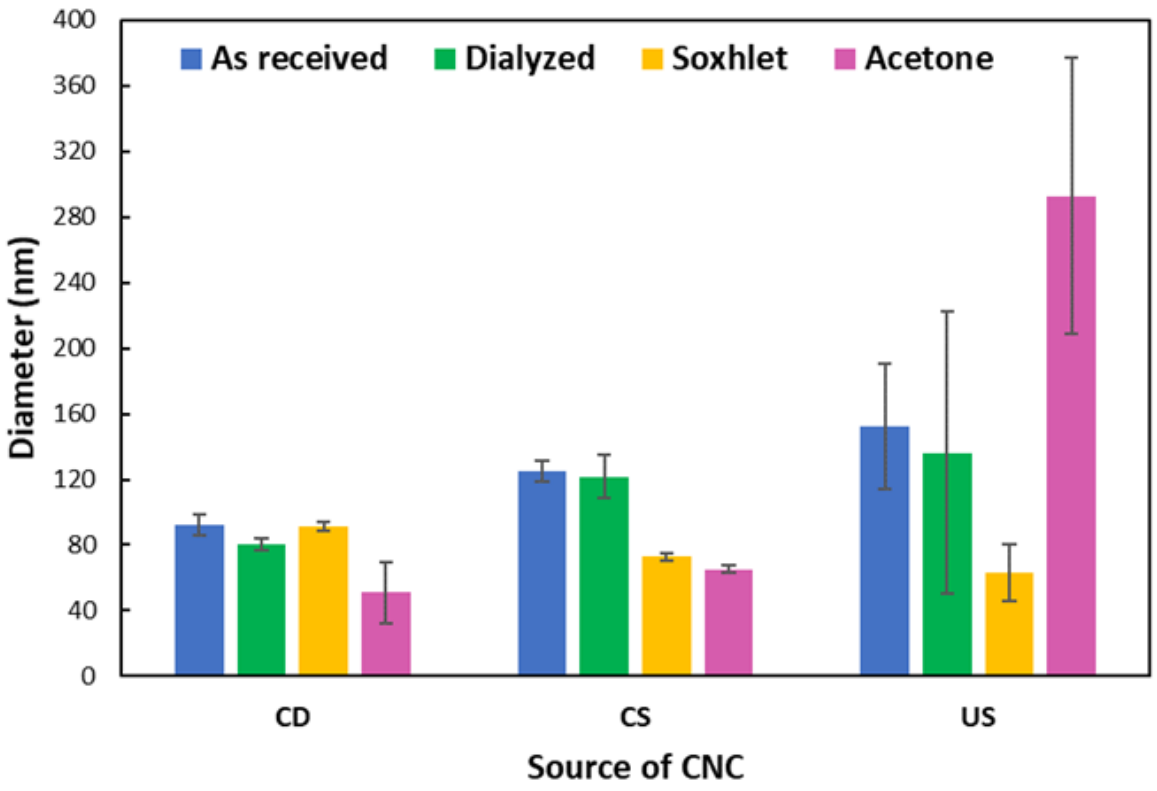
- Dialysis does not significantly change surface charge
- Soxhlet with ethanol and acetone washing decreases surface charges

For US

- Particles remain uncharged with all 3 treatments

Effect of surface treatment on average particle size

Dynamic light scattering



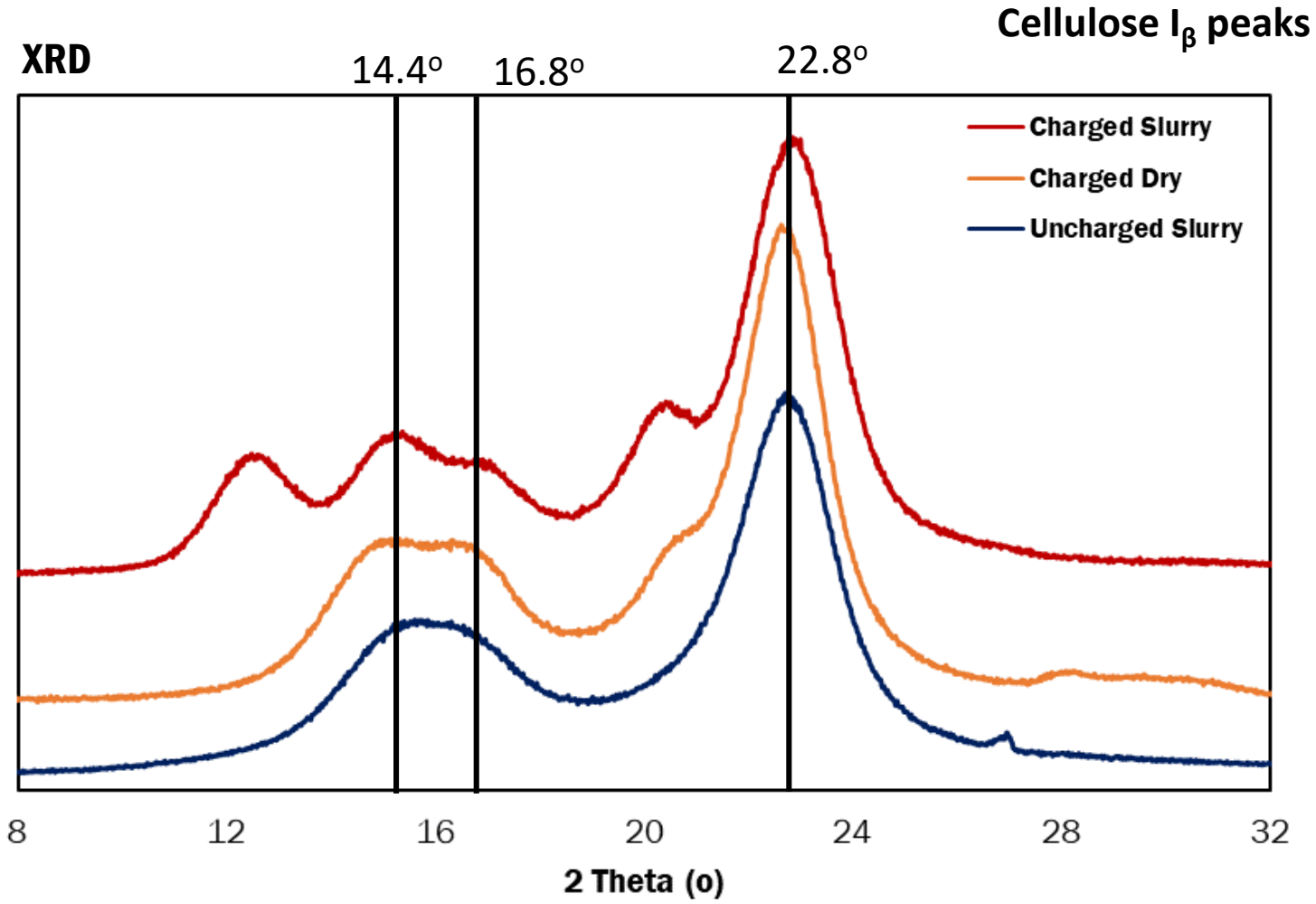
For CD and CS

- Dialysis leads to minimal or no size difference compared to as-received material
- Acetone washing decreases particle size

For US

- Strong variation makes it difficult to draw conclusions

CD and US material are cellulose I_β

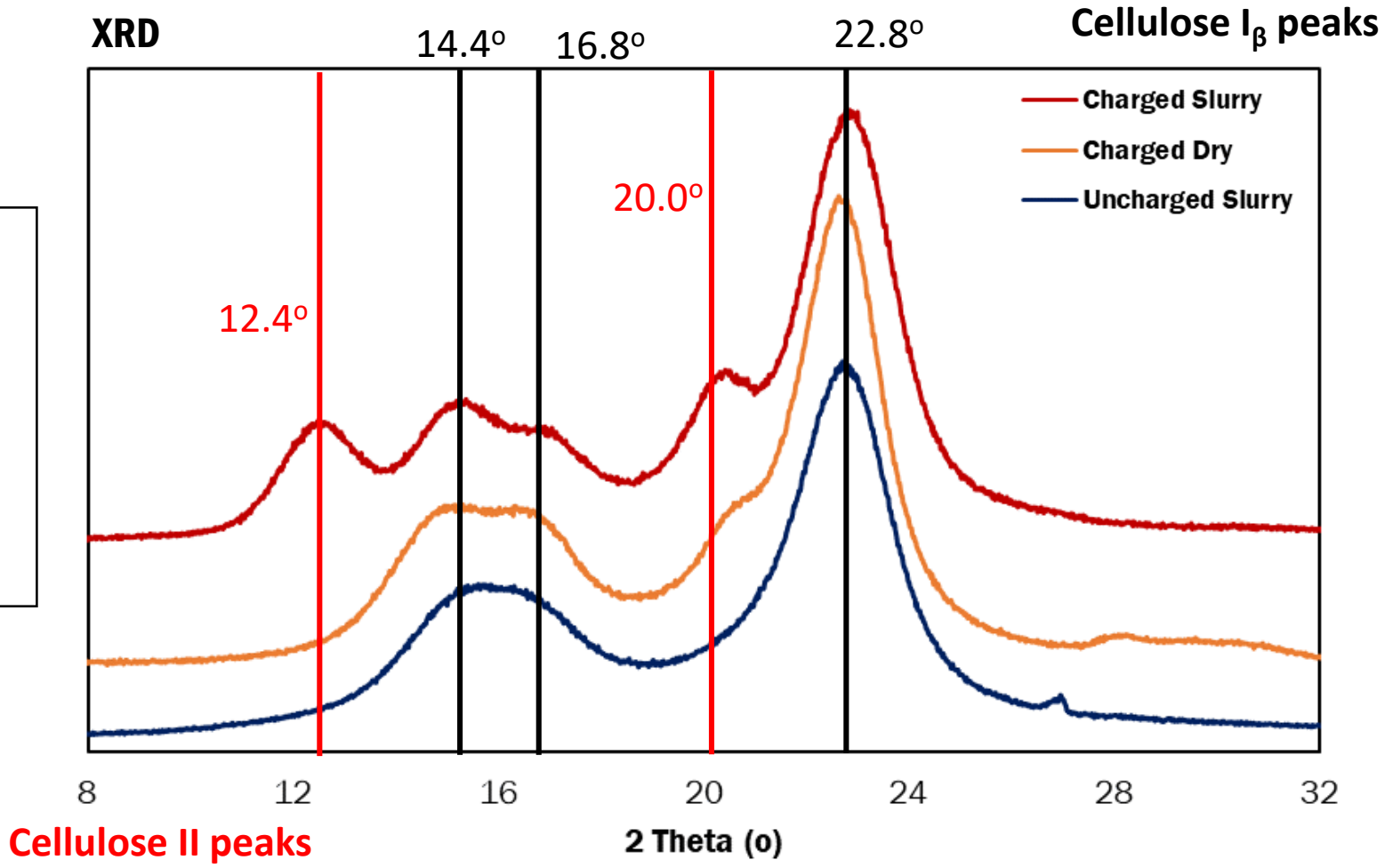


Briois et al. 2013
Kafle et al. 2014

CS contains both cellulose I_β and II

Crystallinity Index
CS = 97.1%
CD = 86.8%
US = 64.4%

Based on an amorphous peak at around 21.4°



Briois et al. 2013
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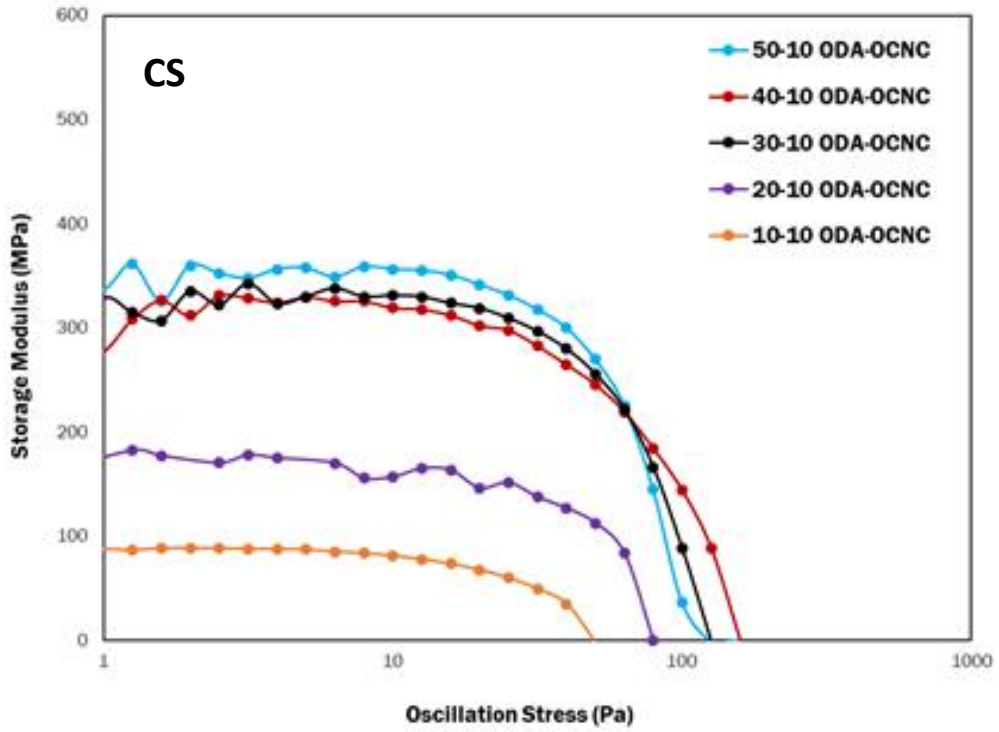
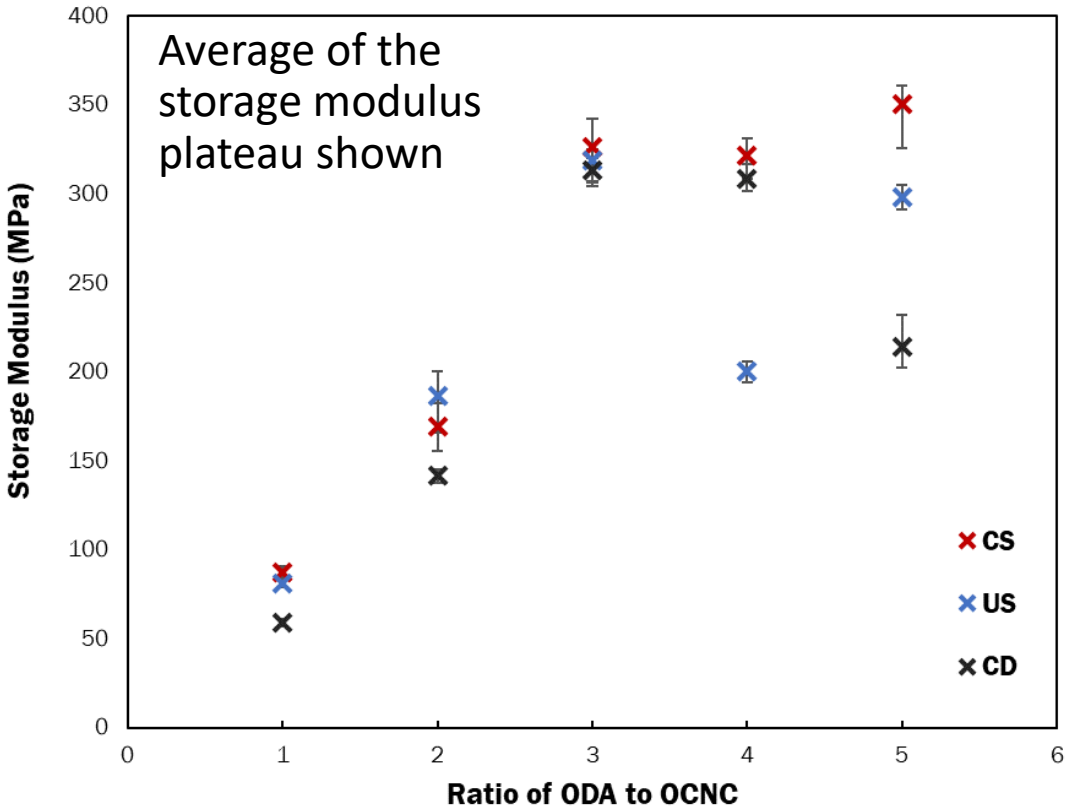
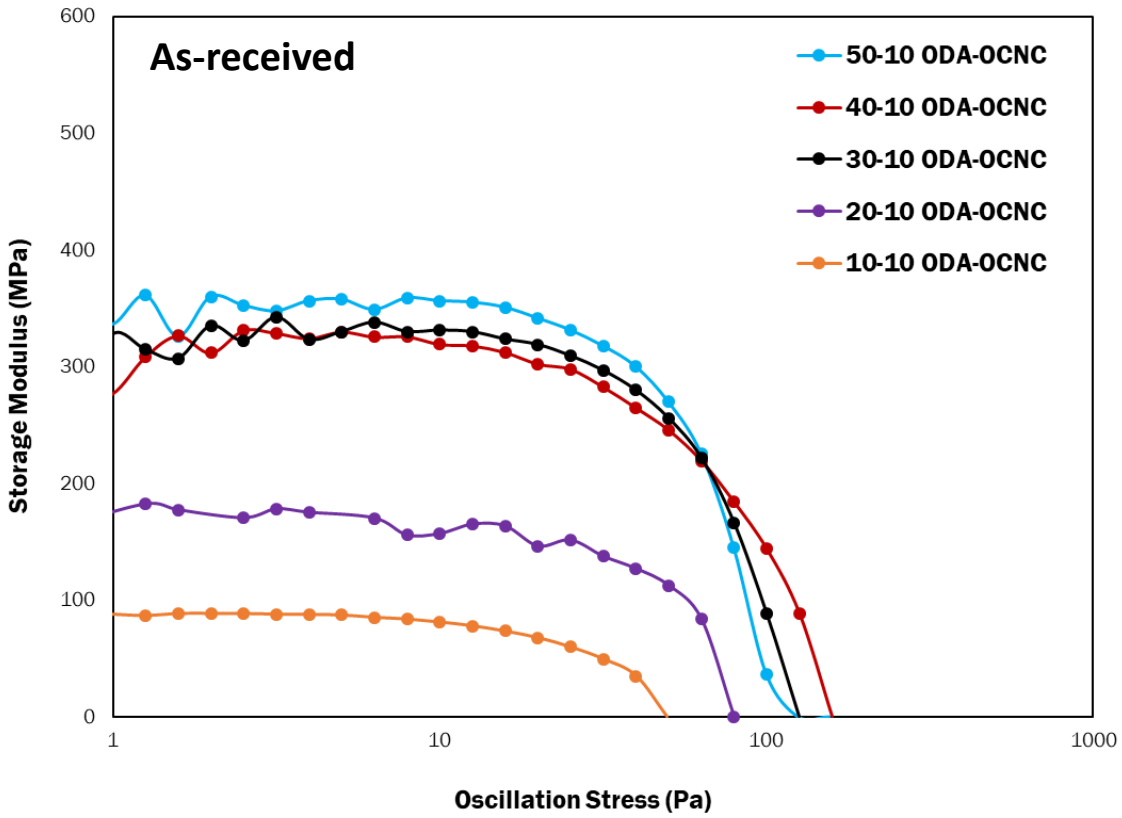
Max gel strength reached at 3:1 ODA-O-CNC ratio

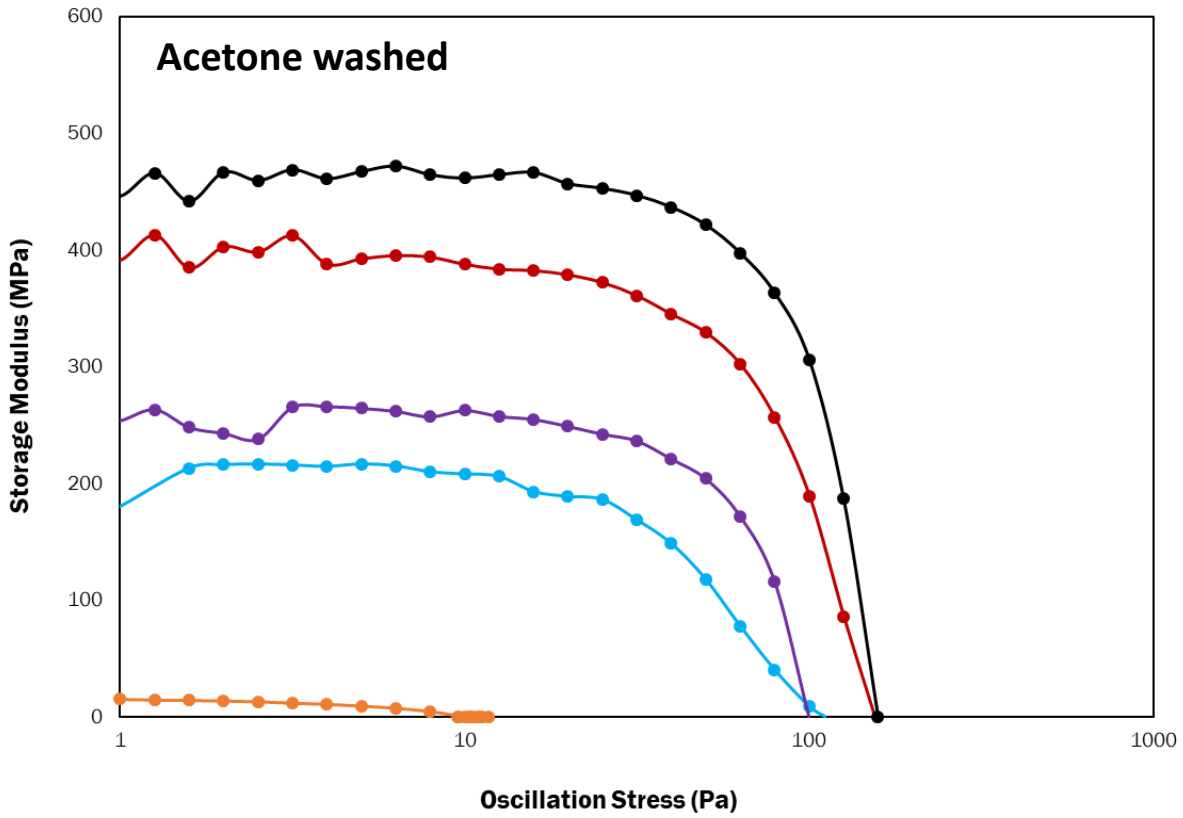




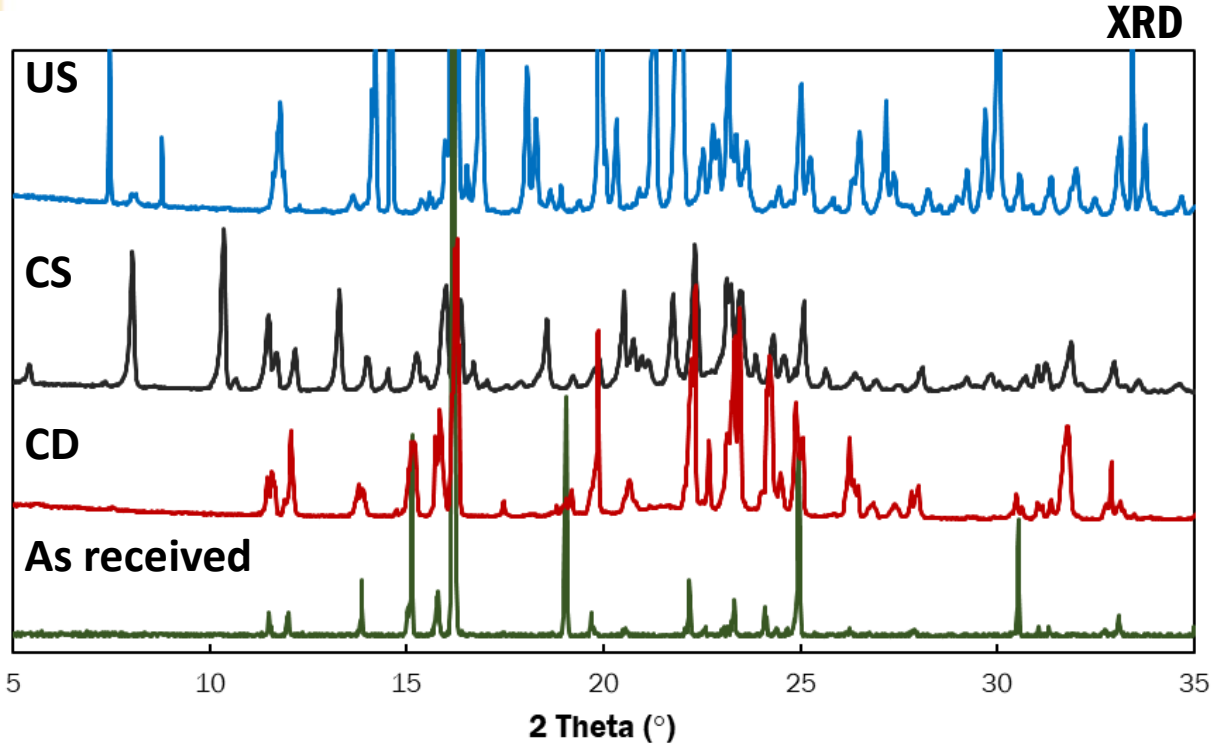
US gels could be aggregating and causing loss in storage modulus

Overall increase in gel strength after acetone washing



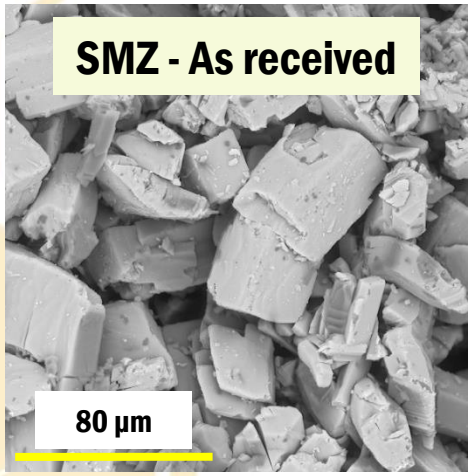


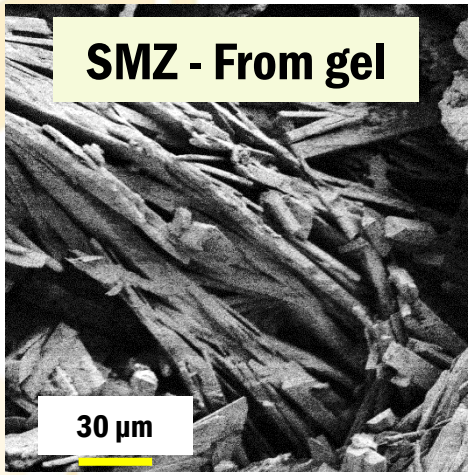
Sulfapyridine polymorph depends on the CNC source



CNC source	Polymorphs of sulfapyridine from recovered gel
None (as received)	III
Charged dried	III
Charged slurry	III, IV, V
Uncharged slurry	II, III, V

Conclusions





- CNC organogels formed by attachment of long alkyl chains to modified CNC surface
- CNC organogels can be used as surfaces to crystallize pharmaceuticals with different behavior
- CNC post treatments also affect organogel properties
- API recovered from gel affected by CNC source

Acknowledgements

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Graduate students

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Ian Campbell
Carly Travis
Elizabeth Sinner
Joshua Randrup
Nadia Zaragoza
Anna Williams
Mitchell Ketcham

@BrettmannLab

Thank you

@BrettmannLab

M E P D
Molecular Engineering
for Product Development

Georgia Tech
Renewable Bioproducts Institute

TAPPI

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Graduate Research Assistant

Georgia Institute of Technology

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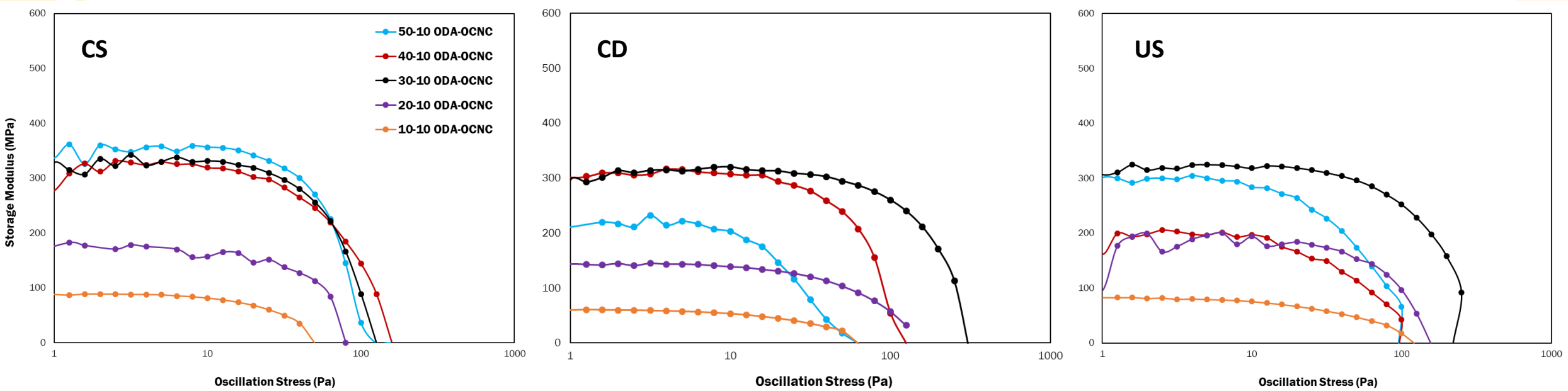
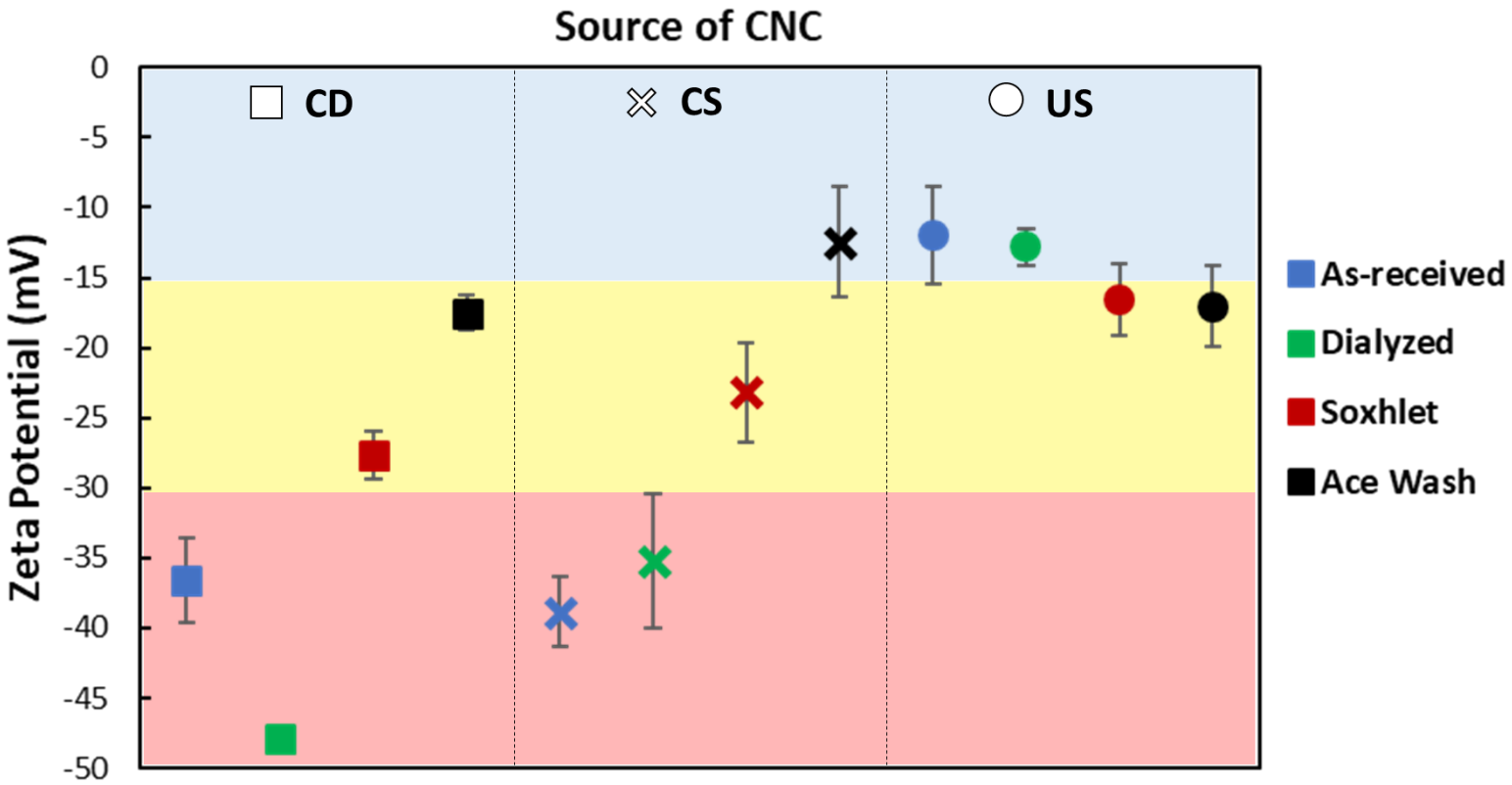
Supplemental Slides

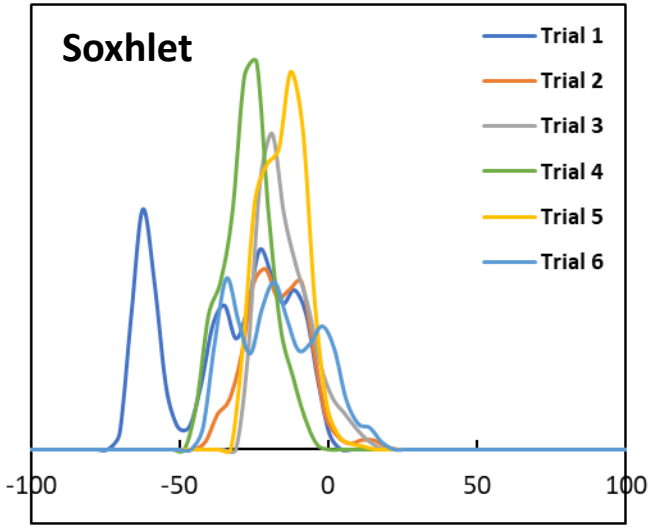
Similar gel strength pattern for all CNCs

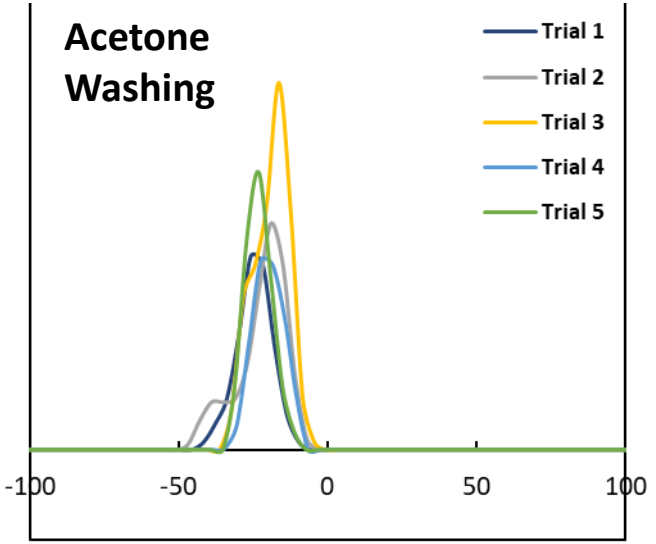


- Max strength seen at 30-10 ODA-CNC
- Either decrease or similar strength if ODA ratio increased further

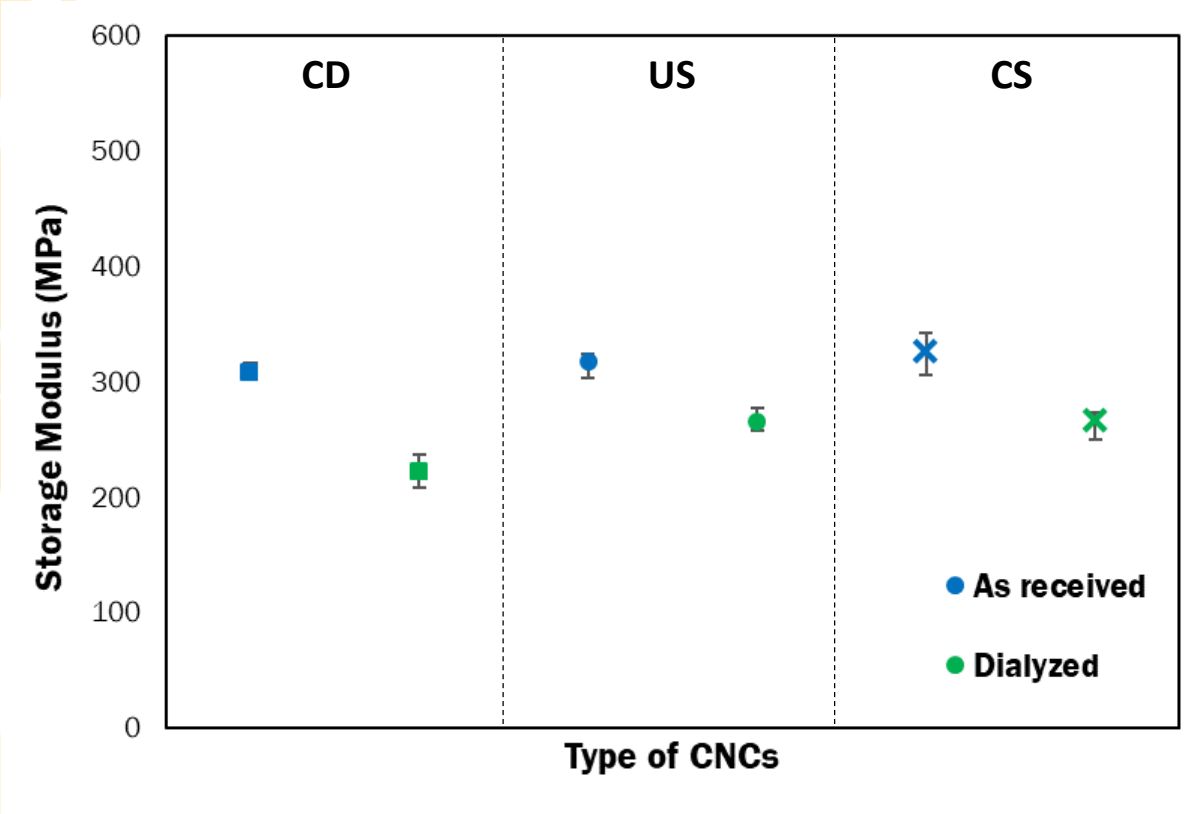
Zeta potential decreased by acetone washing and Soxhlet with ethanol



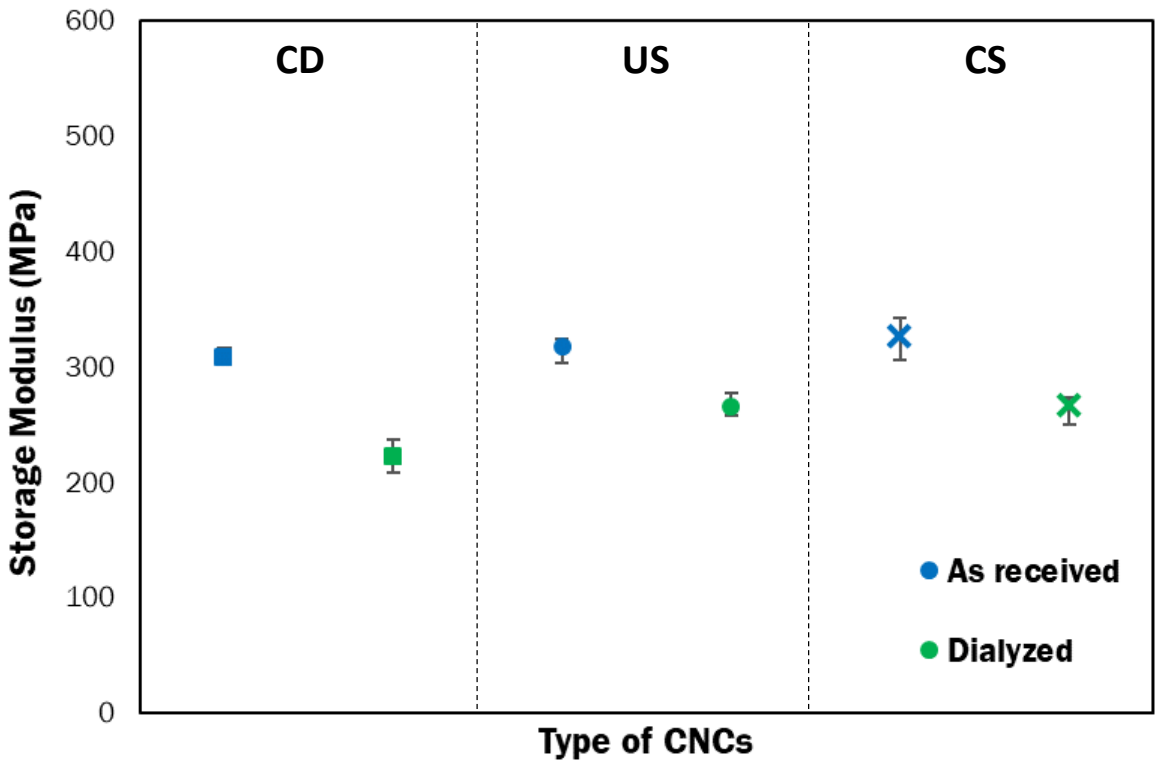


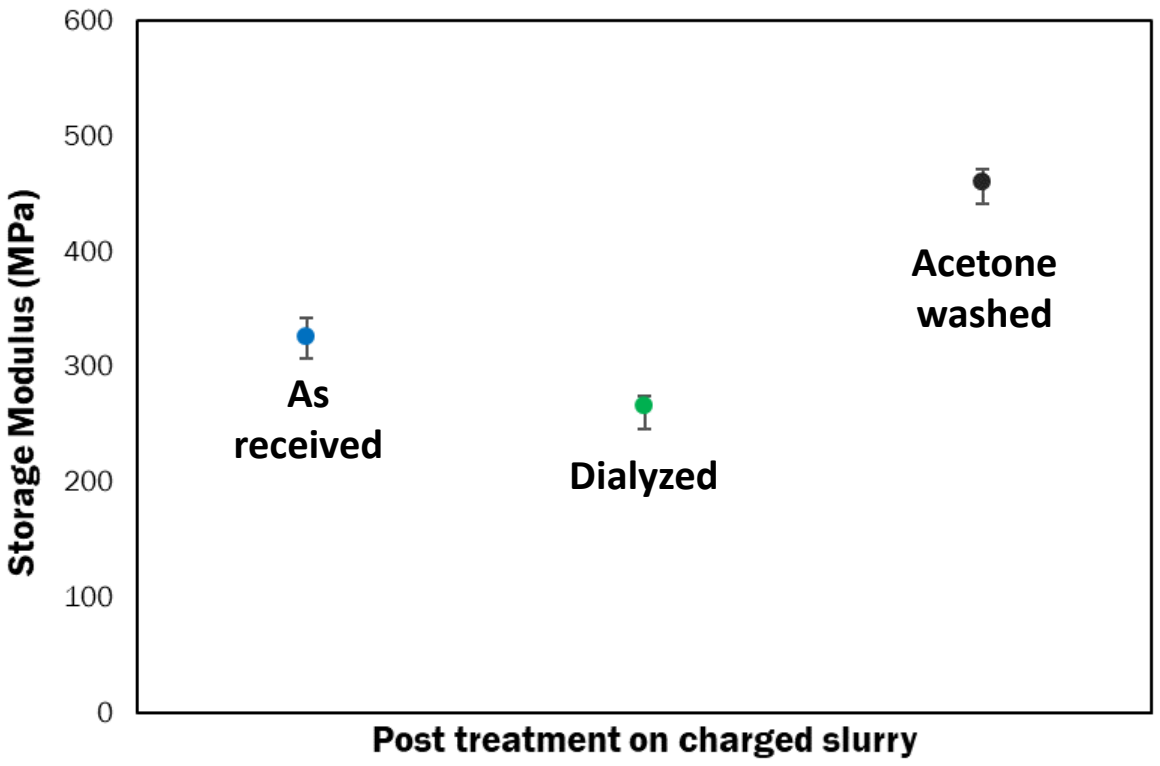


30-10 ODA-OCNC used to compare gels

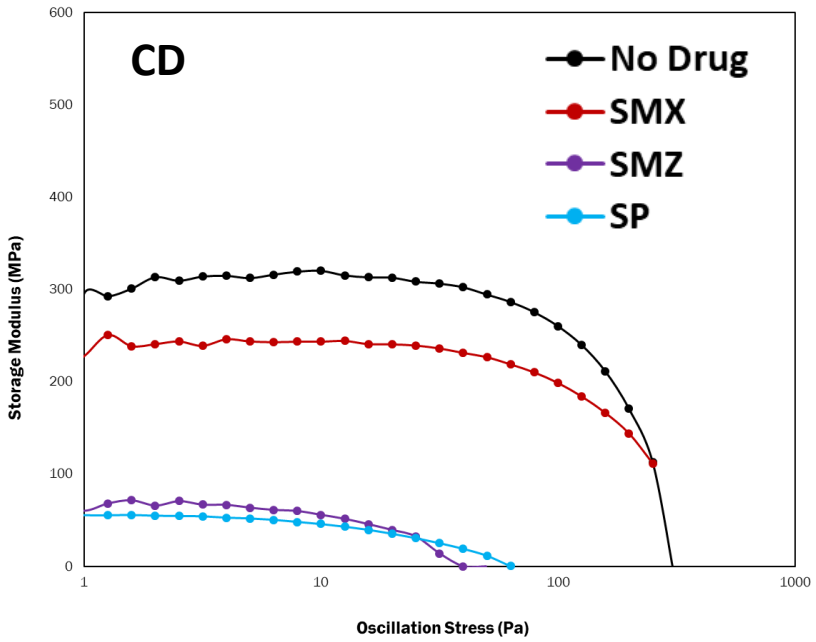


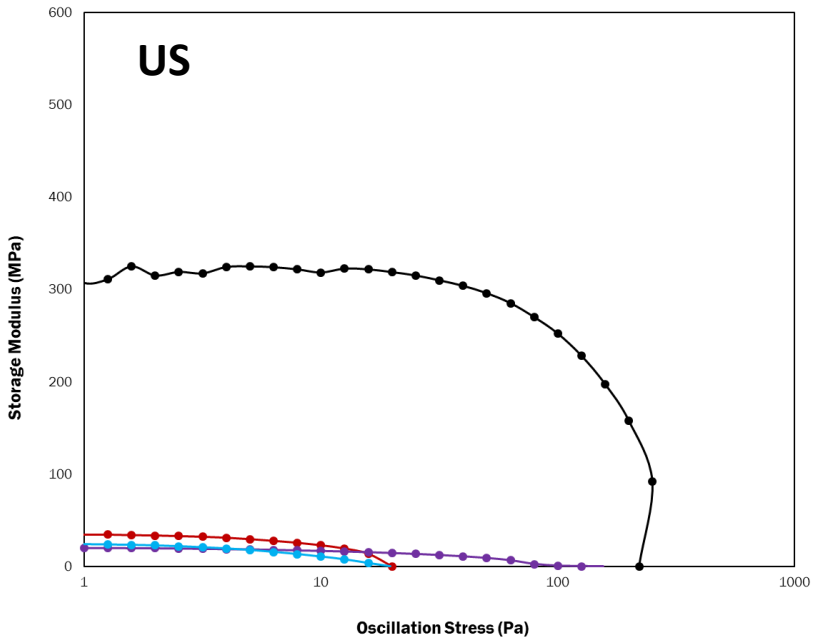
30-10 ODA-OCNC used to compare gels

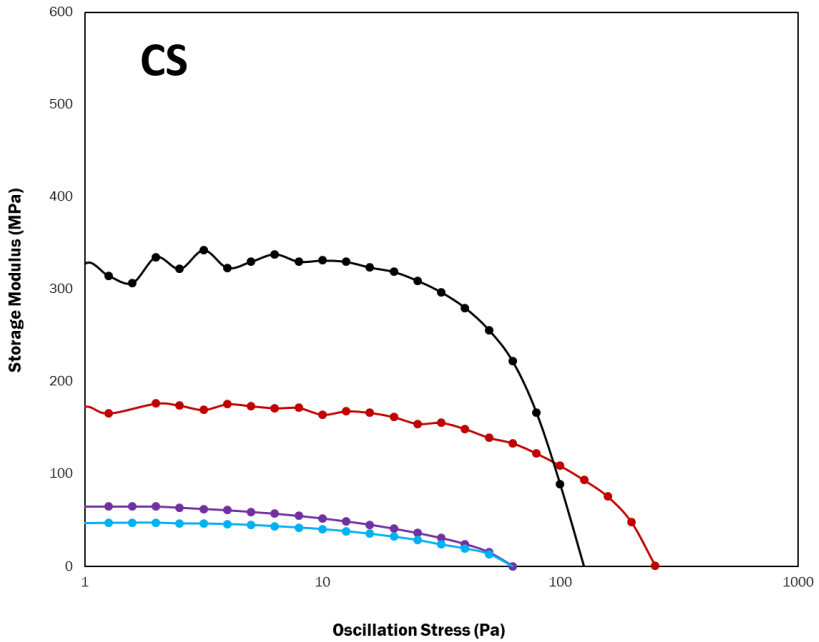




Drug incorporation weakens gels

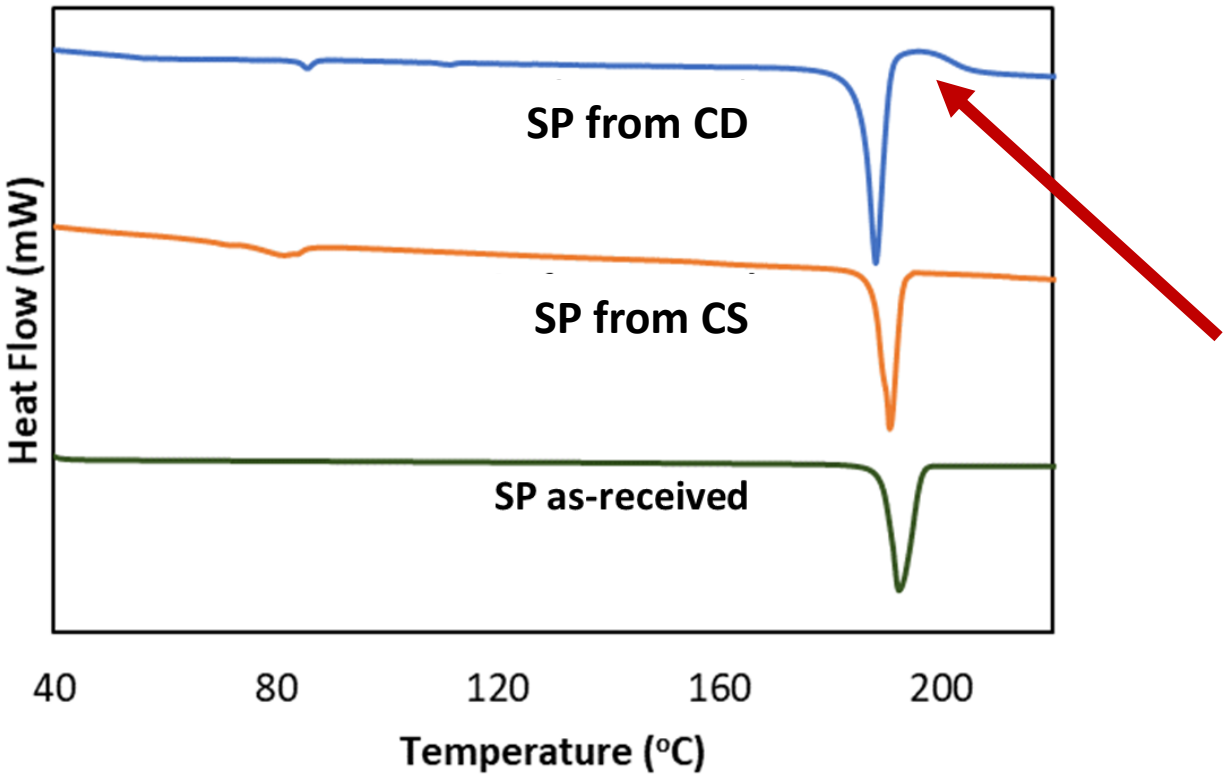






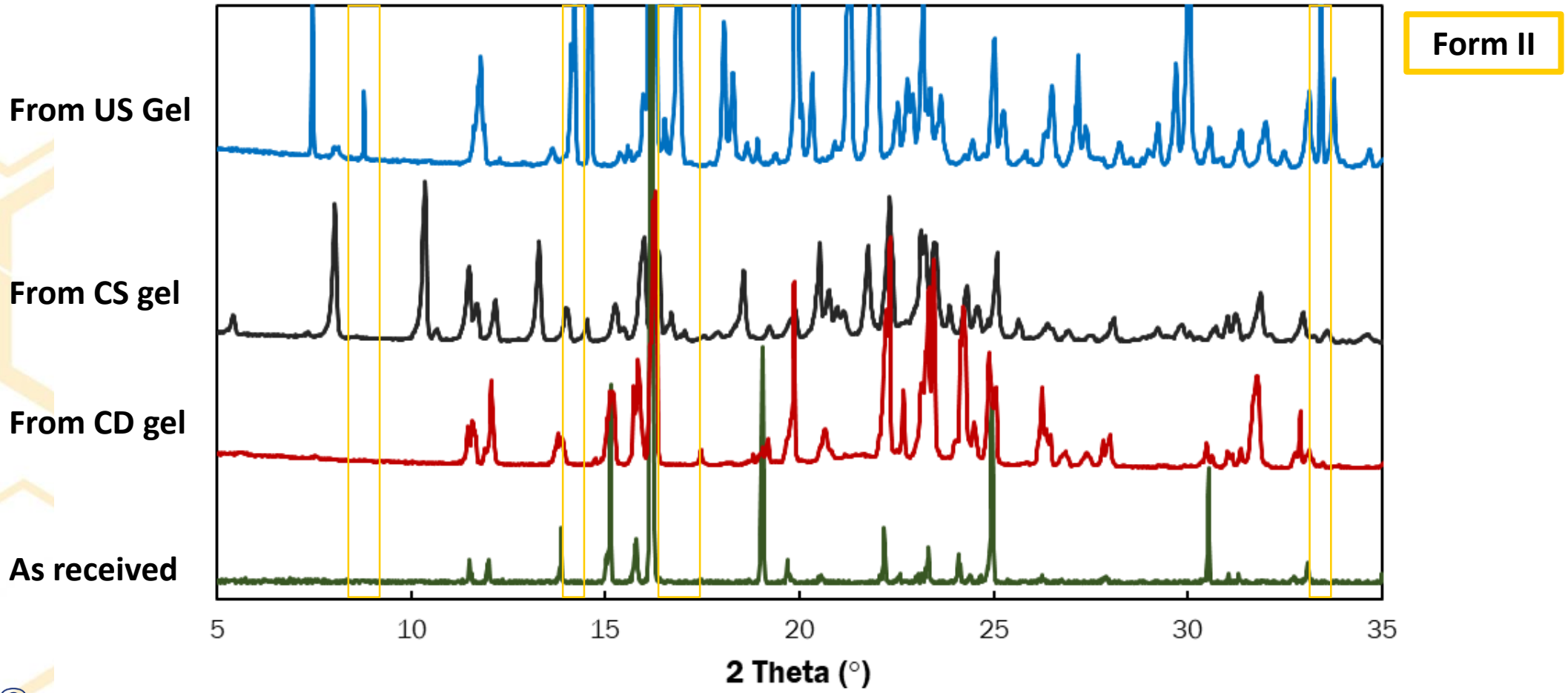
Incorporating drugs into the gel networks breaks up the gel and makes them weaker. All samples contain 10:30:200 mg/mL of O-CNC:ODA:Drug

SP showed recrystallization in CF gels

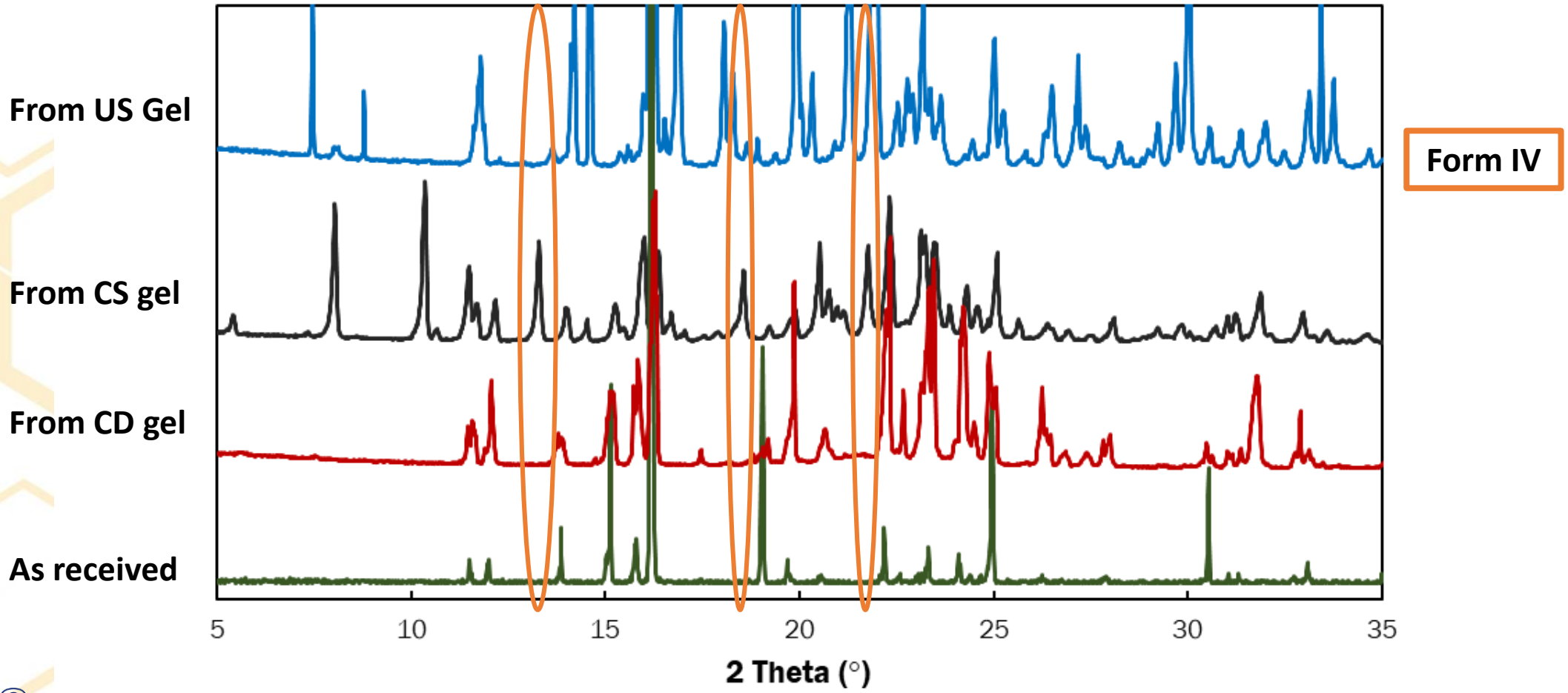
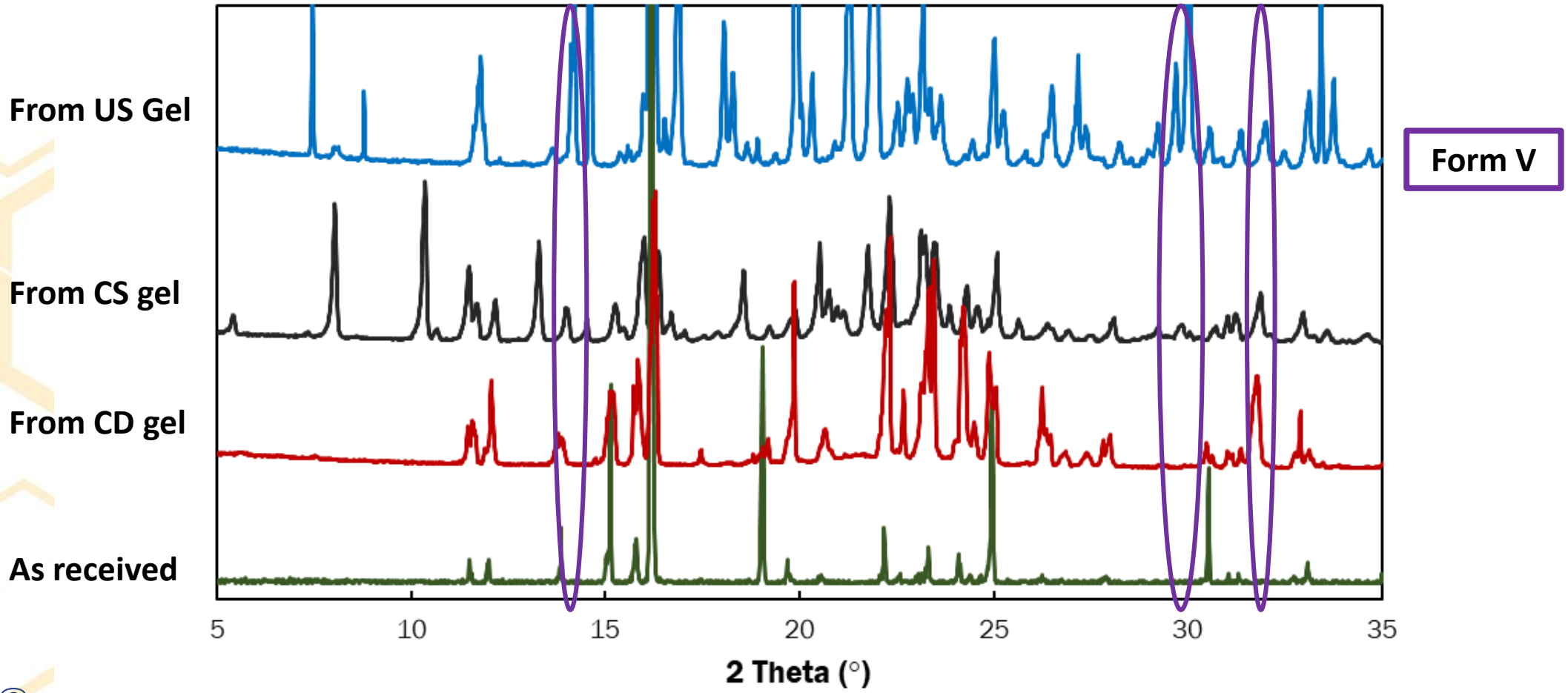


Recrystallization peak seen in CF gel but not in FPL gel indicating differences in API form

US gel sulfapyridine also shows form II



CS gel sulfapyridine shows form IV



US and CS gel sulfapyridine also show form V