PURDUE UNIVERSITY

UNIVERSITY OF KENTUCKY College of Pharmacy

Advanced Analytical Techniques for Characterizing Amorphous Solid Dispersions

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Purdue University

Disclosure

I am a partial owner of Kansas Analytical Services, a company that provides solid-state NMR services to the pharmaceutical industry.

The results presented here are from my academic work at the University of Kansas and the University of Kentucky, and no data from Kansas Analytical Services is presented here.

Outline

I. Motivation
   a. Why Amorphous Solid Dispersions (ASDs)?
   b. Current challenges
II. Crystallinity Detection
III. Drug-Polymer Interactions
IV. Drug-Polymer Homogeneity
V. Drug-Polymer Stability
VI. Protein Stability
VII. Conclusions and Acknowledgements

Impact of Solid-State Form Changes on Biopharmaceutical Properties

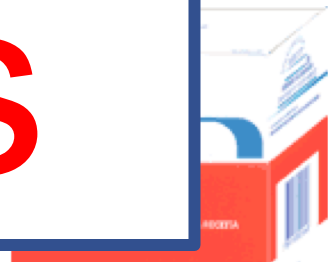
Organic Process Research & Development, 2000 4, 413–417

Deali
Drug

Sanjay
Stephen
Mauro S

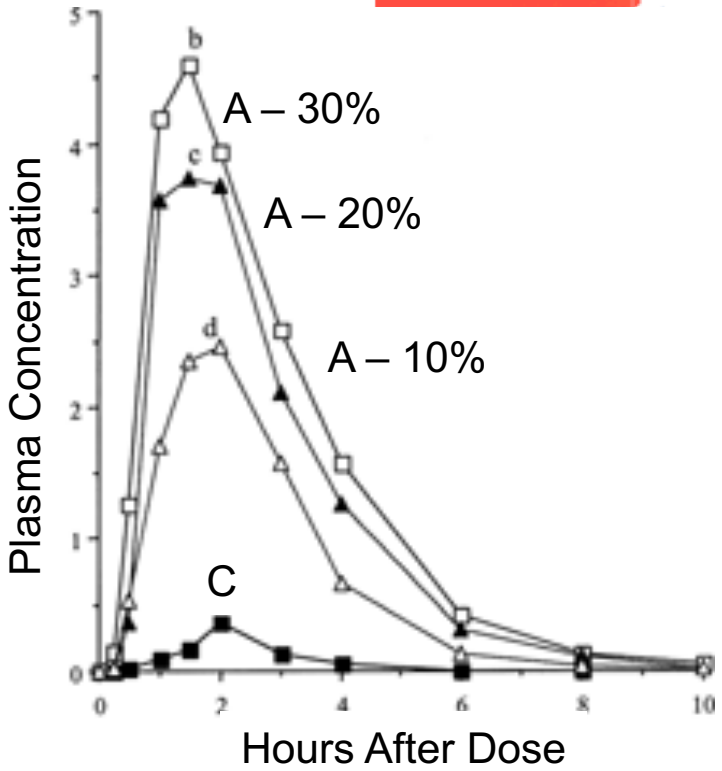
Process
North C

Amorphous



- Discovered 1992, FDA approved 1996
- Problems with dissolution observed 1998
- New polymorphic form discovered with half the solubility
- Forced withdrawal of formulation from market
- Eventually reformulated with both forms

Bioavailability enhancement using amorphous vs. crystalline formulations



Amorphous Solid Dispersions

Twenty years later…

molecular pharmaceutics

Article

Cite This: *Mol. Pharmaceutics* 2018, 15, 1870–1877

Manufacturing Amorphous Solid Dispersions with a Tailored Amount of Crystallized API for Biopharmaceutical Testing

Frank Theil, Johanna Milsmann, Sankaran Anantharaman, and Holger van Lishaut*

AbbVie Deutschland GmbH & Co. KG, 67061 Ludwigshafen, Germany

How has the perspective changed?

Challenges with Current API Delivery

- Drug solubility remains a challenge
- ASDs remain a viable method for increasing solubility for BCS II (IV)
- Hydrogen bonds and van der Waals forces stabilize API in polymer matrices
- Potential for crystallization always exists
- Drug loading of ASD has significant impact – compromise between physical stability and reduced pill burden

Crystallinity in an ASD

- Usually a CQA
- Source – manufacturing or conversion
- Manufacturing - ”easily” detected and controlled
- Conversion – depends upon stability in matrix – T_g, molecular mobility
- Where is the boundary???
- Impact on bioavailability???

Crystallinity in an ASD

- Detecting – is it there?
- Avoiding – drug-polymer interactions, phase separation
- API Loading – how much is too much?
- Conversion – what matters? – T_g, polymer, water, drug loading
- Expansion of concepts to proteins

Amorphous Solid Dispersions – Advanced Techniques for Crystallinity Detection

Traditional methods (partial list)

- Polarized Light Microscopy
- Differential Scanning Calorimetry
- Powder X-ray Diffraction

Advanced Methods

- Transmission Raman Spectroscopy
- Synchrotron X-ray Diffraction
- Second Harmonic Generation
- Solid-State NMR

Amorphous Solid Dispersions – Two-Dimensional X-ray Diffractometry

molecular pharmaceutics

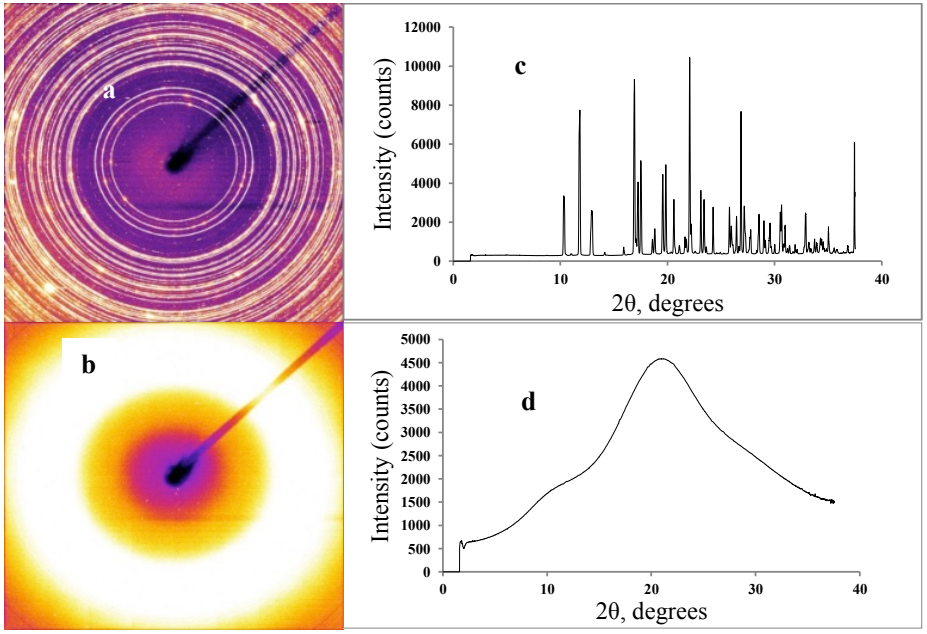
Article

pubs.acs.org/molecularpharmaceutics

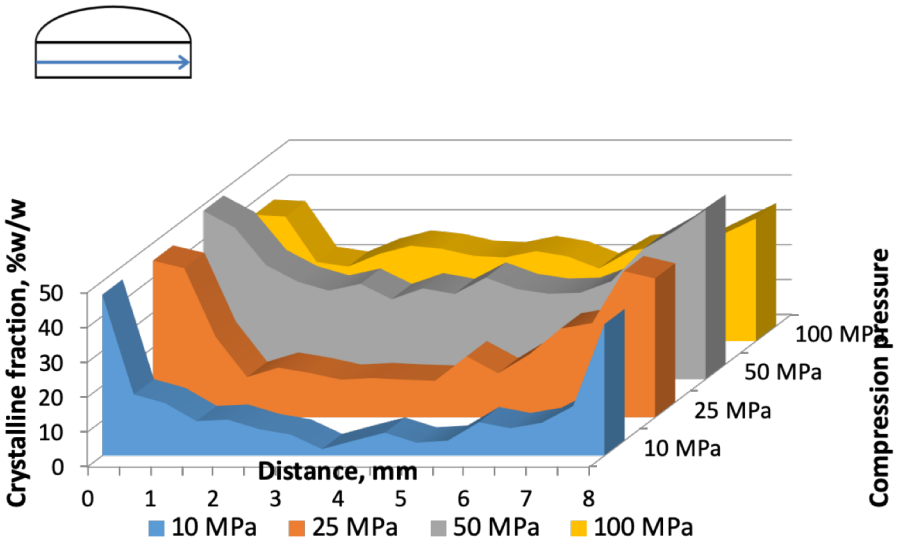
Compression-Induced Crystallization of Amorphous Indomethacin in Tablets: Characterization of Spatial Heterogeneity by Two-Dimensional X-ray Diffractometry

Naveen K. Thakral,[†,‡] Sarat Mohapatra,[‡] Gregory A. Stephenson,[†] and Raj Suryanarayanan*[,‡]

Indomethacin Tablets

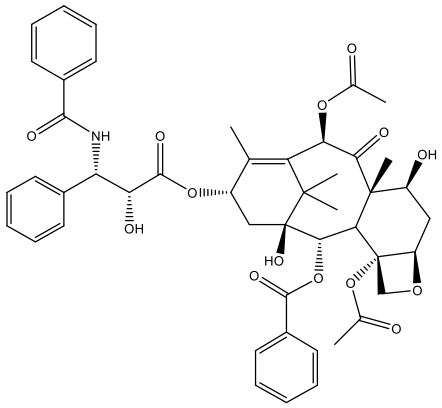


Depth Profiling (Radial) – 24 hours (35 C)

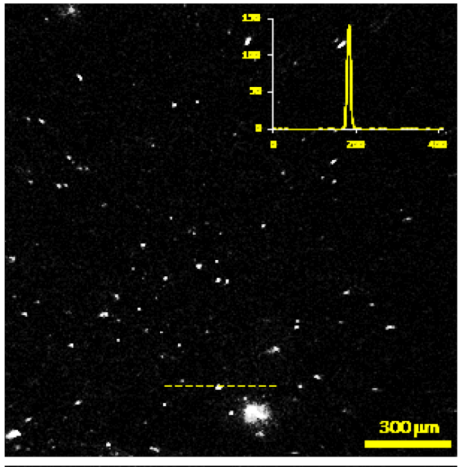


Data courtesy of Raj Suryanarayanan

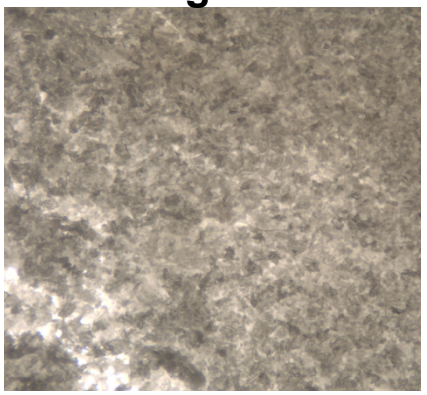
Amorphous Solid Dispersions – Abraxane Crystal Detection Using Second Harmonic Genertion



SHG



Bright field



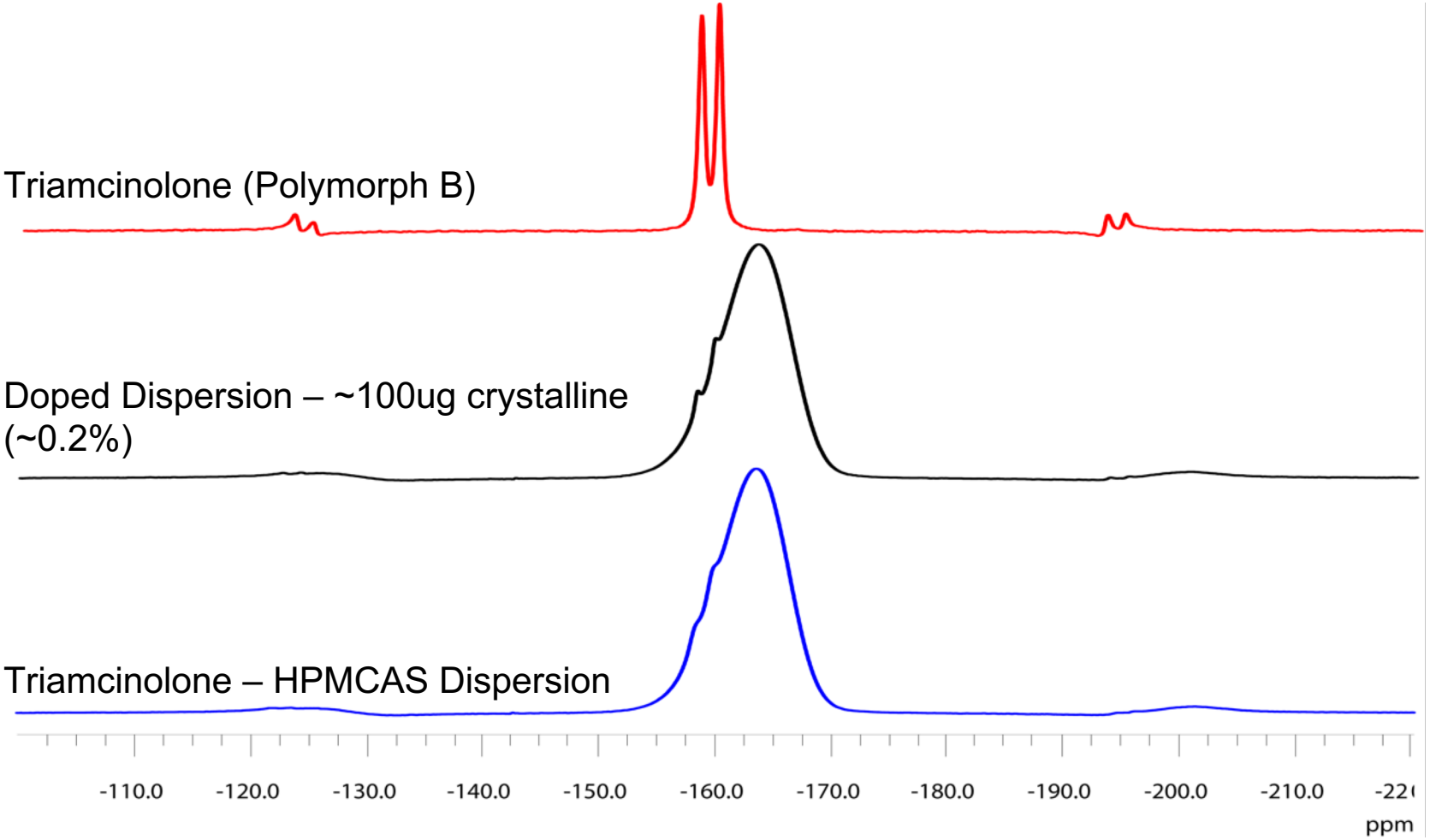
White spots indicate crystals

Crystalline material is present in freeze-dried Abraxane® powder - but is it the drug or is it an excipient?

Schmitt et al. Mol. Pharmaceutics. 2015 12(7):2378-2383.

Data courtesy of Lynne Taylor

^{1}H-^{19}F CPMAS NMR Spectra of 50%-50% Triamcinolone-HPMCAS Amorphous Solid Dispersions



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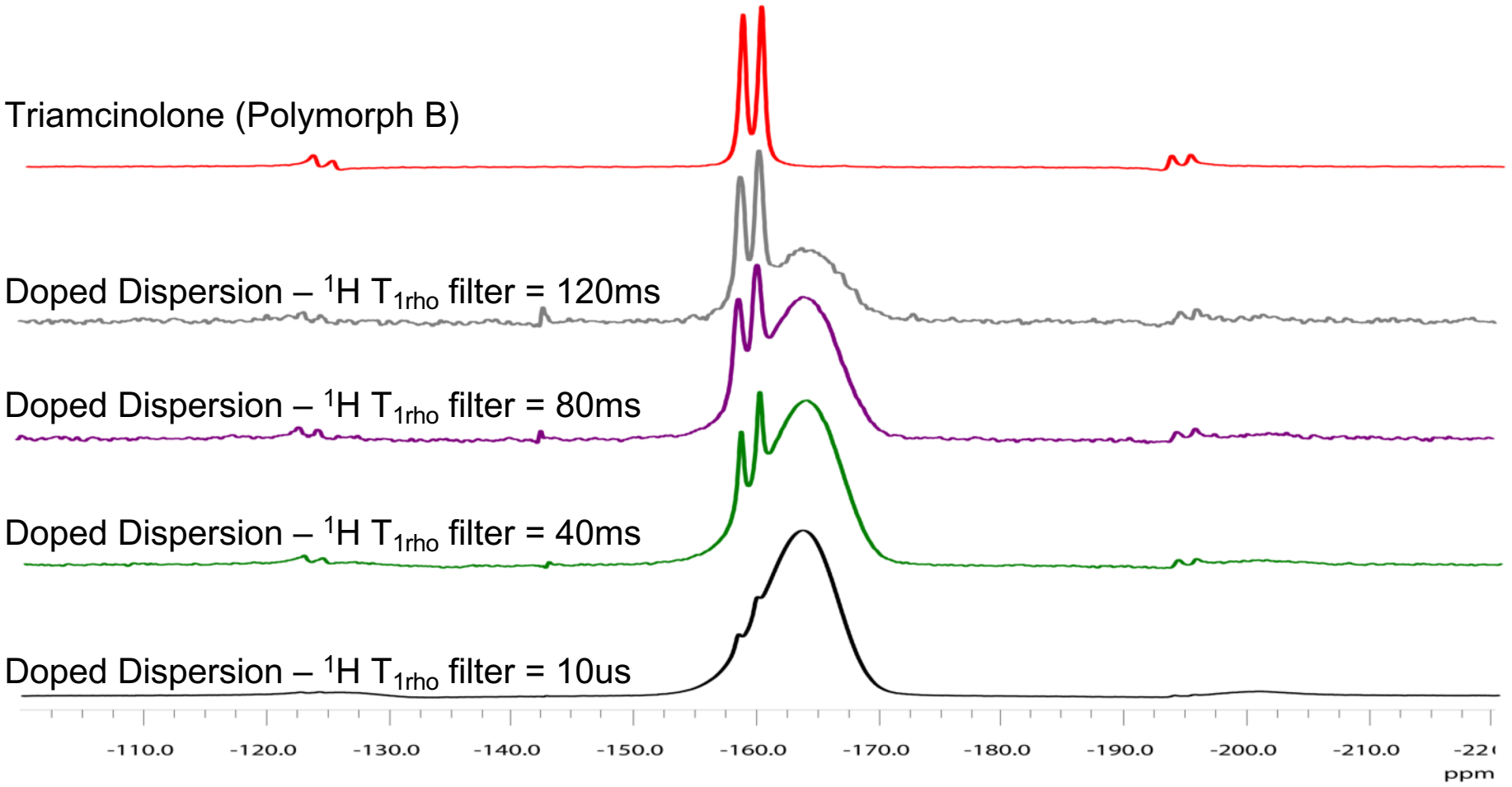

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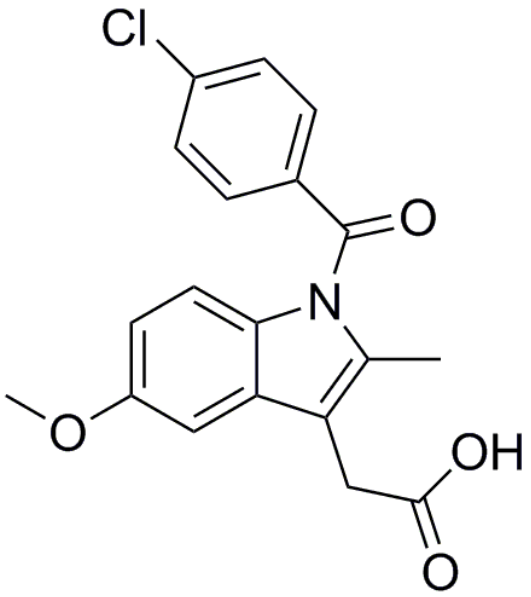
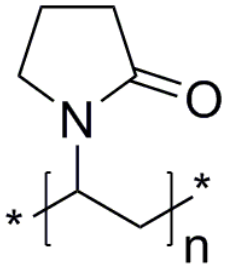
Hydrogen-Bonding Interactions of IMC Amorphous Solid Dispersions

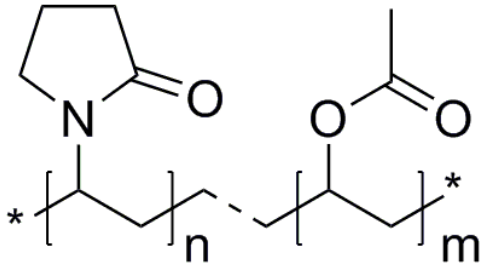
Model System



Indomethacin
H-bond donor and acceptor



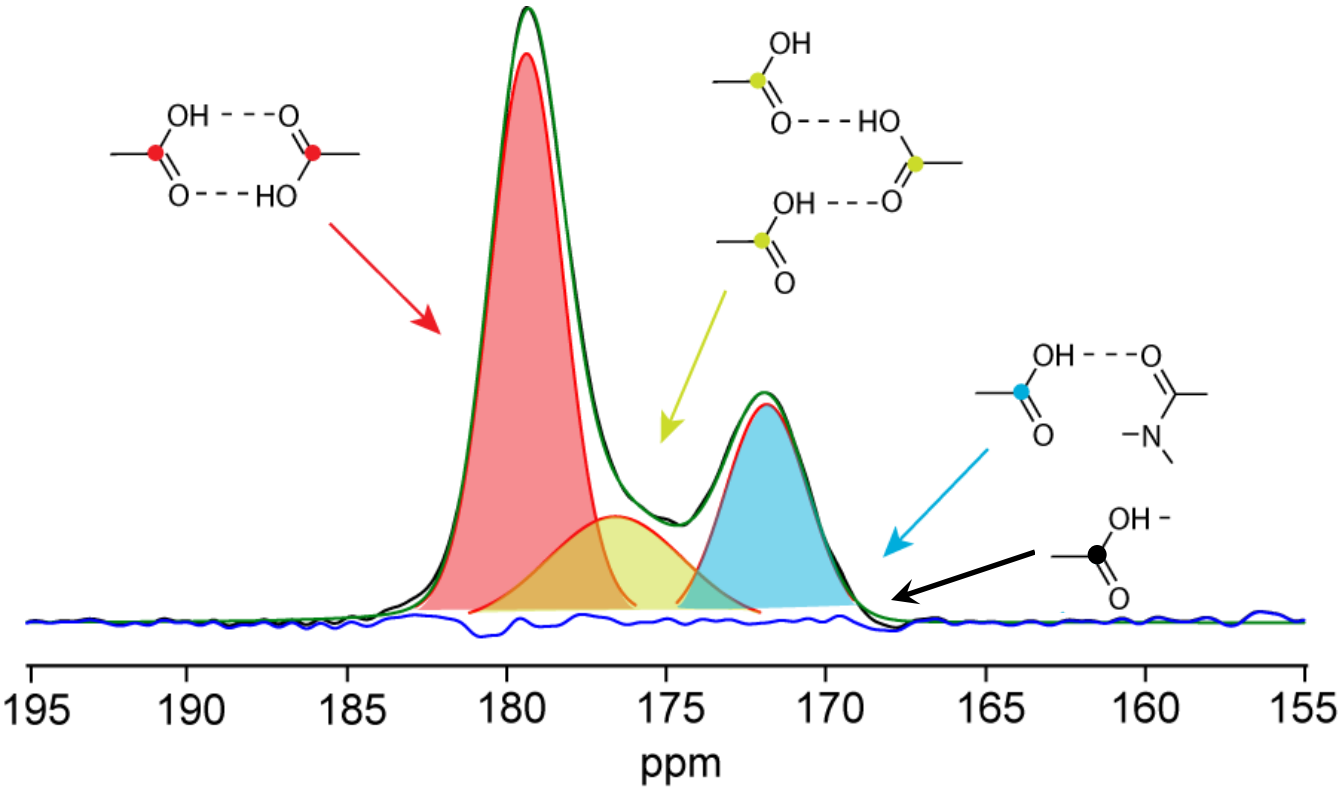
PVP
H-bond acceptor



PVP/VA
H-bond acceptor

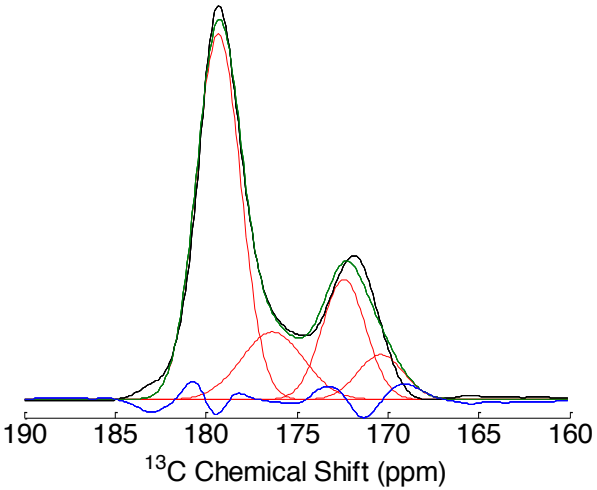
Hydrogen Bonding of Amorphous Indomethacin

- 179 ppm = cyclic dimer
- 176 ppm = disordered chains/rings
- 172 ppm = carboxylic acid-amide complex
- 170 ppm = free

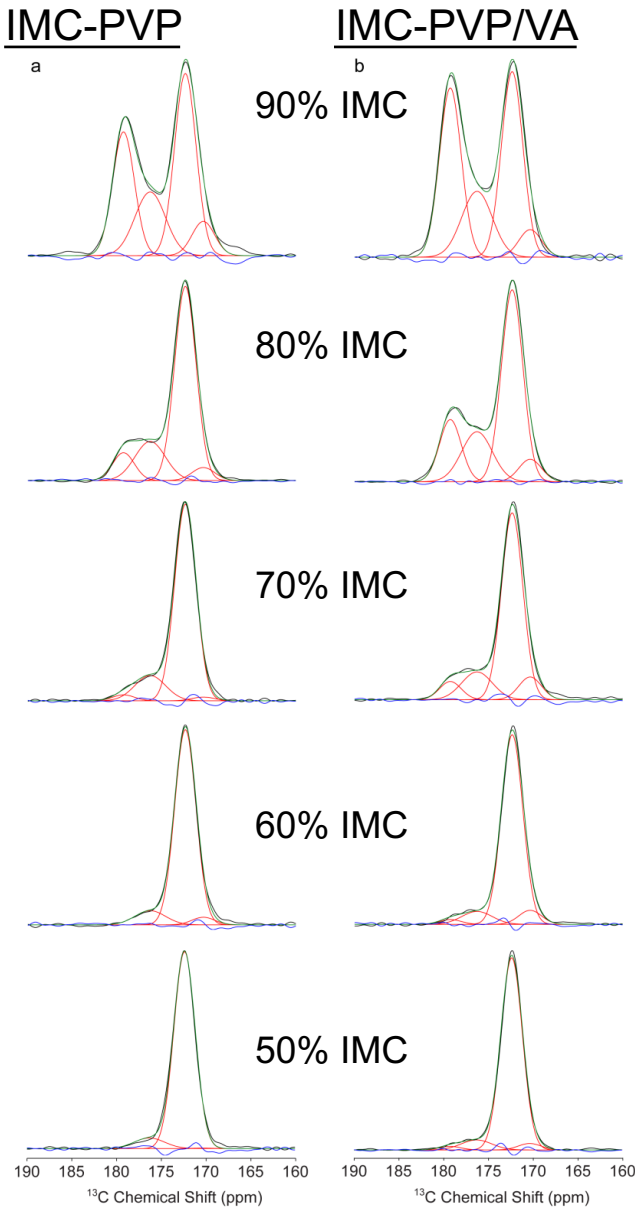


IMC Carboxylic Acid in Amorphous Solid Dispersions

Amorphous IMC

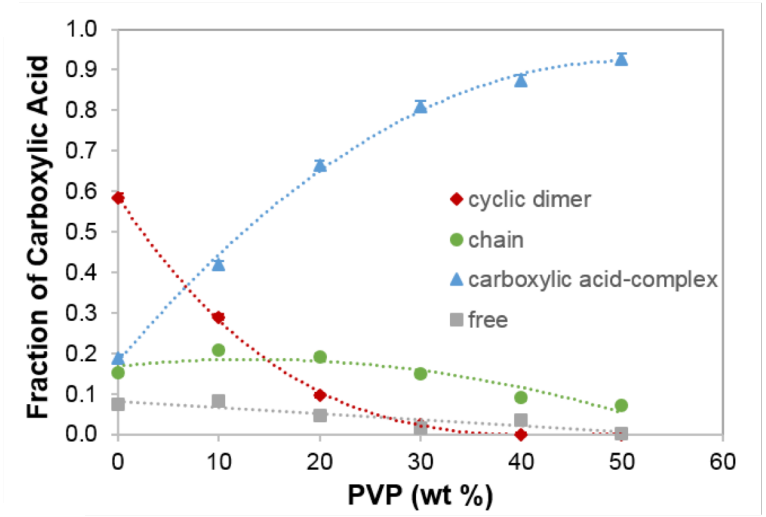


Chemical Shift (ppm)	Species	Peak Area (%)	Linewidth (Hz)
179.3 ± 0.006	cyclic dimer	58.5 ± 0.5	216 ± 0.8
176.3 ± 0.02	carboxylic acid chain	15.2 ± 0.4	303 ± 5
172.4 ± 0.004	carboxylic acid-amide	18.9 ± 0.4	212 ± 0.6
170.4 ± 0.05	free carboxylic acid	7.5 ± 0.3	225 ± 5

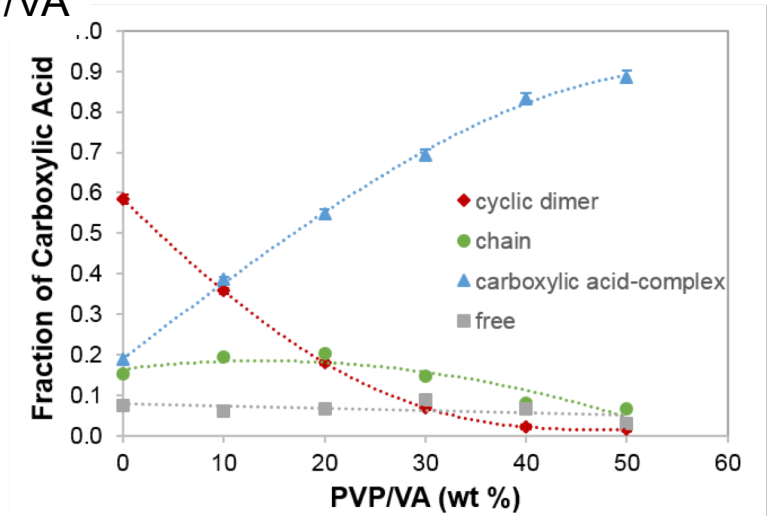


Hydrogen-Bonding Interactions in IMC Amorphous Solid Dispersions

IMC-PVP



IMC-PVP/VA

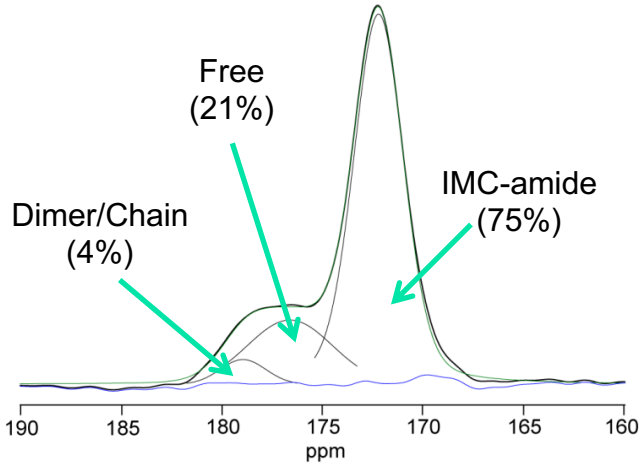


Summary:

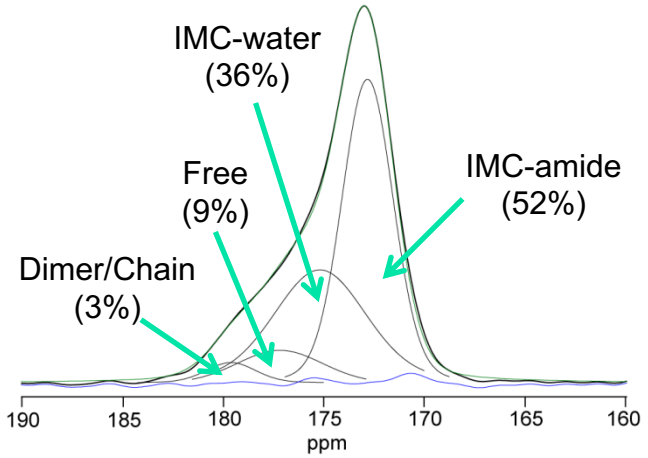
- PVP disrupted IMC cyclic dimers; with 40% (wt) of PVP present, no cyclic dimers could be detected.
- PVP/VA also disrupted the IMC self interactions in a similar fashion as PVP, but less effectively.

H-Bonding Interactions of 80-20 IMC-PVP ASD

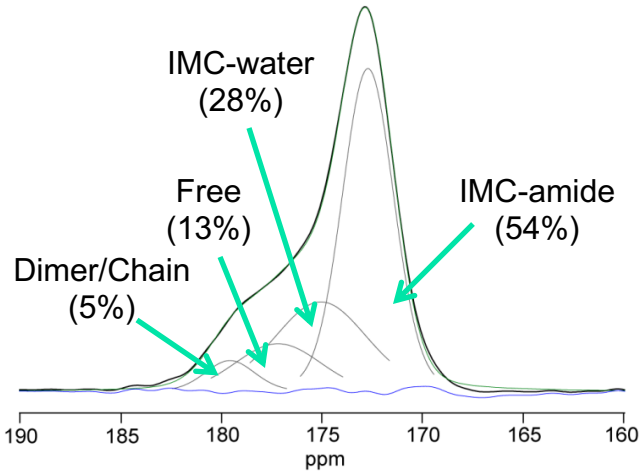
0.2% (wt) water

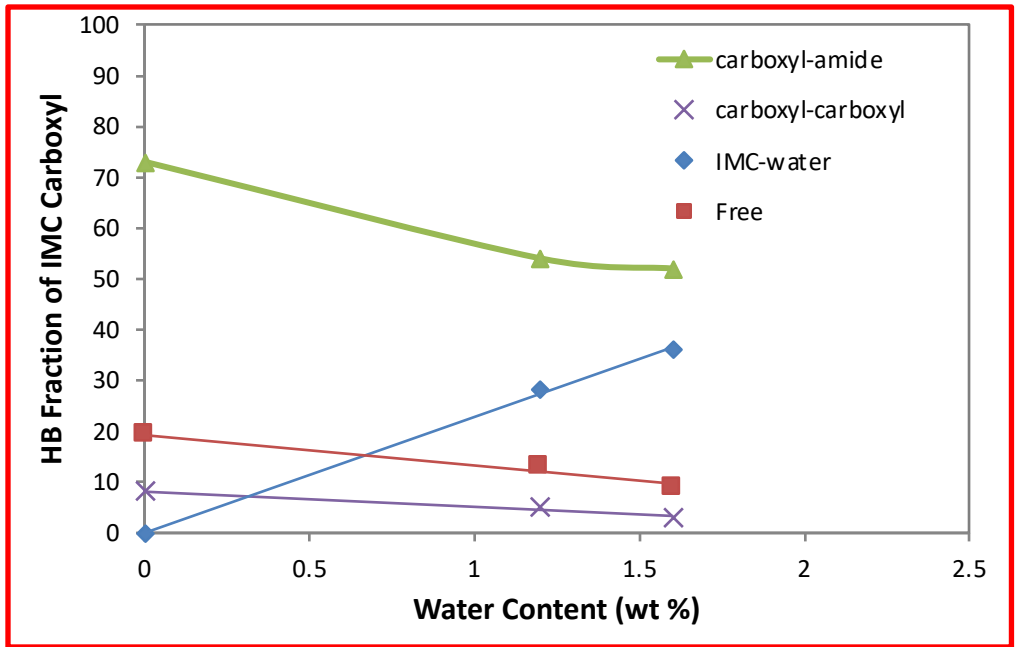


1.6 % (wt) water

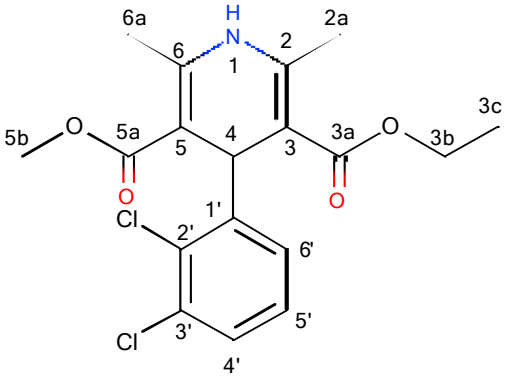


1.2 % (wt) water

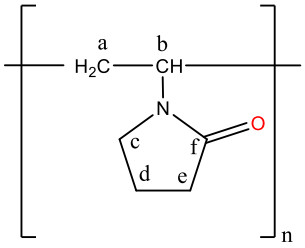




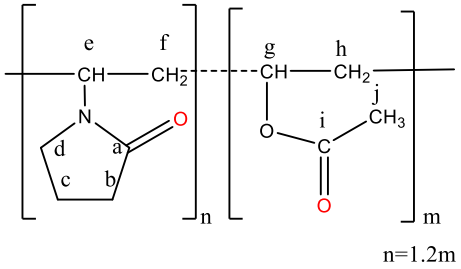
Amorphous Solid Dispersions – Model Systems



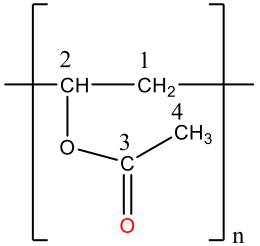
Felodipine (FEL)



PVP



PVP/VA

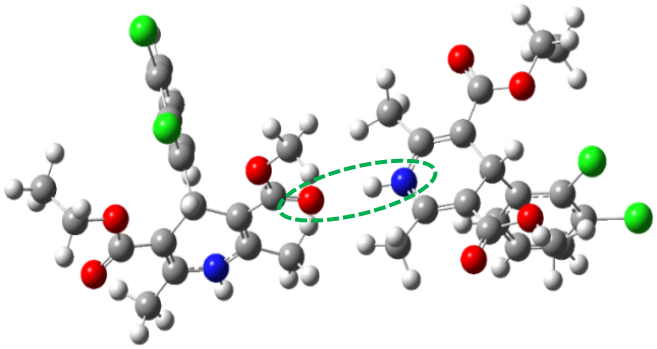


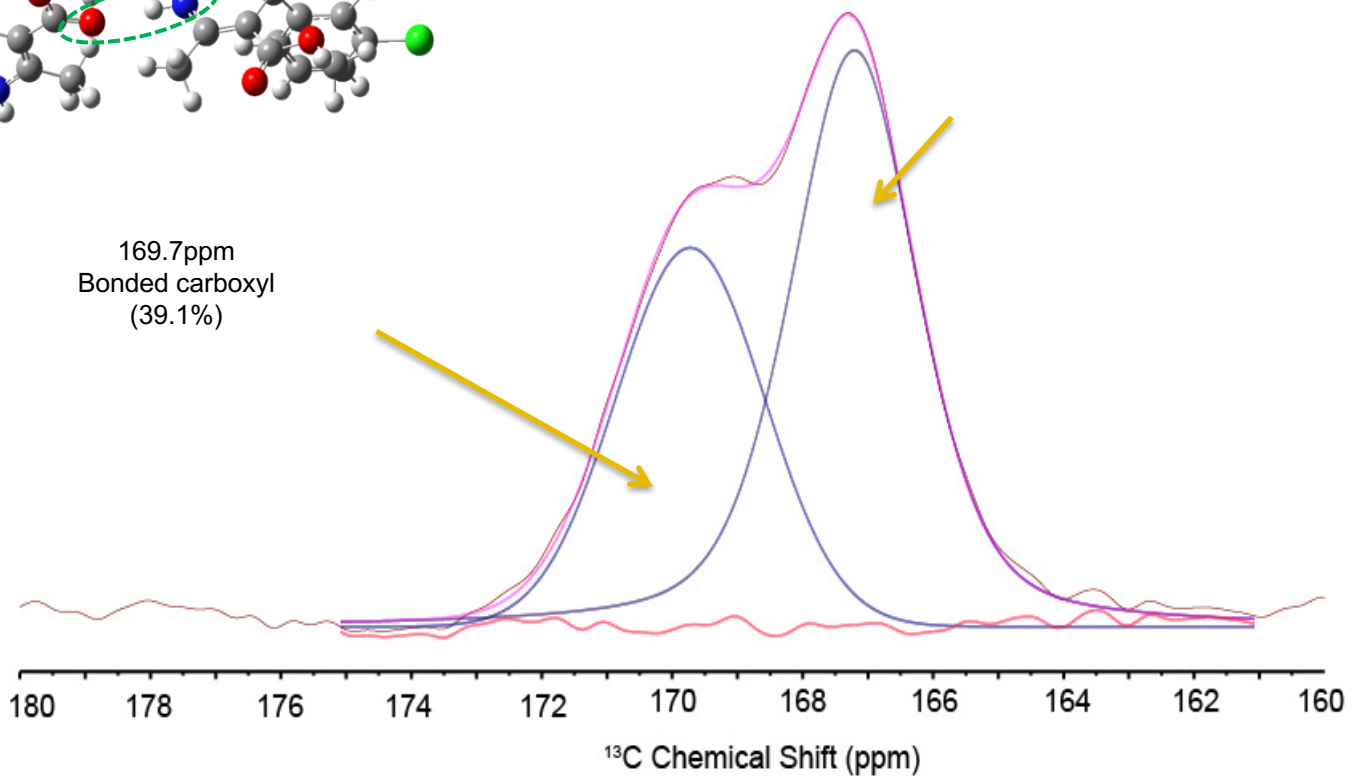
PVAc

Compound	MW (g/mol)	T_m (ºC)	T_g (ºC)	H- bond Acceptors/Donors
Felodipine	384.25	144.4	46.2	Both
PVP	~25000	---	170.0	Acceptor
PVP/VA	~45000-47000	---	109.0	Acceptor
PVAc	~100,000	---	44.4	Acceptor

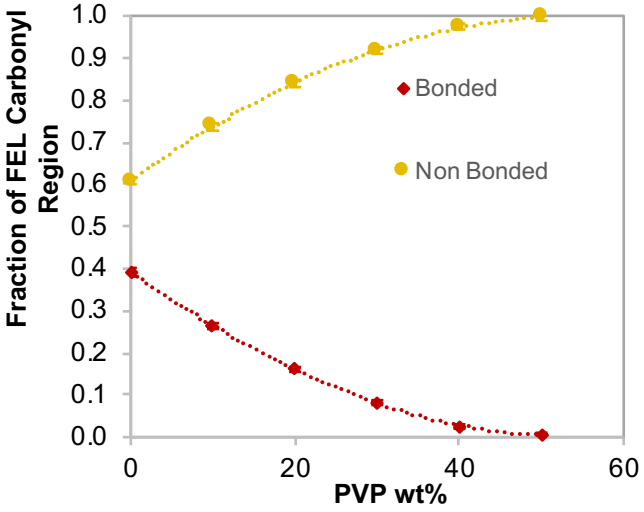
PVP: Polyvinylpyrrolidone; PVP/VA: Polyvinylpyrrolidone/vinylacetate; PVAc: Polyvinylacetate

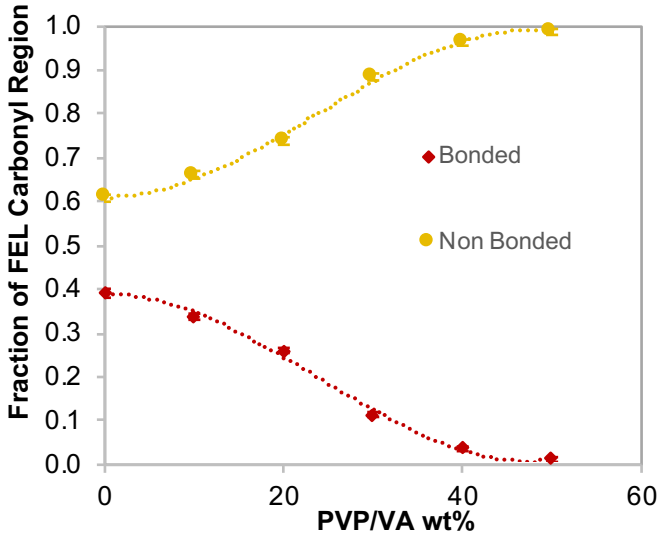
Carbonyl Carbon in Amorphous FEL





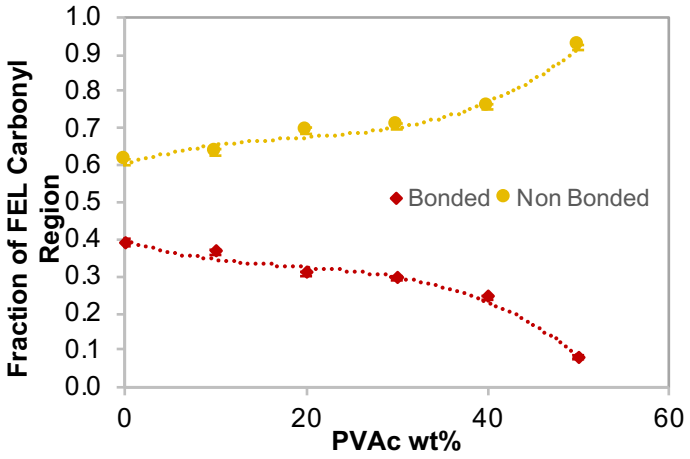
^{13}C CPMAS NMR Spectra of Carbonyl Carbons of FEL – PVP, PVP/VA, PVA

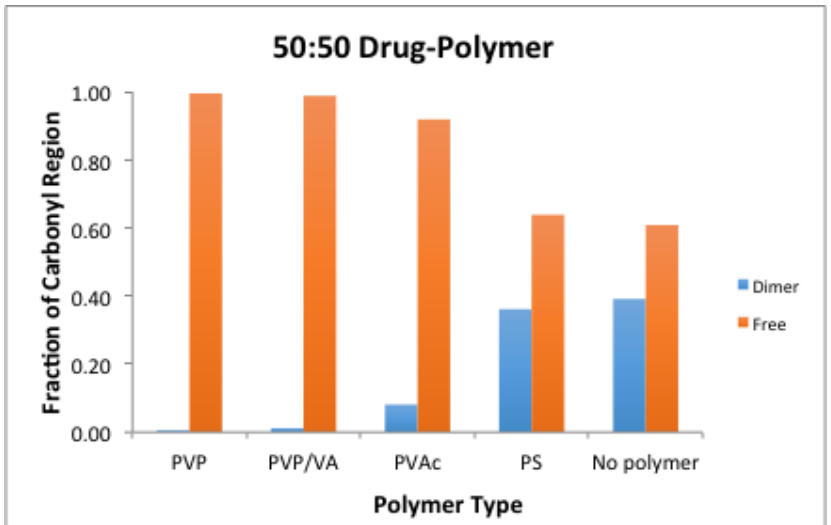




Fraction of Non-bonded C=O ↑

Fraction of Bonded C=O ↓





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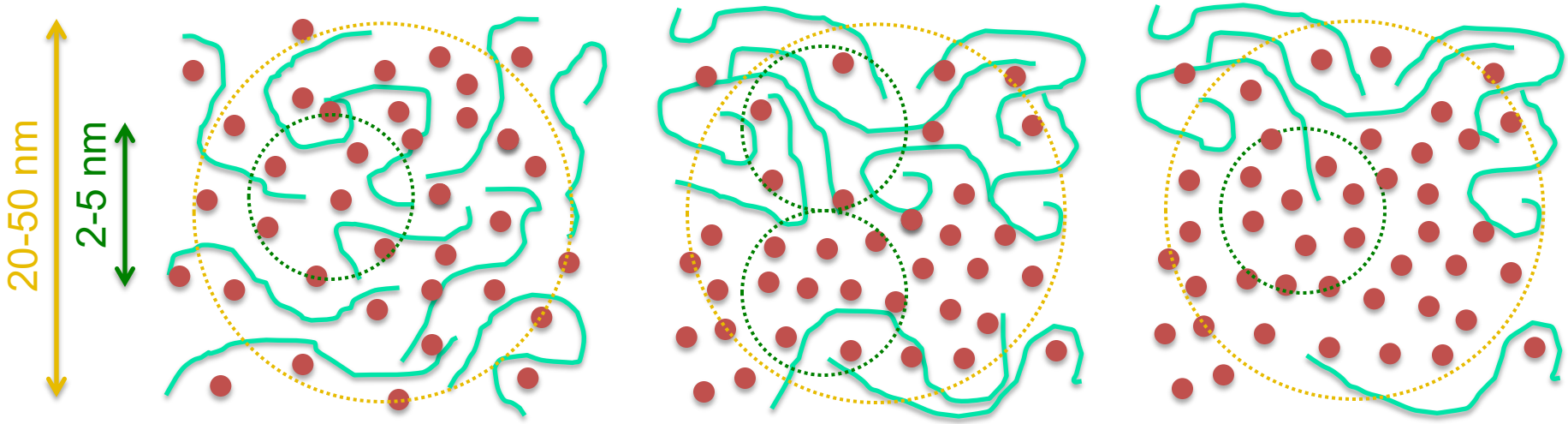
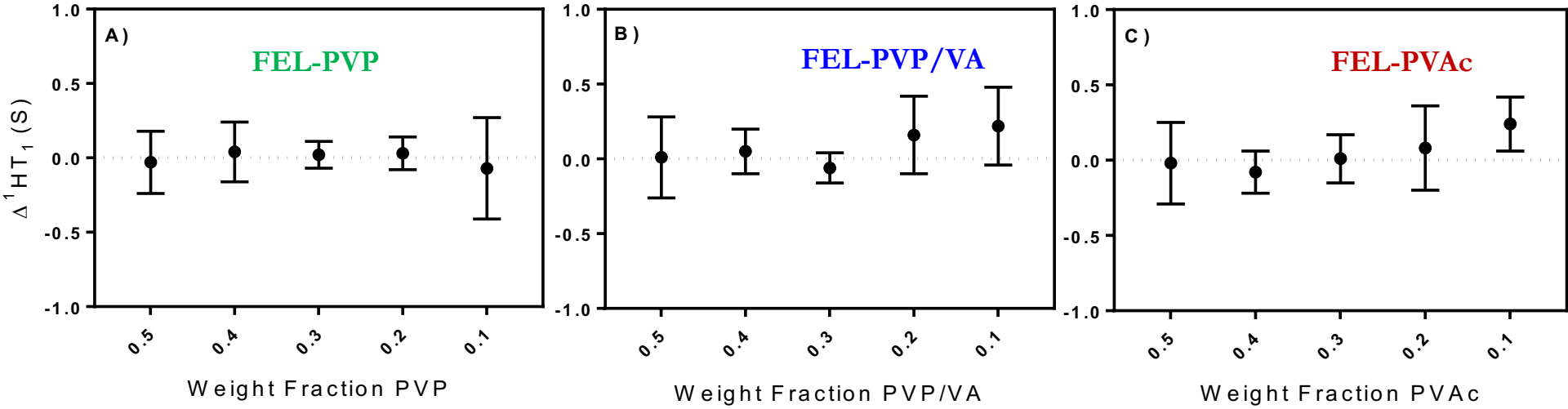
Miscibility Determination Using Solid-State NMR Spectroscopy



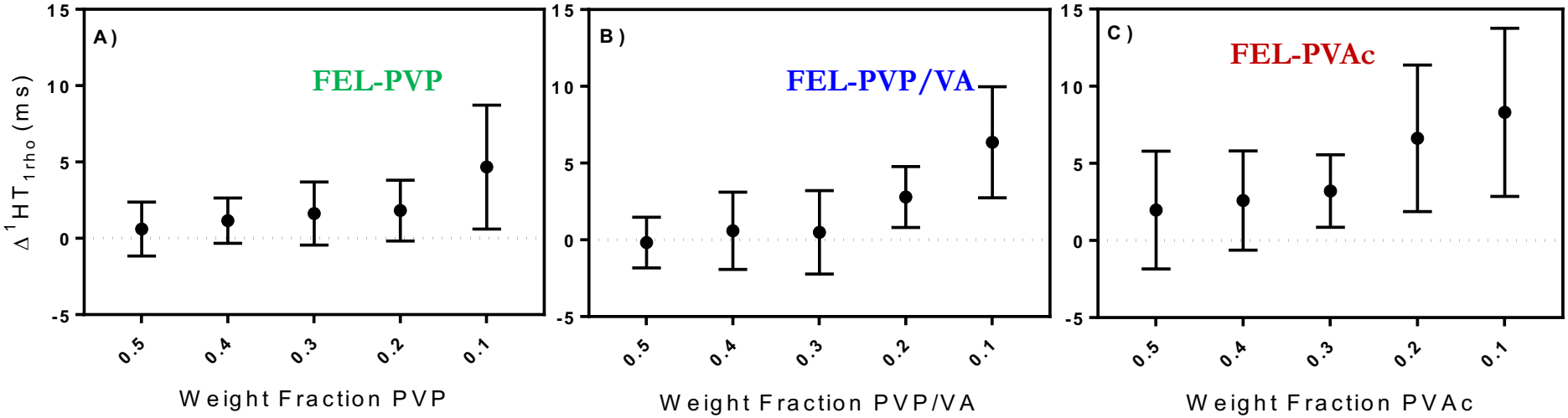
T1 values	T1ρ values	Number of Phases
Same	Same	1 (domain size < 2-5nm)
Same	Different	2 (domain size 5-20 nm)
Different	Different	2 (domain size > 20-50 nm)

^1H T_1 Differential Between Drug and Polymers



Plots of ^1H T_1 differential between FEL and PVP-VA in ASDs as a function of polymer weight fraction. The error bar represents 95% confidence interval associated with the fit. Dashed line represents the zero.

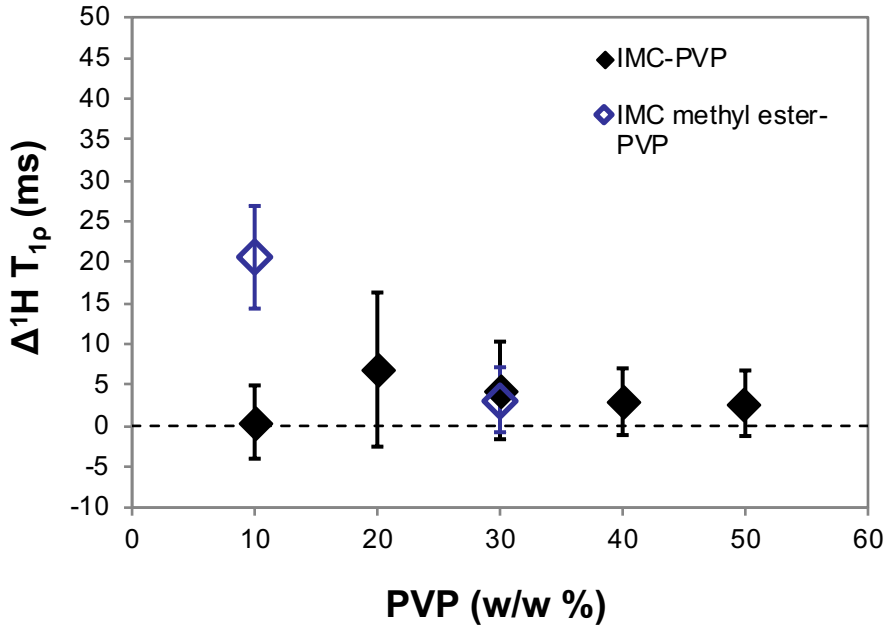
^1H $T_{1\rho}$ Differential Between Drug and Polymers

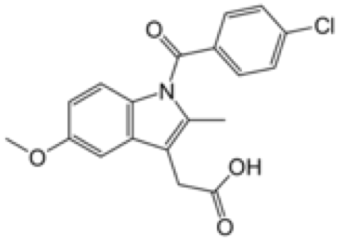


Plots of $^1HT_{1\rho}$ differential between FEL and PVP-VA in ASDs as a function of polymer weight fraction. The error bar represents 95% confidence interval associated with the fit. Dashed line represents the zero.

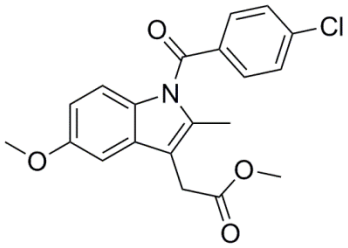
How does H-Bonding Influence Miscibility?

Differences of SSNMR ^{1}H $T_{1\rho}$ Relaxation Times





Indomethacin
H-bond donor and acceptor



Indomethacin methyl ester
H-bond acceptor

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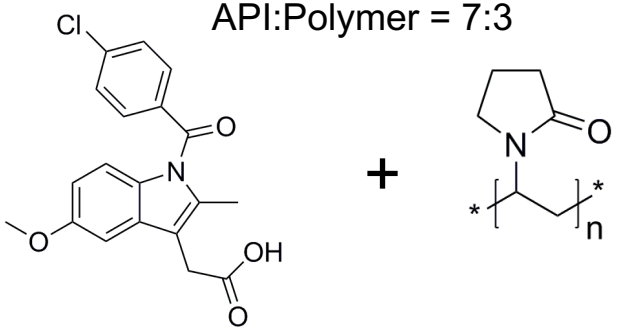
Physical Stability of 70:30 IMC : PVP K25

API:Polymer = 7:3



Indomethacin + PVP

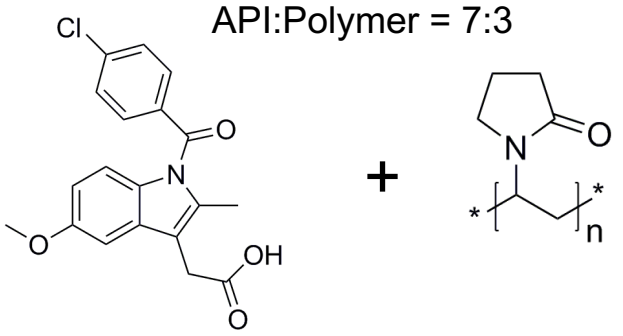
Storage Conditions

50 ° C/ 0% RH	T_g = 72 ° C	→ amorphous
40 ° C/57% RH	T_g = 52 ° C	→ amorphous
40 ° C/75% RH	T_g = 41 ° C	→ crystallized after 1 month

70:30 IMC : PVP K25									
	50 °C dry			40 °C 57%RH			40 °C 75%RH		
	Crystallize ?	T_g (°C)	$T_{storage}$-T_g (°C)	Crystallize ?	T_g (°C)	$T_{storage}$-T_g (°C)	Crystallize ?	T_g (°C)	$T_{storage}$-T_g (°C)
Time 0	No	62.4	-12.4	No	62.4	-22.4	No	62.4	-22.4
1 wk	No	71.7	-21.7	No	52.7	-12.7	No	41.4	-1.4
2 wks	No	71.4	-21.4	No	52.8	-12.8	No	41.1	-1.1
1 mnth	No	70.7	-20.7	No	51.8	-11.8	**Yes**	**41.3**	**-1.3**
2 mths	No	73.0	-23.0	No	50.4	-10.4	**Yes**	**39.9**	**0.1**
6 mths	No	74.3	-24.3	No	52.0	-12.0	**Yes**	**43.7**	**-3.7**

- 70:30 IMC:PVP K25 only crystallized at 40 ° C and 75% RH
- **Is the temperature (above T_g), the water, or both the cause for the crystallization?**

Physical Stability of 70:30 IMC: PVP K12 and PVP/VA at 70 °C



Indomethacin

API:Polymer = 7:3

+

PVP

Storage Conditions

50 ° C/ 0% RH T_g = 72 ° C → amorphous

40 ° C/57% RH T_g = 52 ° C → amorphous

40 ° C/75% RH T_g = 41 ° C → crystallized after 1 month

IMC : PVP K12 -- Oven at 70 °C					IMC : PVP/VA -- Oven at 70 °C				
Ratio	$T_{storage}$-T_g	0 wk	1 wk	20 wks	Ratio	$T_{storage}$-T_g	0 wk	1 wk	28 wks
50-50	-12.0 °C	No	No	No	50-50	- 4.5 °C	No	No	No
60-40	- 6.0 °C	No	No	No	60-40	+ 1.5 °C	No	No	No
70-30	-0.5 °C	No	No	No	70-30	+ 7.0 °C	No	No	No
80-20	+ 8.5 °C	No	No	No	80-20	+ 12.5 °C	No	**Yes**	**Yes**
90-10	+ 15.5 °C	No	**Yes**	**Yes**	90-10	+ 18.0 °C	No	**Yes**	**Yes**

- IMC crystallizes into different polymorph based on polymer (PVP/VA: Alpha, PVP k12: Gamma)
- **Crystallization only occurs at both high temperatures (> 10 °C above T_g) and at high drug concentrations**
- **Which is the bigger cause for the crystallization, T_g or polymer concentration?**

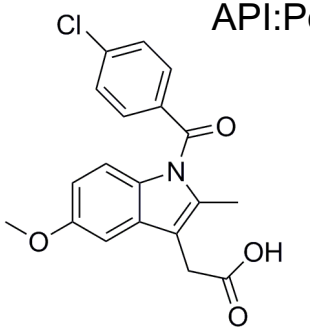
Physical Stability of 70:30 IMC: PVP K12 at 60, 70, and 80 °C

IMC : PVP K12 -- Oven at 80 °C				
Ratio	$T_{storage}$-T_g	0 wk	1 wk	6 wks
50-50	- 0.0 °C	No	No	No
60-40	+ 6.5 °C	No	No	No
70-30	+ 13.6 °C	No	No	No
80-20	+ 18.2 °C	No	No	**YES**
90-10	+ 28.2 °C	No	**YES**	**YES**

IMC : PVP K12 -- Oven at 70 °C				
Ratio	$T_{storage}$-T_g	0 wk	1 wk	6 wks
50-50	- 10.0 °C	No	No	No
60-40	- 3.6 °C	No	No	No
70-30	+ 3.6 °C	No	No	No
80-20	+ 8.2 °C	No	No	No
90-10	+ 18.2 °C	No	**YES**	**YES**

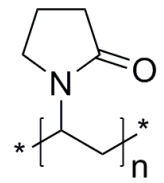
IMC : PVP K12 -- Oven at 60 °C				
Ratio	$T_{storage}$-T_g	0 wk	1 wk	6 wks
50-50	- 20.0 °C	No	No	No
60-40	- 13.6 °C	No	No	No
70-30	- 6.4°C	No	No	No
80-20	- 1.9 °C	No	No	No
90-10	+ 8.2 °C	No	**No**	**YES**

API:Polymer = 7:3



Indomethacin

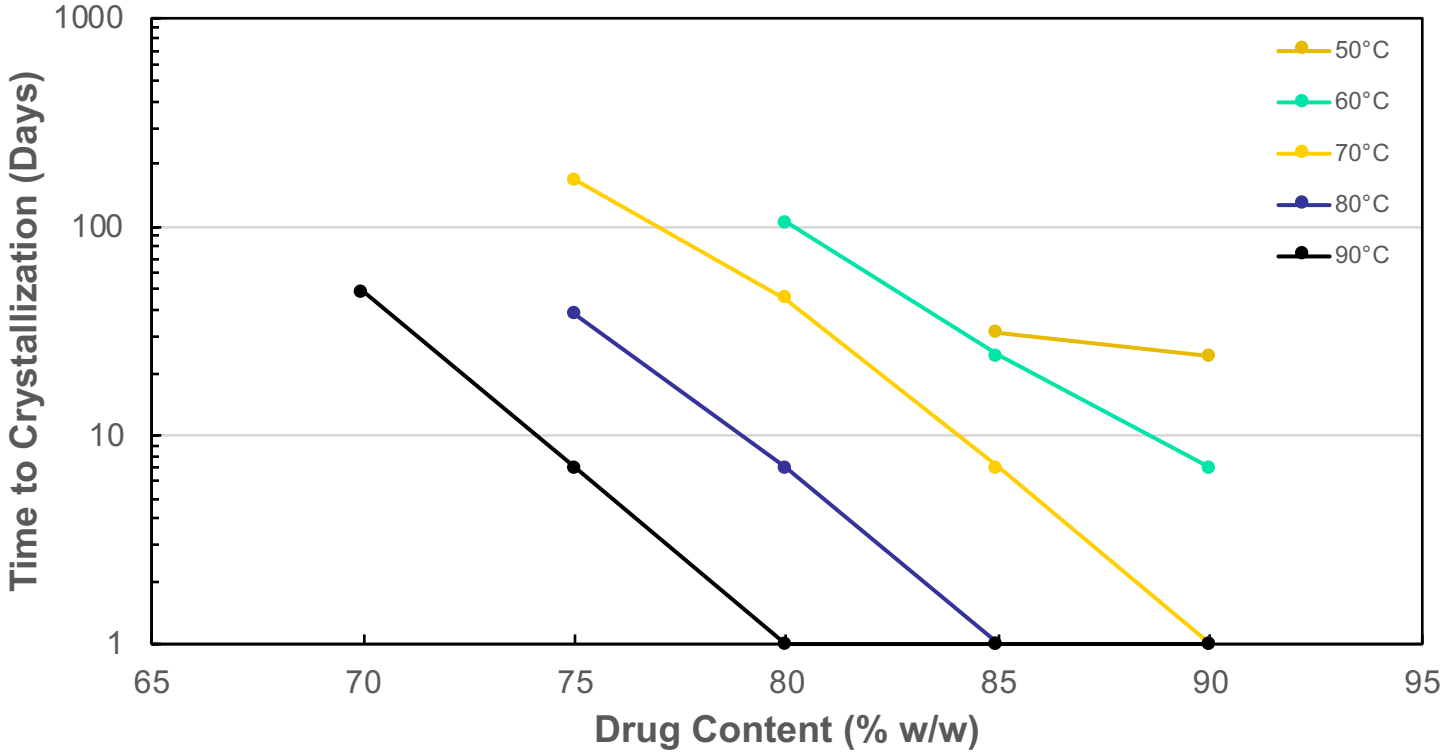
+



PVP

- **Crystallization occurs at high drug concentrations, but lower drug loading can retard crystallization at high temperatures (> 10 °C above T_g)**
- **Which is the bigger cause for the inhibition of crystallization, T_g or polymer concentration? Polymer concentration!**

Physical Stability of IMC: PVP K12 at 50, 60, 70, 80, and 90 °C



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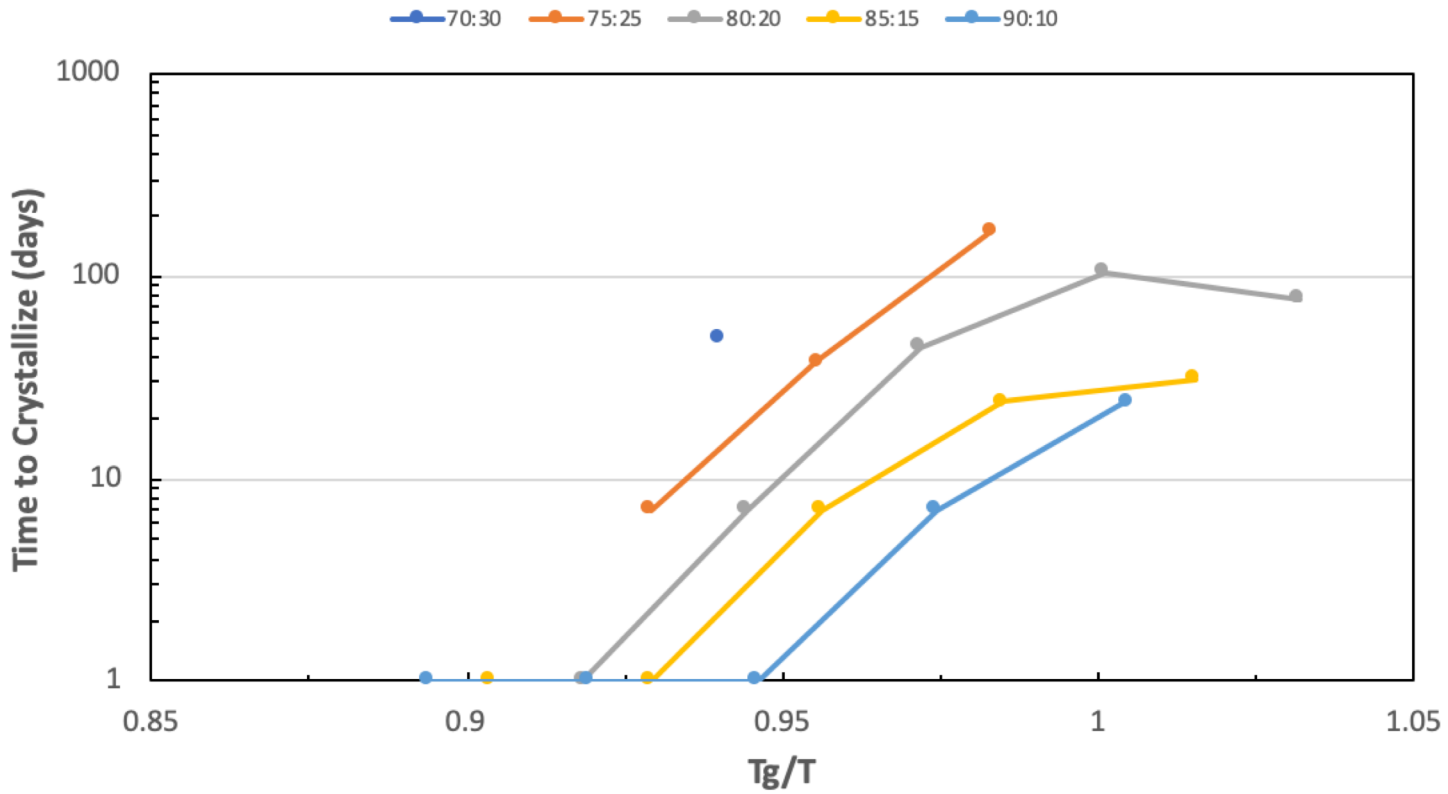


- **Crystallization occurs at high drug concentrations, but lower drug loading can retard crystallization at high temperatures (> 10 °C above T_g)**
- **Which is the bigger cause for the inhibition of crystallization, T_g or polymer concentration? Polymer concentration!**

Outline

I. Motivation
   a. Why Amorphous Solid Dispersions (ASDs)?
   b. Current challenges
II. Crystallinity Detection
III. Drug-Polymer Interactions
IV. Drug-Polymer Homogeneity
V. Drug-Polymer Stability
VI. Protein Stability
VII. Conclusions and Acknowledgements

Stabilizing Protein Therapeutics Using Freeze Drying or Lyophilization

- Many challenges for formulation of proteins due to complex structure:
  - Many sites for degradation
  - Aggregation

Steps in Freeze Drying

Freezing

- Lock API and excipient in place

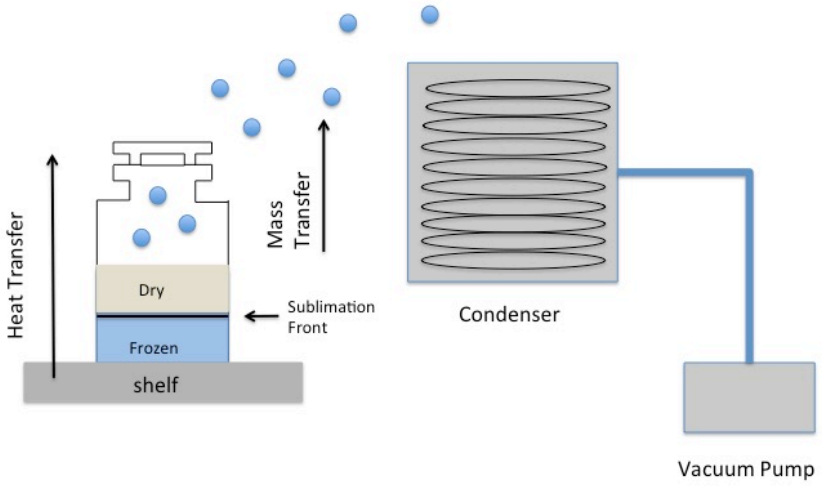
Primary Drying

- Removal of 95% of water
- Sublimation

Secondary Drying

- Removal of leftover bound water
- Desorption

Freeze Drying Process



Protein Phase Separation

- Looked at two proteins in six different sugars to determine phase separation after lyophilization was performed.
  - Proteins: IgG and LDH (20% protein)
  - Excipients:
    - Trehalose
    - Inulin (2 kDa, 5 kDa)
    - Dextran (2 kDa, 5 kDa, 70 kDa)

- Systems were one of the three cases based on protein and excipient:
  - Intimately mixed (Same ^{1}H T_1 and ^{1}H T_{1rho})
  - Partially miscible (Common ^{1}H T_1, different ^{1}H T_{1rho})
  - Phase separated (Different ^{1}H T_1 and ^{1}H T_{1rho})

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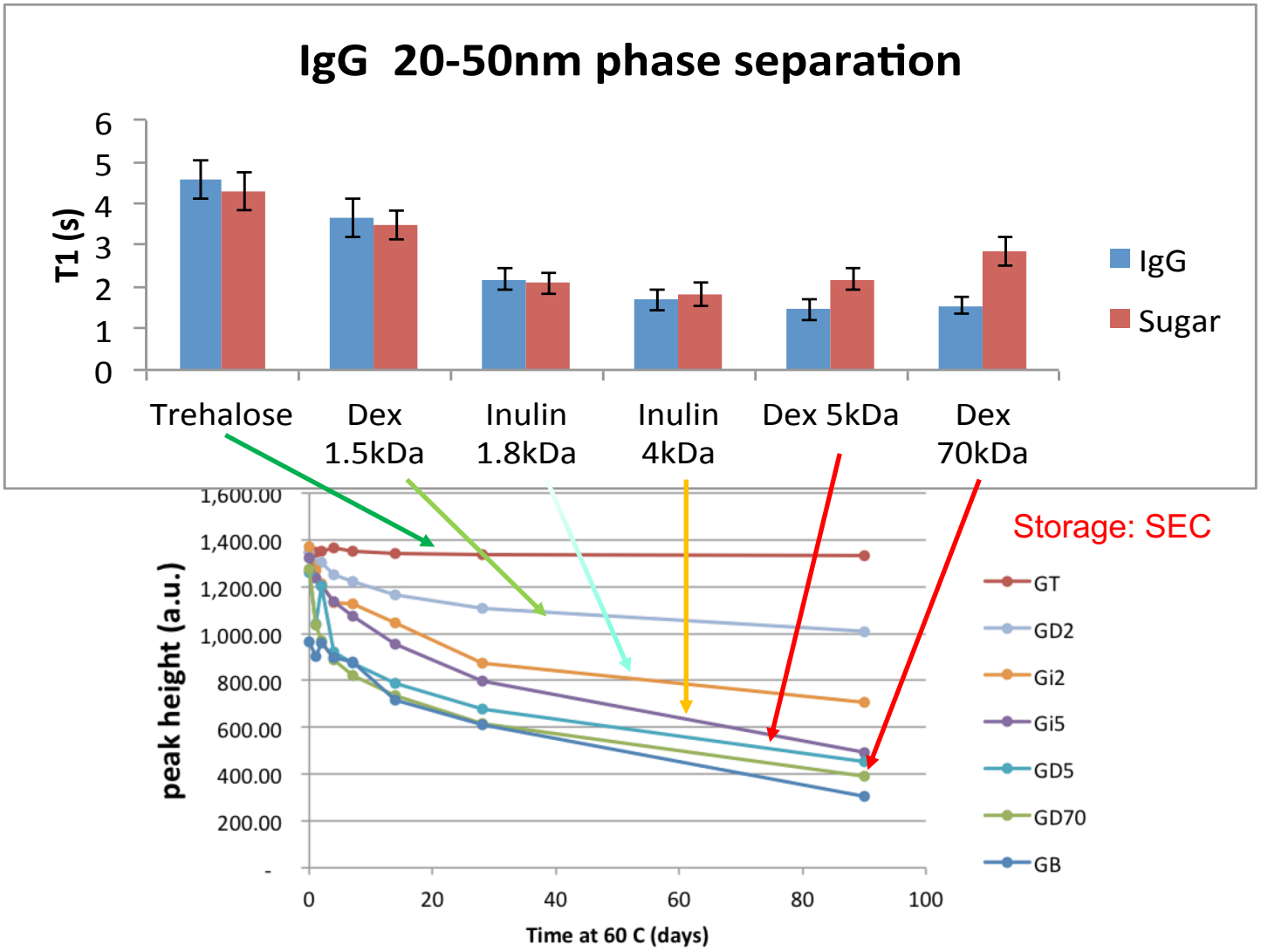
Protein Phase Separation

Protein – Sugar Sample	Protein ^1H T_1 (s)	Sugar ^1H T_1 (s)	Protein ^1H T_{1rho} (ms)	Sugar ^1H T_{1rho} (ms)
IgG – Trehalose	4.6±0.5	4.3±0.5	9.0±0.7	10.4±0.5
IgG – Inulin 2 kDa	2.2±0.3	2.1±0.3	7.8±0.5	6.8±0.3
IgG – Inulin 5 kDa	1.7±0.2	1.8±0.3	9.3±0.6	6.3±0.3
IgG – Dextran 1.5 kDa	3.7±0.5	3.5±0. 4	17.0±1.0	21.9±0.6
IgG – Dextran 5 kDa	1.5±0.3	2.2±0.3	12.3±0.9	22.8±0.5
IgG – Dextran 70 kDa	1.5±0.2	2.9±0.4	10.0±0.6	17.4±0.5
LDH – Trehalose	1.7±0.2	2.0±0.2	10.1±0.7	11.3±0.3
LDH – Inulin 2 kDa	1.6±0.2	1.9±0.2	9.7±0.7	7.2±0.3
LDH – Inulin 5 kDa	0.90±0.10	1.4±0.2	10.5±1.0	7.6±0.4
LDH – Dextran 1.5 kDa	2.4±0.3	2.4±0.2	15.1±1.6	22.7±0.7
LDH – Dextran 5 kDa	1.9±0.2	1.8±0.2	14.3±0.7	23.5±0.8
LDH – Dextran 70 kDa	1.9±0.2	1.8±0.2	15.0±1.6	26.0±1.1

Protein Phase Separation and Stability



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Conclusions

- ✓ Challenges facing ASDs include crystal detection (manufacturing and stability), stabilizing using hydrogen bonding, high API loading
- ✓ Advanced techniques for crystal detection include Raman, Synchrotron X-ray, SHG, and SSNMR
- ✓ Drug stability in polymeric systems depends extensively on water content, drug loading, and drug/polymer interactions
- ✓ Similar approaches can be used to evaluate protein stability

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Julie Calahan	Dr. Sean Delaney	Dr. Steve Rheiner	Ben Nelson

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