Mylan School of Pharmacy
DUQUESNE UNIVERSITY
www.pharmacy.duq.edu
Graduate School of Pharmaceutical Sciences

Structural Characterization of Solid Composite Materials as a Tool for Drug Product Formulation and Development

Peter L.D. Wildfong

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Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd

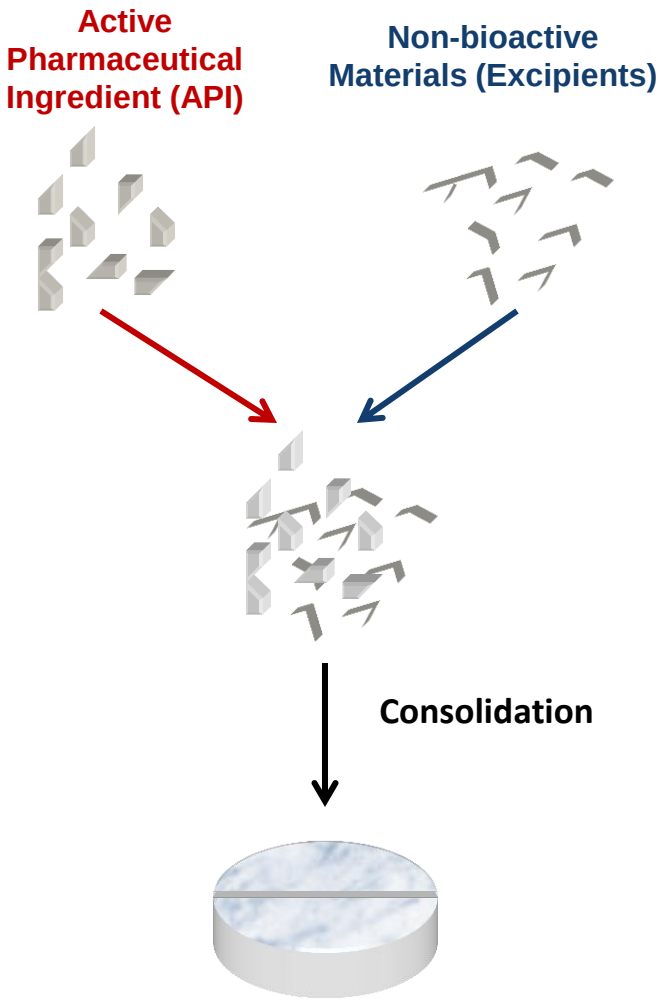
ICDD Website - www.icdd.com

Introduction

- **Product development is improved by linking material structure and physicochemical behavior:**
  - Material structure affects product performance
  - Impact on product performance depends on contributions from all of its components
- **Structural responses to preparation can impact formulation decisions:**
  - How appropriate is a material for a given formulation or process?
  - How will inclusion of a material in a formulation/processing stream affect that material?
  - How does the combination of materials affect API structure?

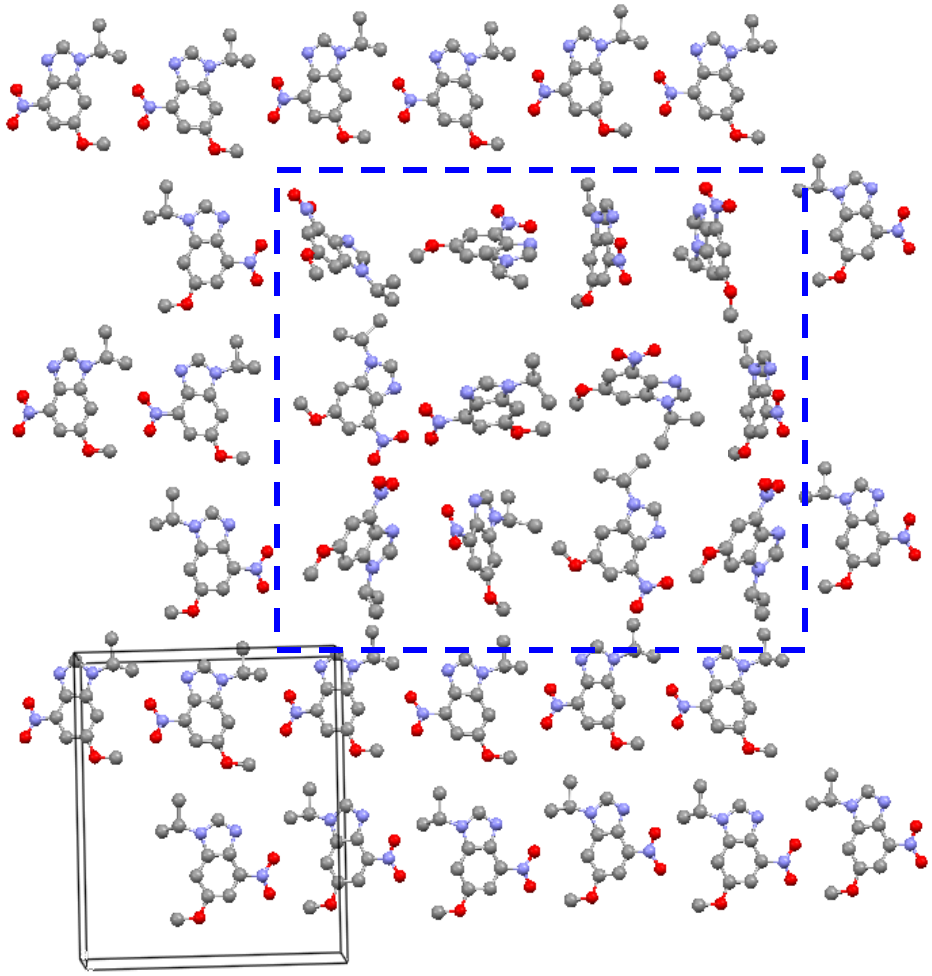
Case I: Compaction

- **>80% of APIs are formulated as tablets**
- **High-shear stress applied in consolidation:**
  - Accumulation of dislocations during deformation
  - Changes in response to consolidation can impact product quality
  - Mechanical responses to an applied stress is different for different materials
- **How is this impacted when more than one material is consolidated?**
  - Does the presence of a diluent change the mechanical response of the API?

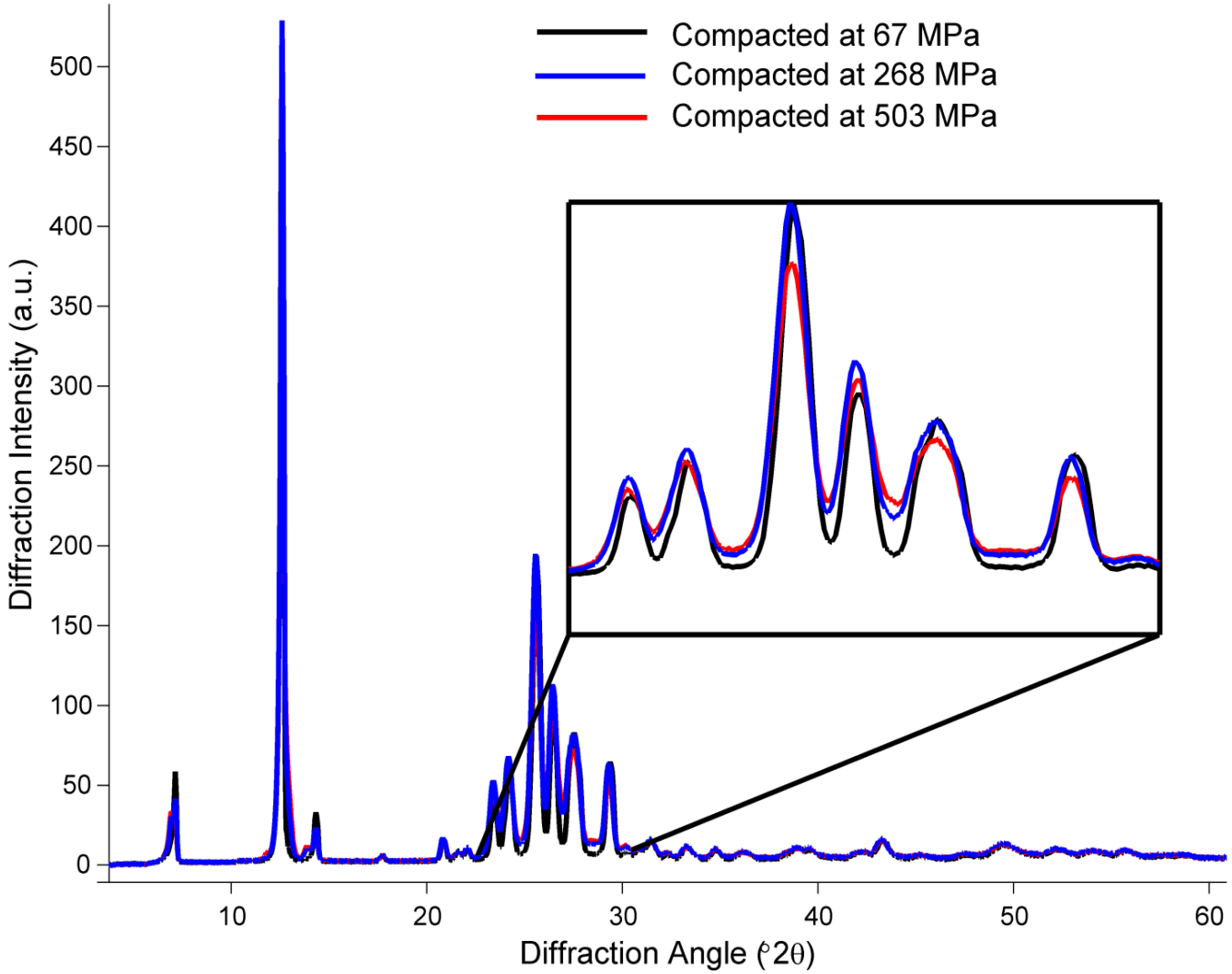


Accumulation of Structural Disorder

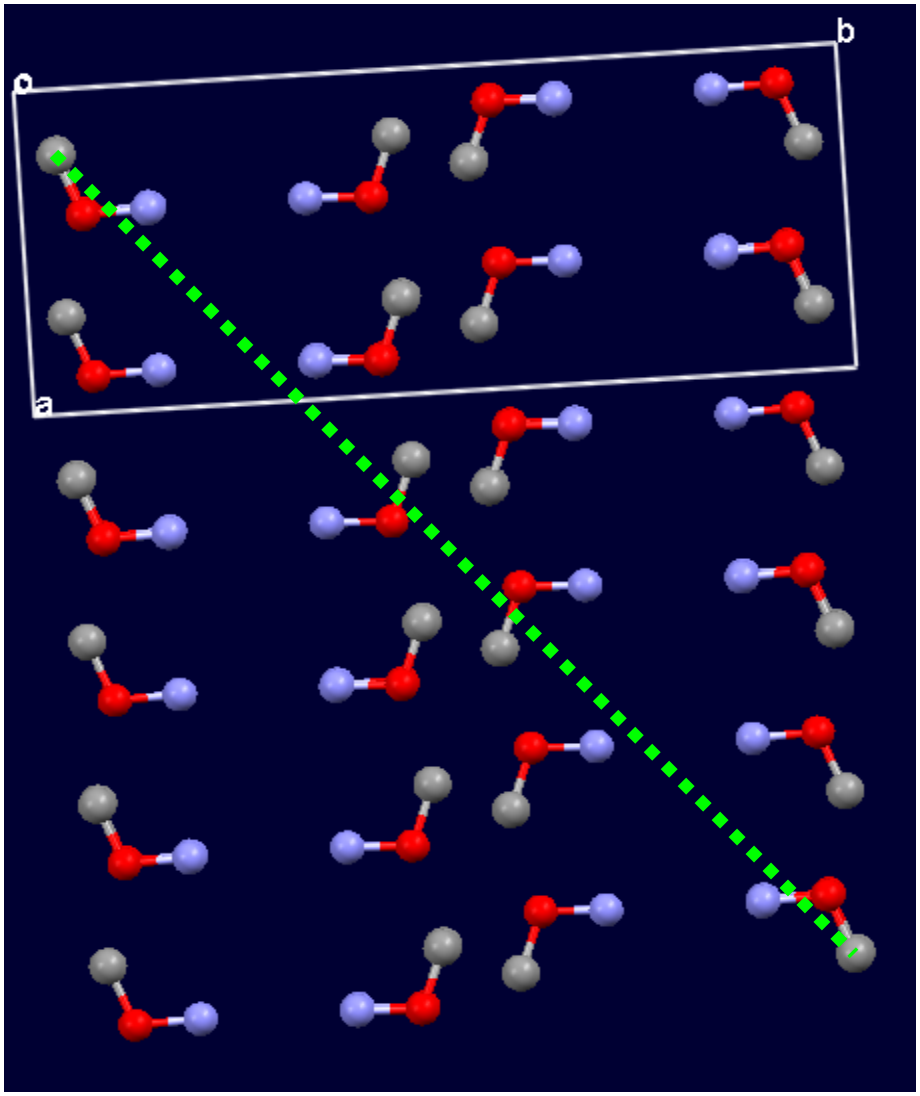
- **Plastic deformation of a material is dislocation mediated**
- **Defect accumulation results in regions that are disordered relative to the crystal structure**
- **Increasing shear stress increases the extent of deformation**
  - Does regional disorder increase as well?

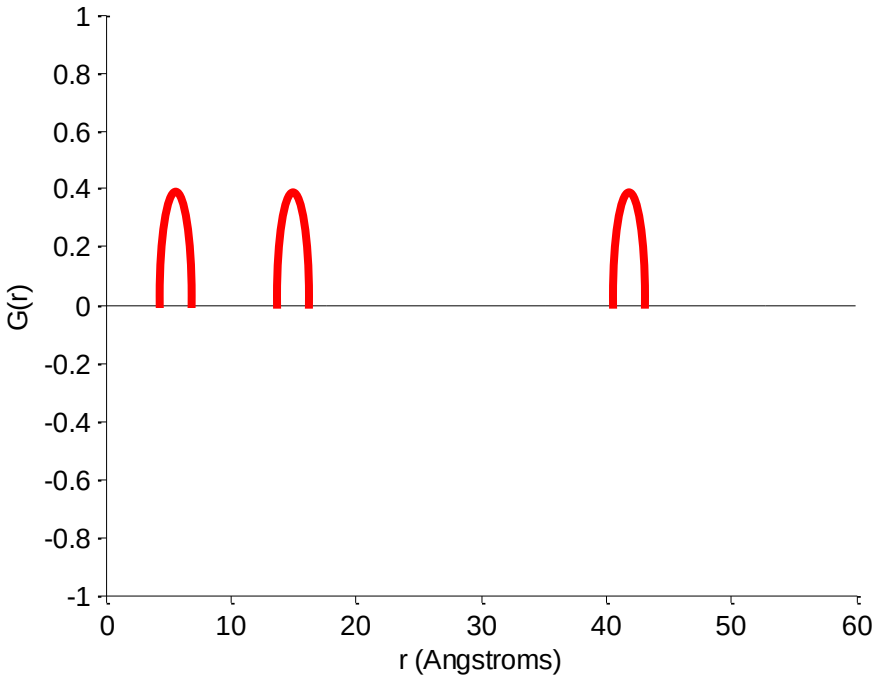


Anhydrous theophylline compacted at different pressures

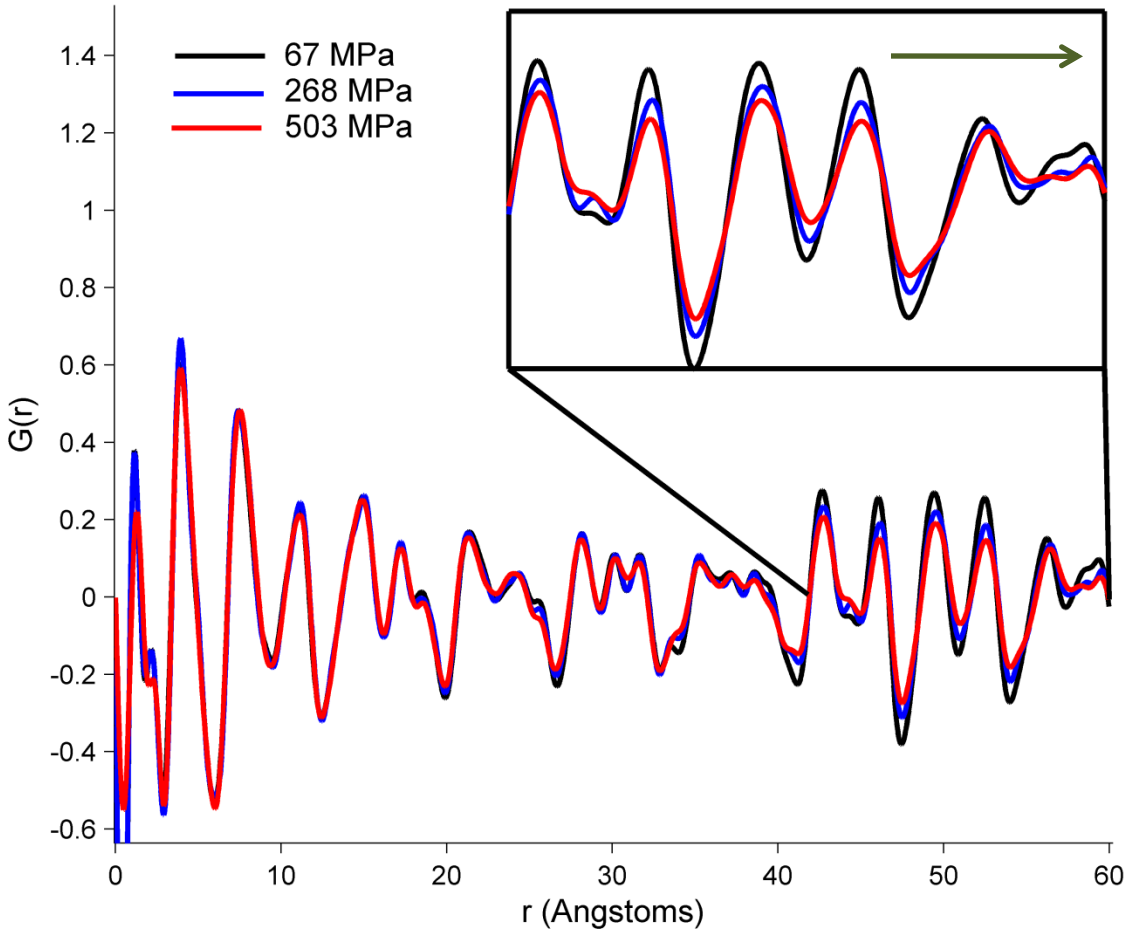


What Does the PDF Tell Us?



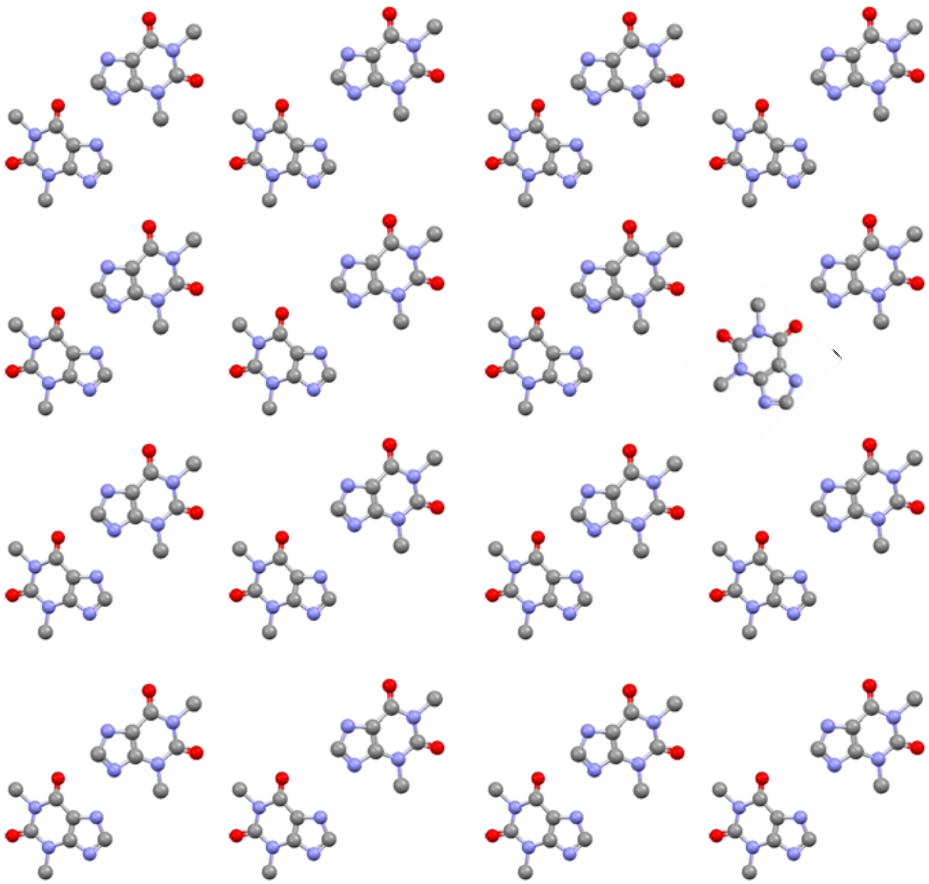


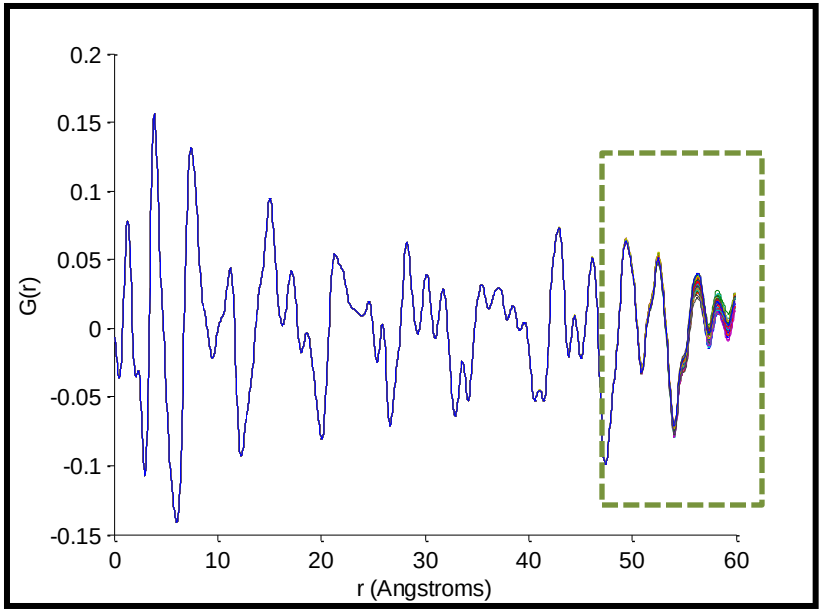
Anhydrous theophylline compacted at different (PDF)



At larger radial distances probability peaks dampen and shift with increasing compaction pressure

Monte Carlo Simulated Disorder

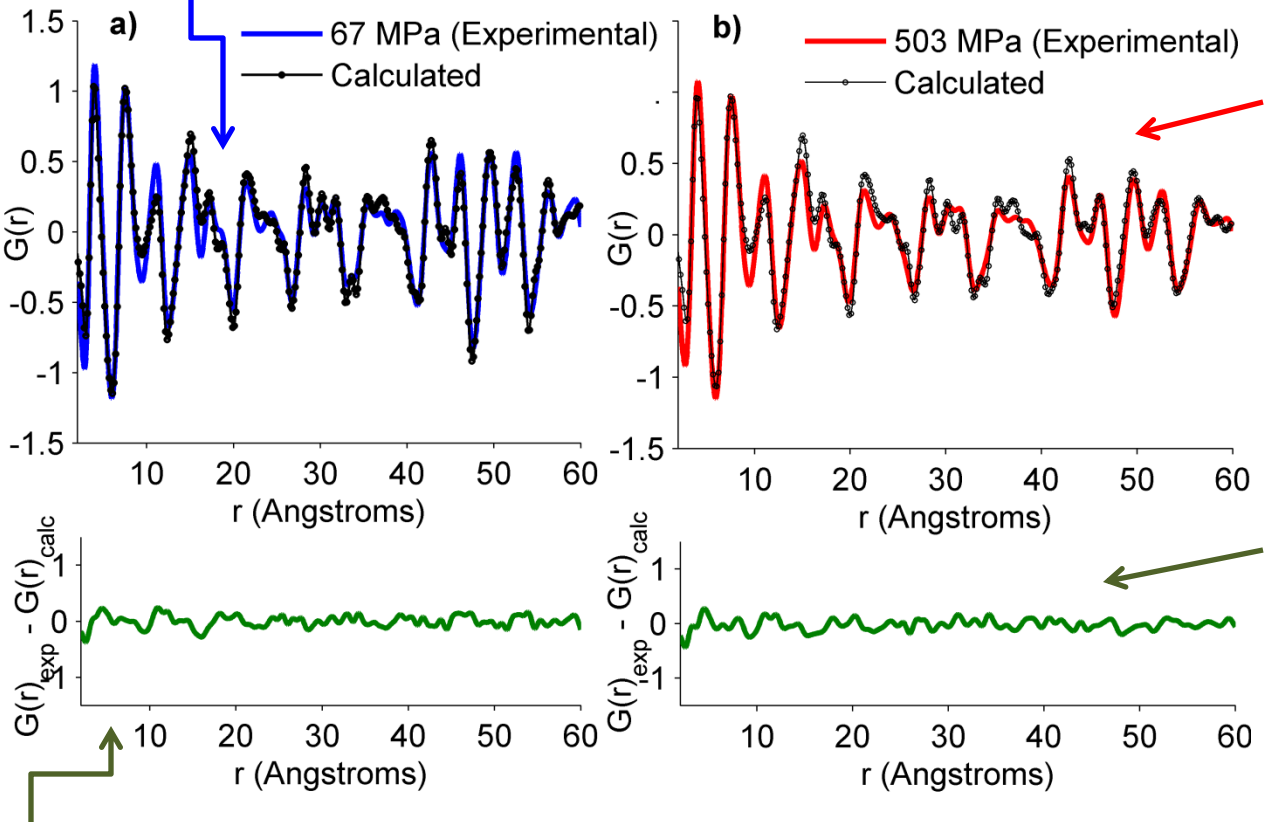




A simulated PDF pattern is calculated for each lattice perturbation to see the effects on peak dampening

Monte Carlo Simulated Disorder

Low pressure compaction results in no observable regional disorder

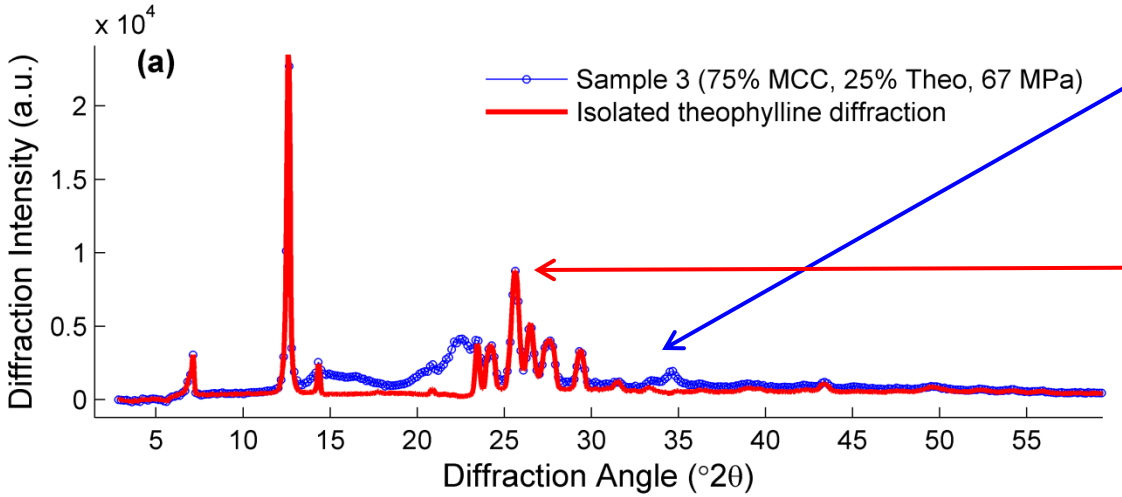


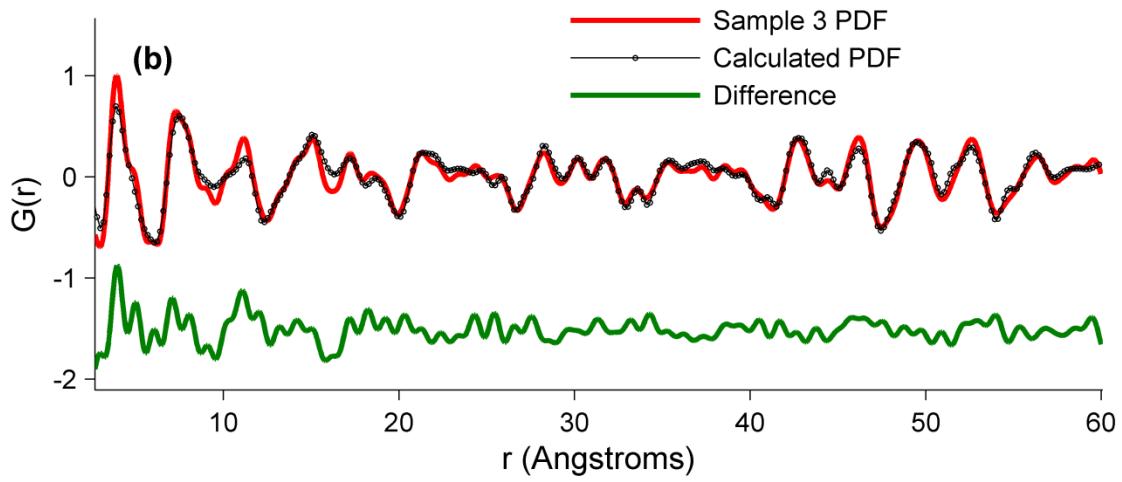
~1% "simulated disorder" PDF shows same dampening and shifts as PDF from theophylline compacted at high stress

PDF calculated from simulated "disordered" crystal agrees well with observed PDF following compaction

PDF from known theophylline structure agrees well with observed PDF following compaction

Application to Consolidated Mixtures





Composite PXRD pattern contains diffraction and scattering from both materials

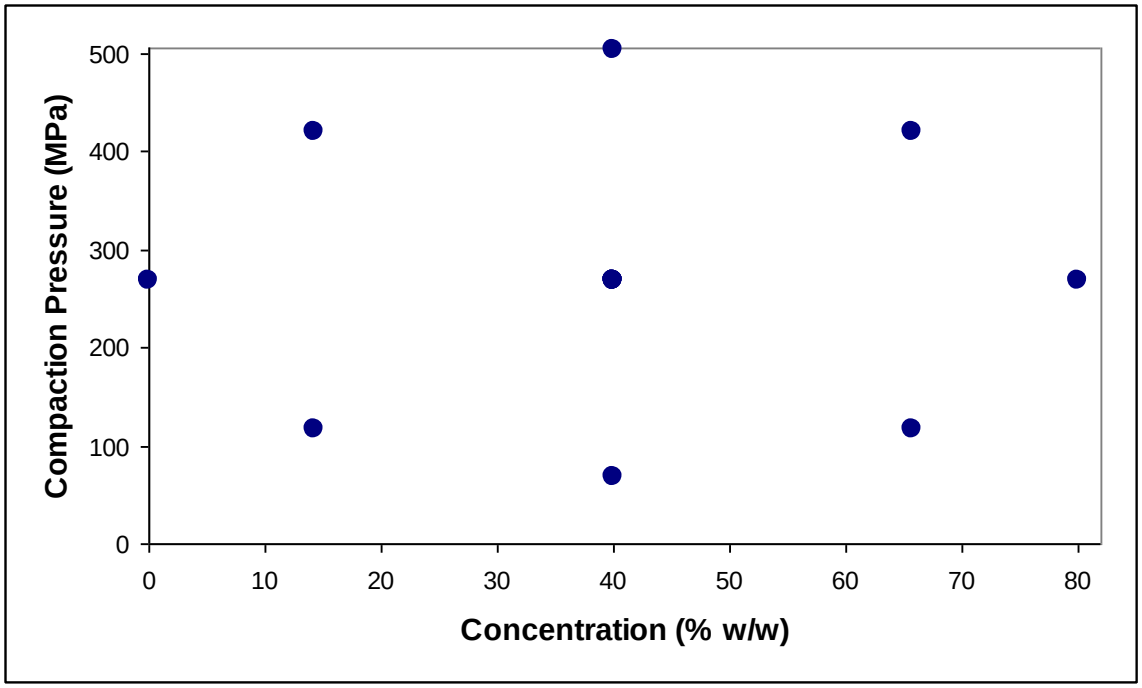
Diffraction attributable to theophylline is mathematically separated

PDF transform

PDF for theophylline compressed with diluent at a given pressure is compared with PDF uncompressed theophylline

Application to Consolidated Mixtures

- **13 mm right cylinder compacts (theophylline + diluent)**
  - Microcrystalline cellulose (Avicel PH 101); deforms plastically
  - Lactose Monohydrate; deforms by fragmentation
- **Circumscribed central composite design**
  - 2 variables: Compaction pressure and excipient concentration
  - Central point replicated (n = 5)



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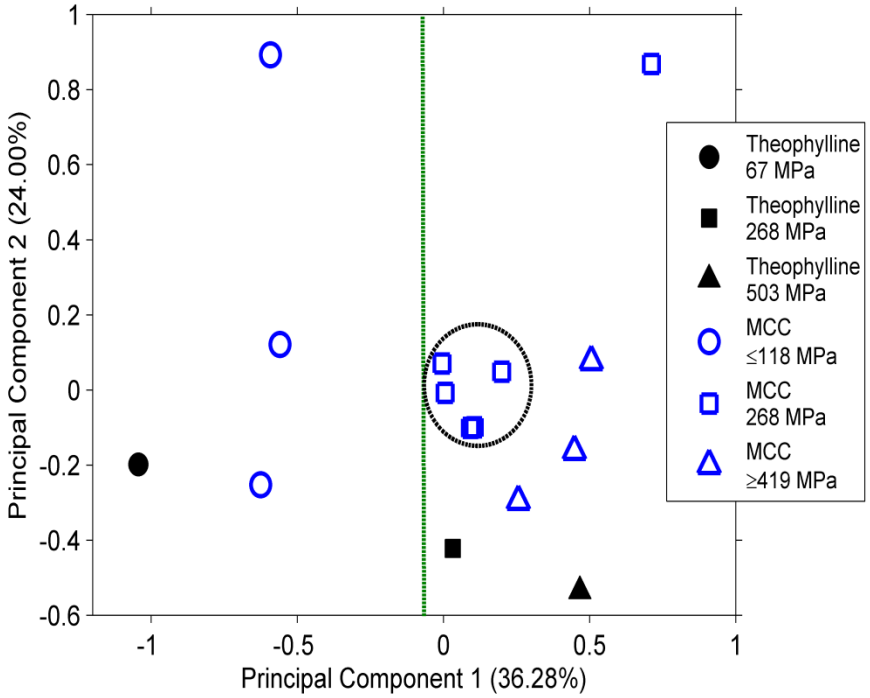
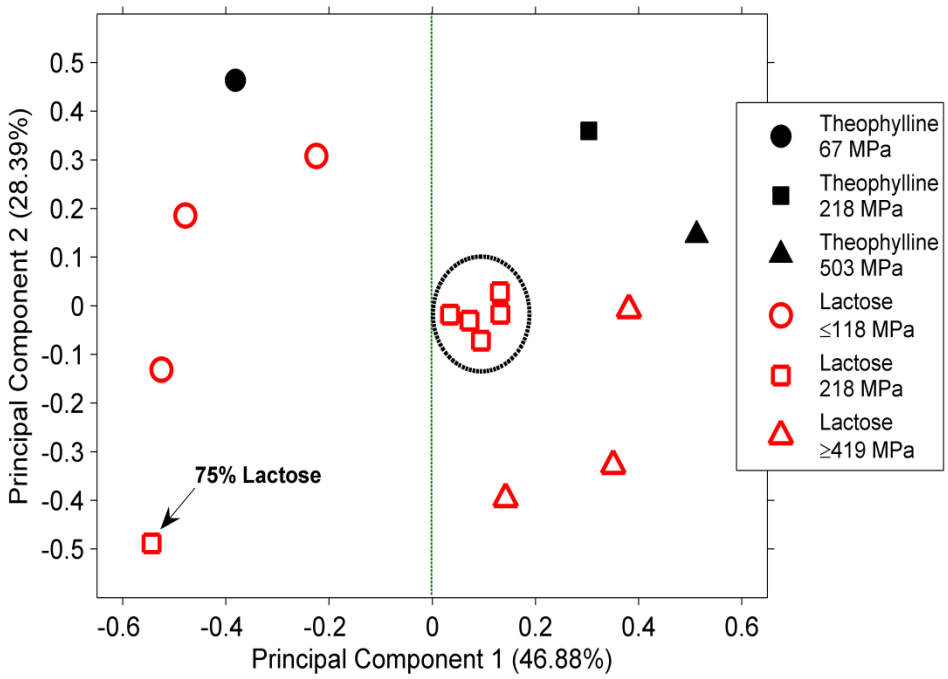
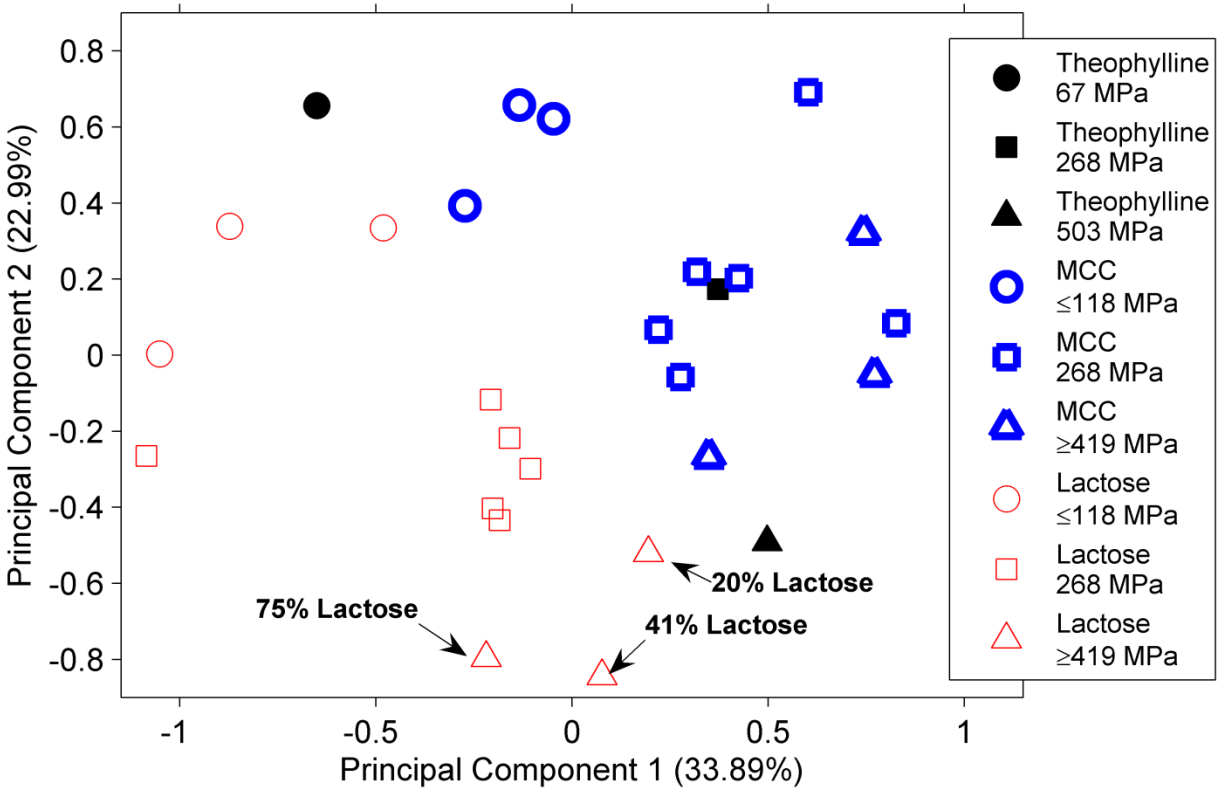




Application to Consolidated Mixtures



Case II: Amorphous Drug Dispersions

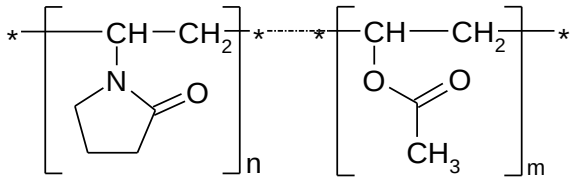
- **Amorphous solid API dispersed in water soluble carrier polymer**
  - Take advantage of higher apparent solubility of API
  - Intercalation of API molecule between polymer chains physically stabilizes drug
- **Dispersion preparation is empirically done**
  - Estimate drug/polymer miscibility
  - Physical characterization is challenging
  - Formulated rather than engineered
  - Conflicting data on stability indicating requirements
- **Material limitations at the critical decision point**
  - Small quantities of API at candidate nomination
  - Is a solid dispersion feasible?
    - May not be answerable at nomination point
- **Can dispersion potential be predicted using information that could be measured using small quantities of material?**

Hancock and Parks, Pharm. Res. **17(4):** 397-404, 2000.
Hancock and Zografii, J. Pharm. Sci. **86(1):** 1997.
Moore and Wildfong, J. Pharm. Innov. **4(1):** 36-49, 2009.

Binary Amorphous Solid Dispersions

Is there a way of describing an API that correlates with its ability to form a binary amorphous molecular solid dispersion with PVPva using the hot-melt process.

- **Molecular descriptors aim to represent a 3-D structure with one single integer**
  - Derived from the fundamental concept that the structure of a compound is responsible for its properties
- **From these descriptors, there may be an underlying combination capable of predicting dispersion potential**

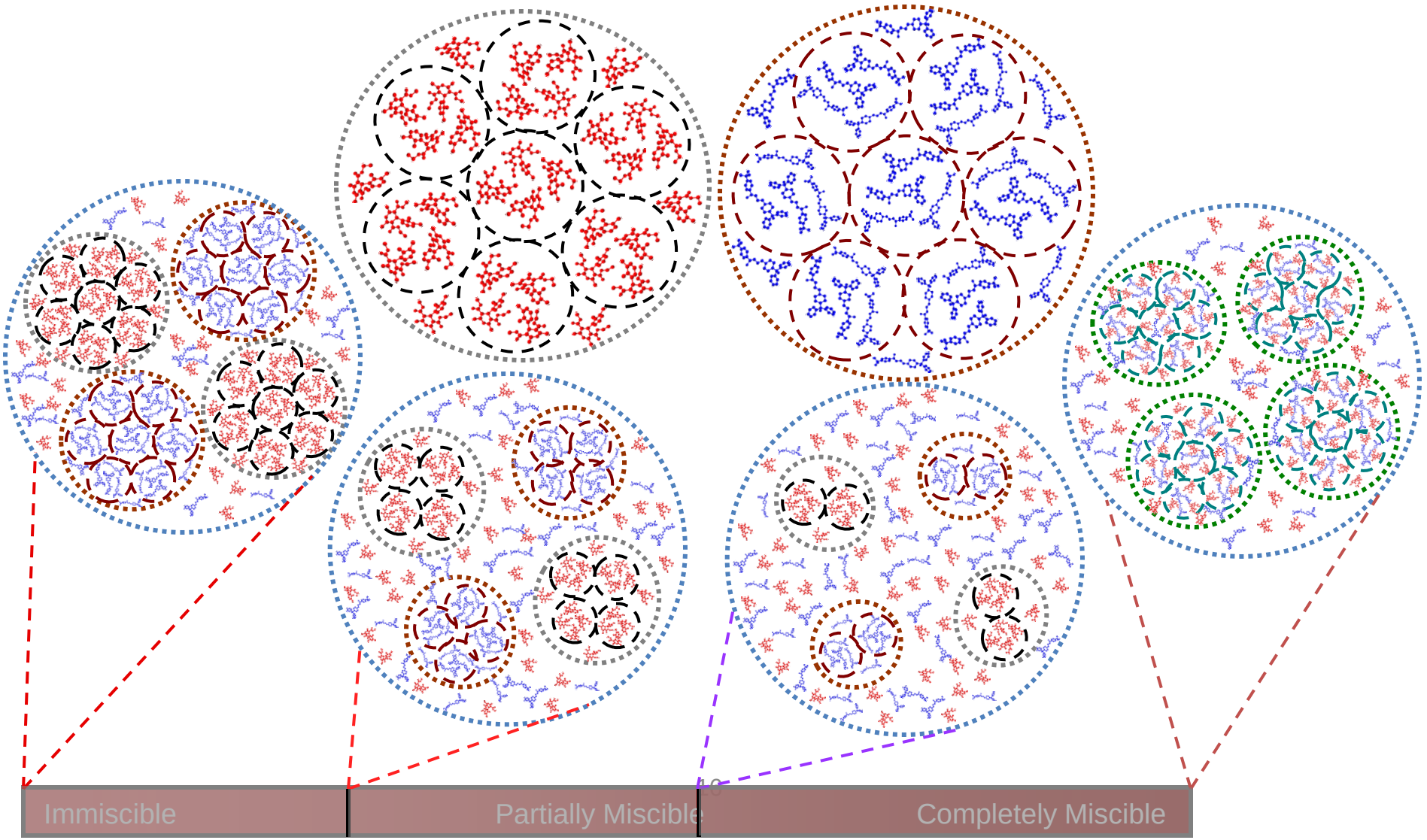
API + 

PVPva

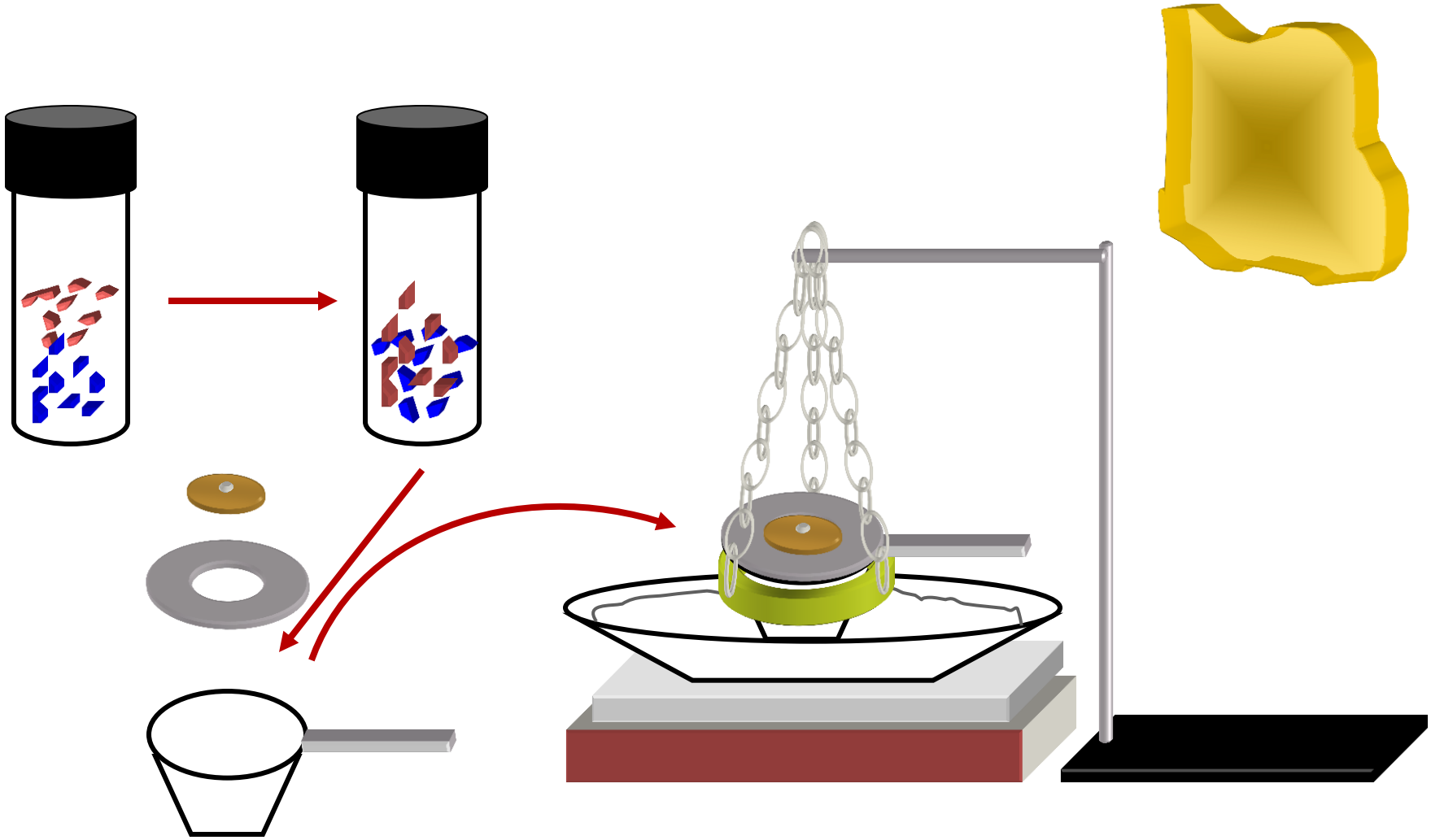
→ Dispersion (Y/N?)

} Model observed behaviour using descriptors

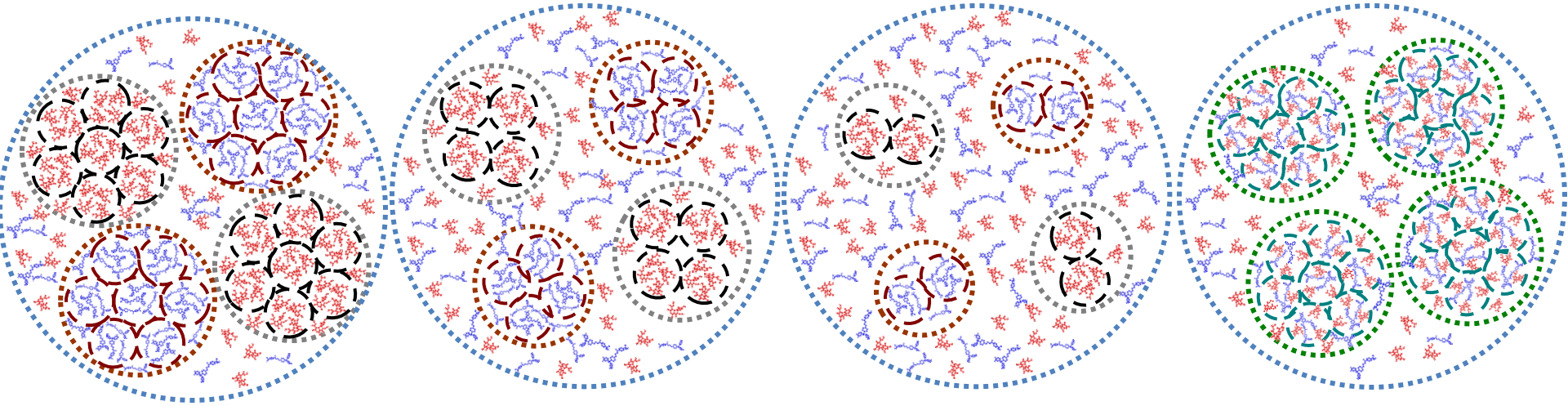
Binary Amorphous Solid Dispersions

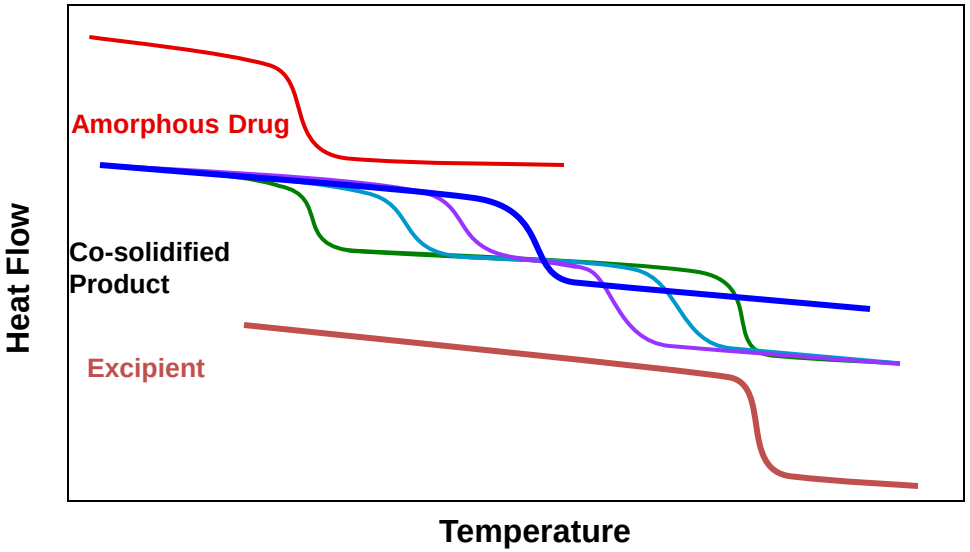


Solid Dispersion Preparation



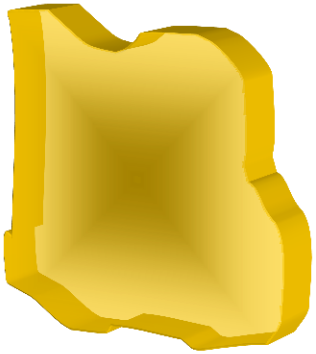
DSC Miscibility Assessment

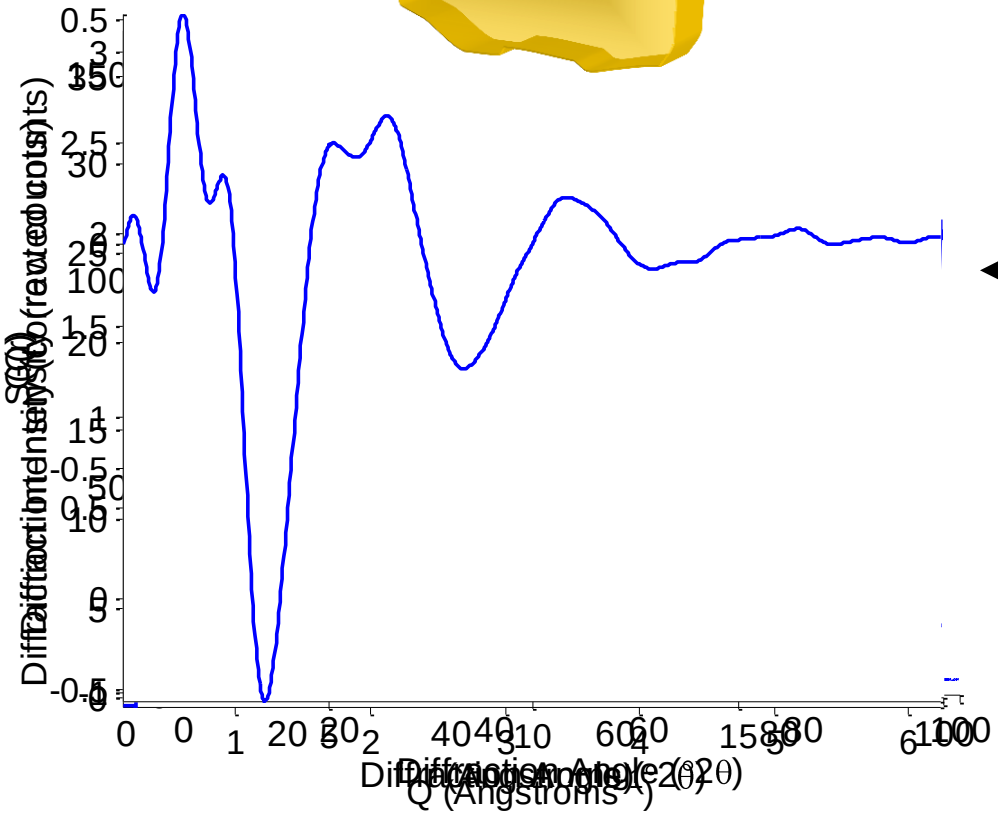




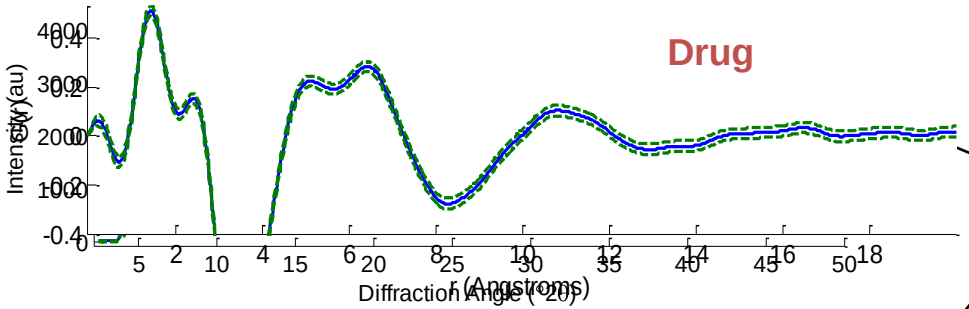
- Sometimes standard DSC analyses not sensitive to phase separation
  - Amorphous domain sizes
  - Concentration differences
  - Partial miscibility creates convoluted T_g event
- Heat sample for measurement
  - Force miscibility
- Need additional characterization techniques

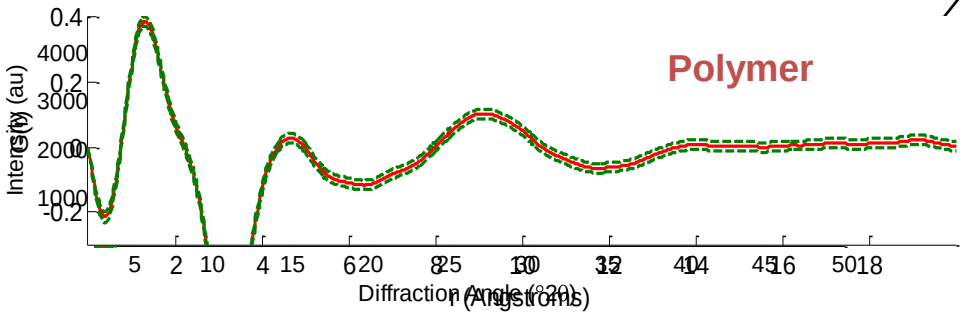
PDF of Dispersion Samples

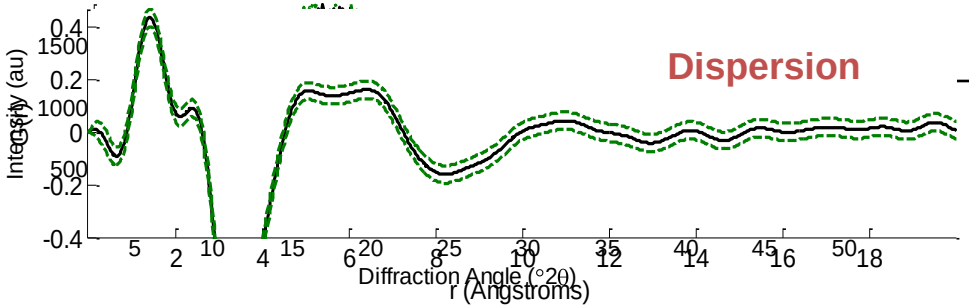


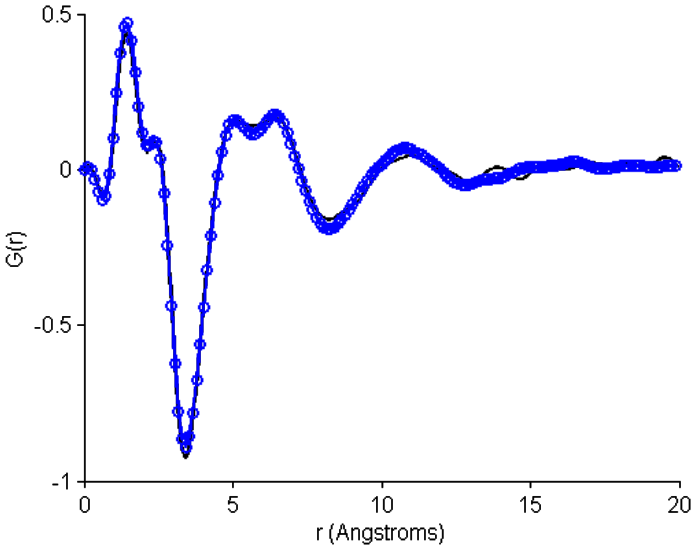


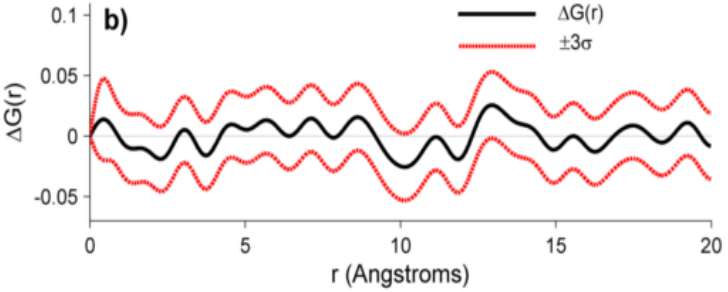
PDF Method using Error Estimates











A. Newman *et al.*, 2008. *J. Pharm. Sci.* (97)11 4840 – 4856.

M. Moore, Z. Shi, P.L.D. Wildfong, 2010, Pharm. Res. **27(12):** 2624-2632.

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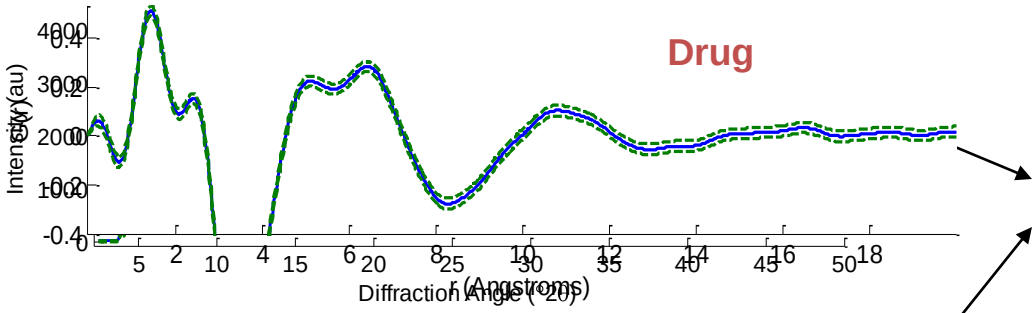

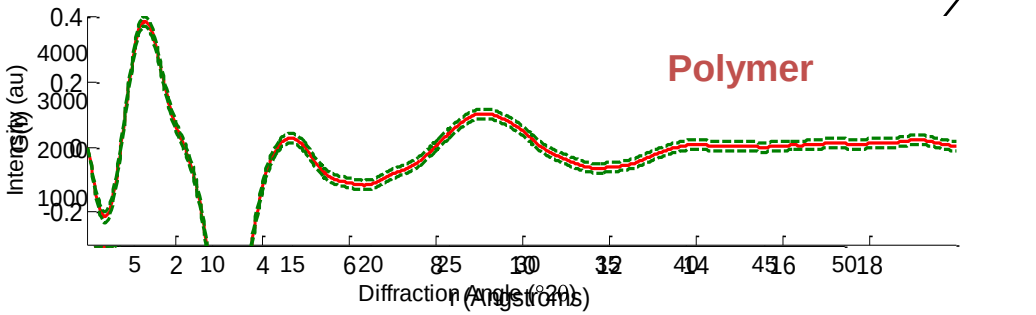

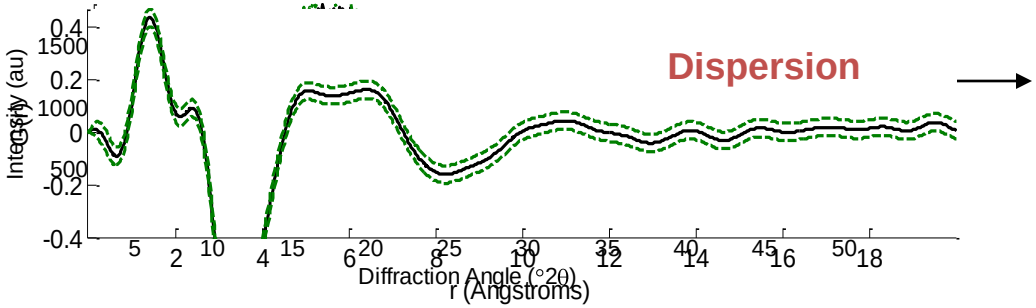

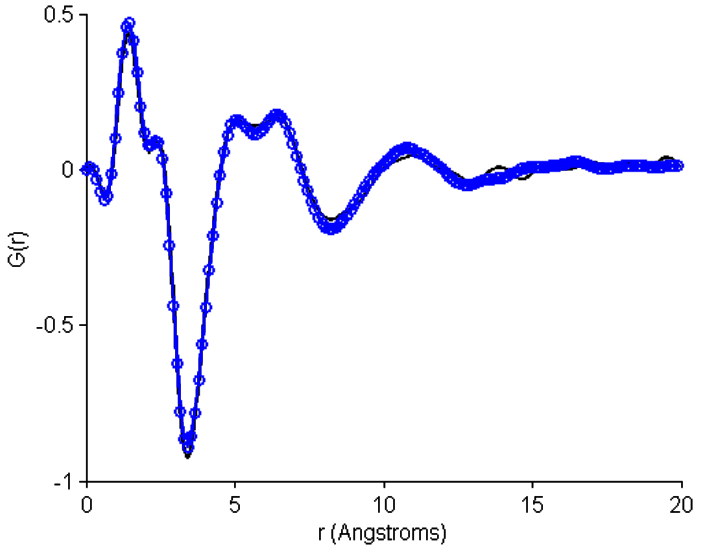

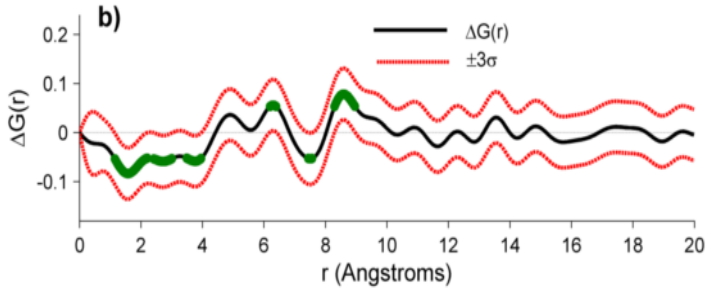

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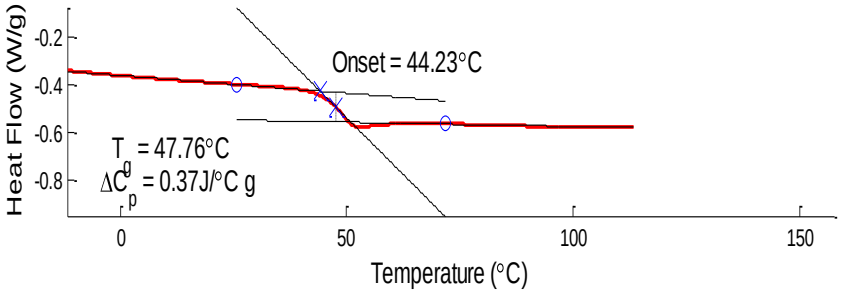
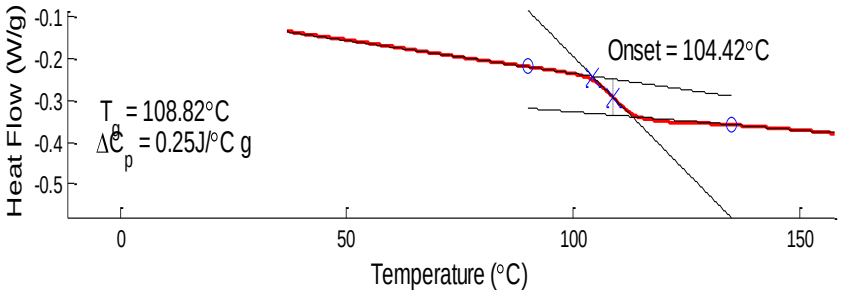
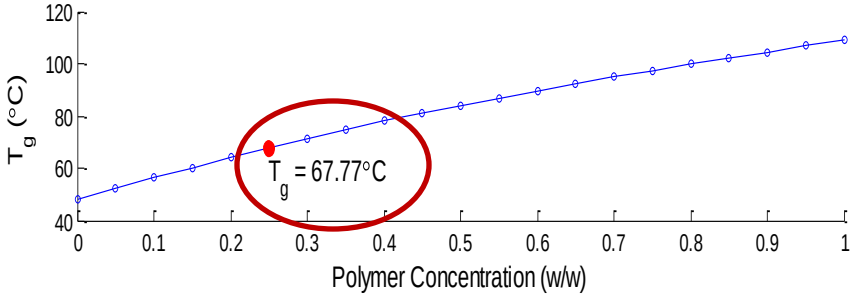
Classification Examples

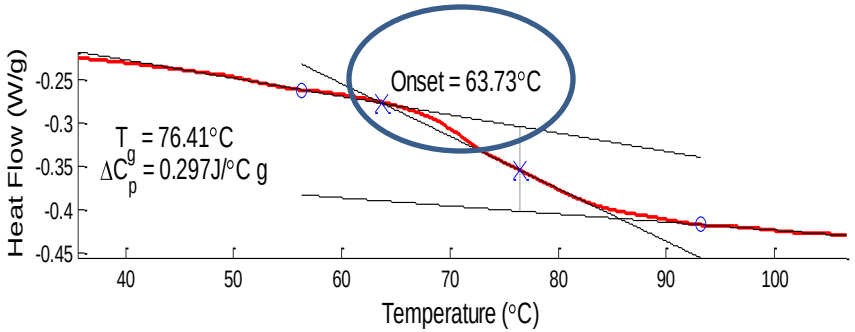
- Amorphous molecular solid dispersion
  - Felodipine:PVPva
- Phase-separated solid dispersion (DSC & PDF)
  - Quinidine:PVPva
- Phase-separated solid dispersion (PDF)
  - Terfenadine:PVPva

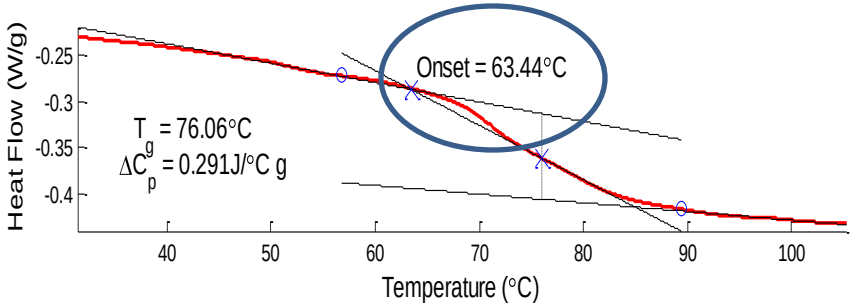
Felodipine: PVPva 75:25 w/w

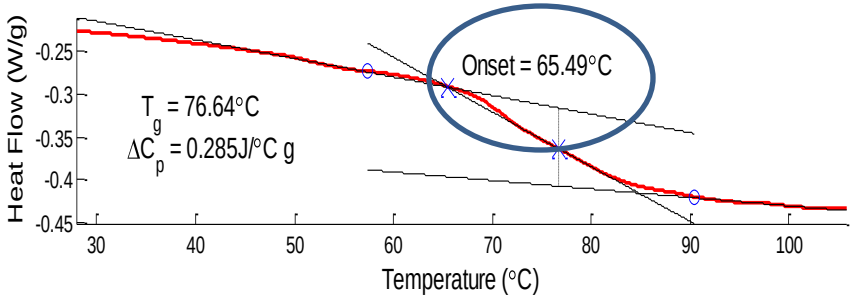








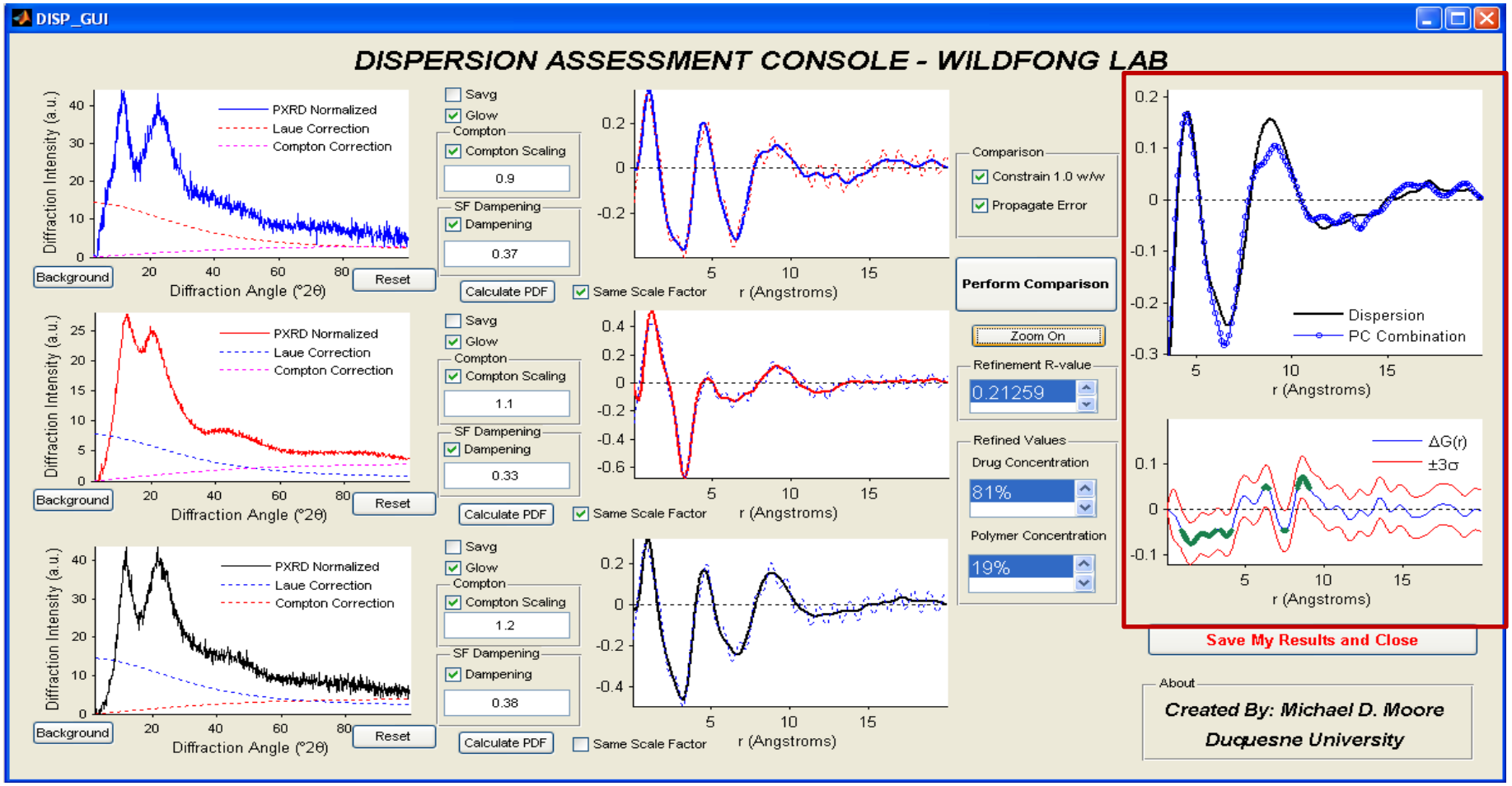




Predicted T_g = 67.77 °C

Measured T_g = 64.9 °C

Felodipine: PVPva 75:25 w/w



PDF contains distances not explained by pure component PDF addition. Binary Molecular Amorphous Dispersion

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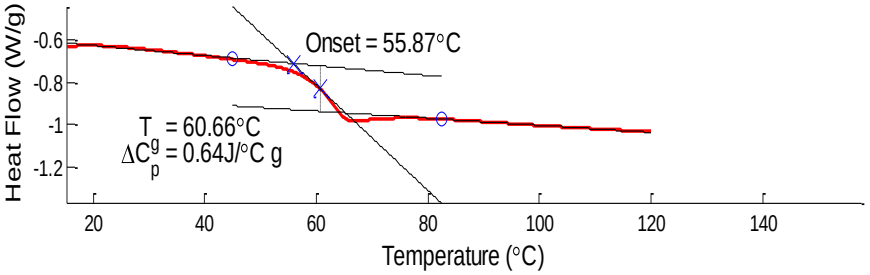
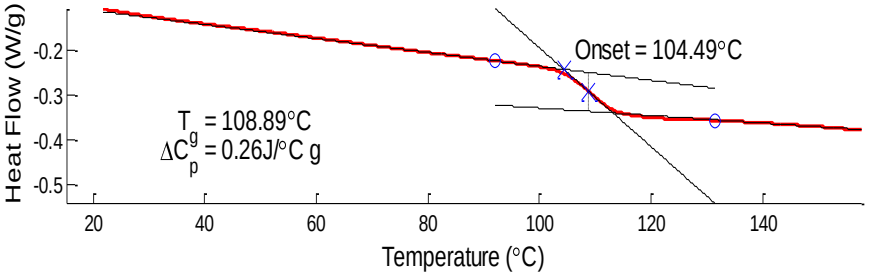
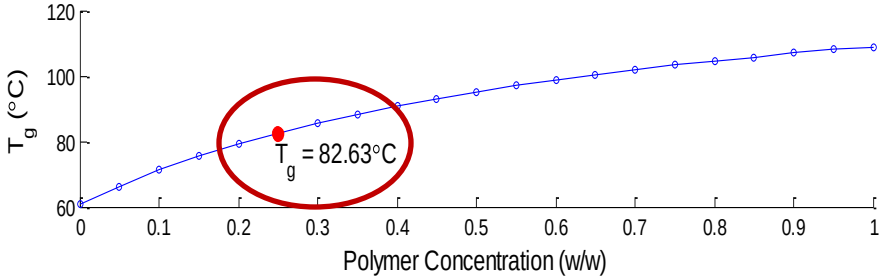
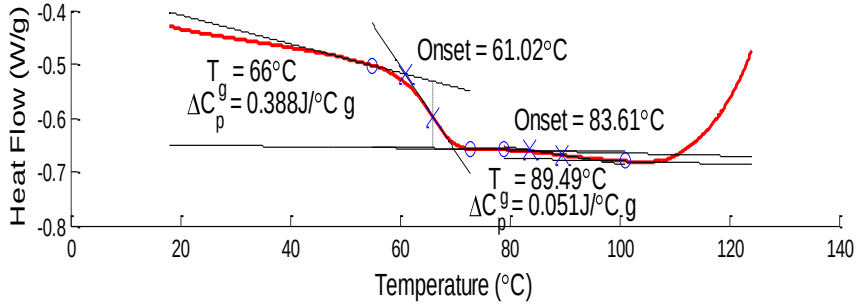
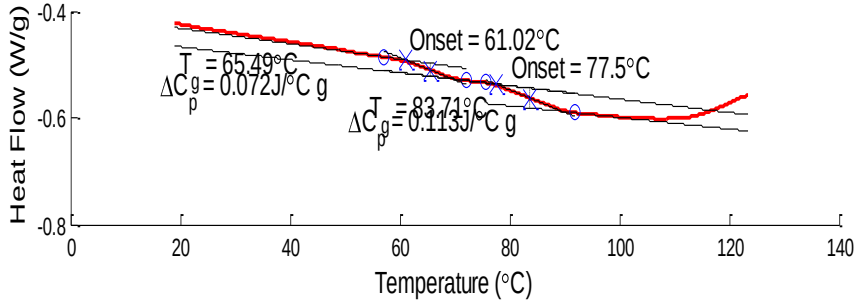
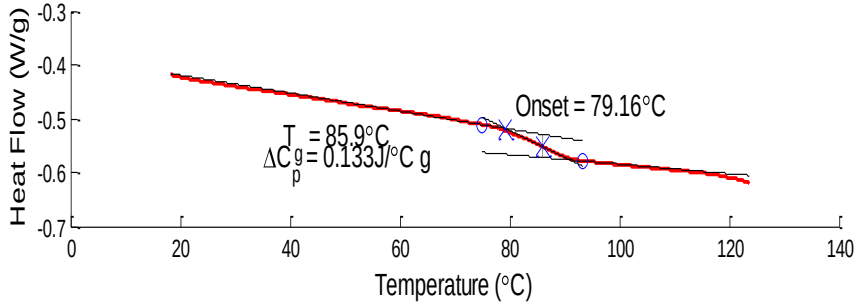








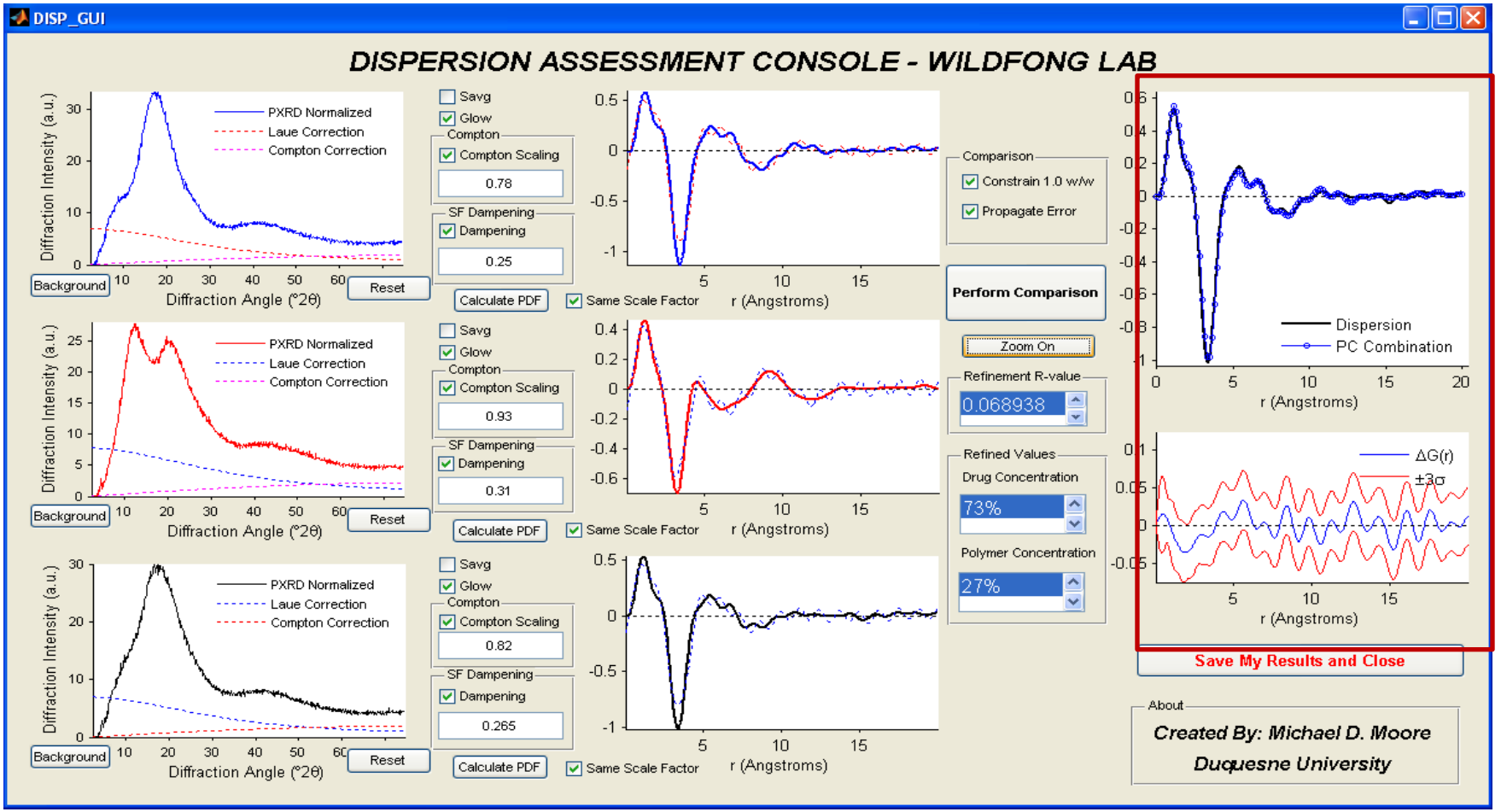




Predicted T_g = 82.63 °C

2 x T_g events for two samples

Quinidine: PVPva 75:25 w/w



PDF contains no new distances relative to pure component PDF addition. Physical Mixture (phase separated)

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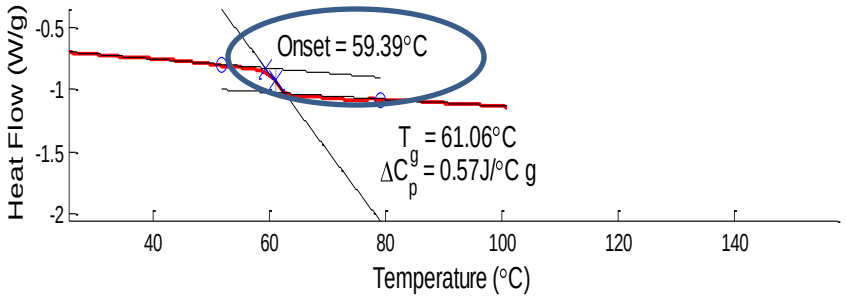
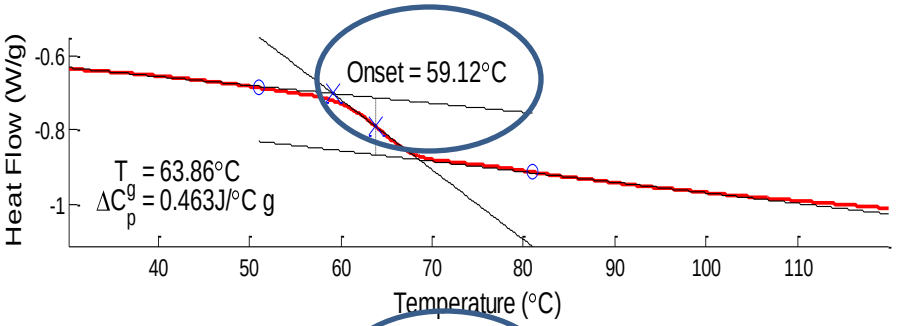
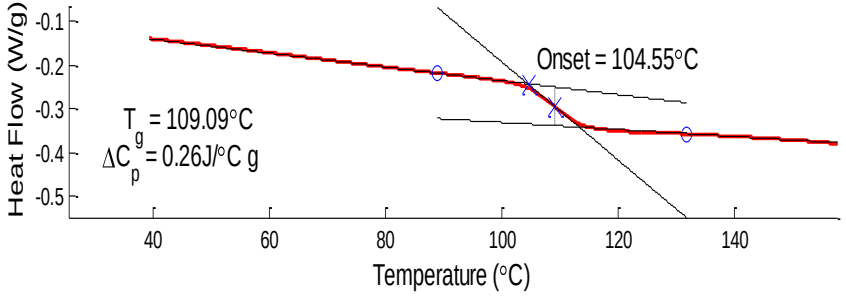
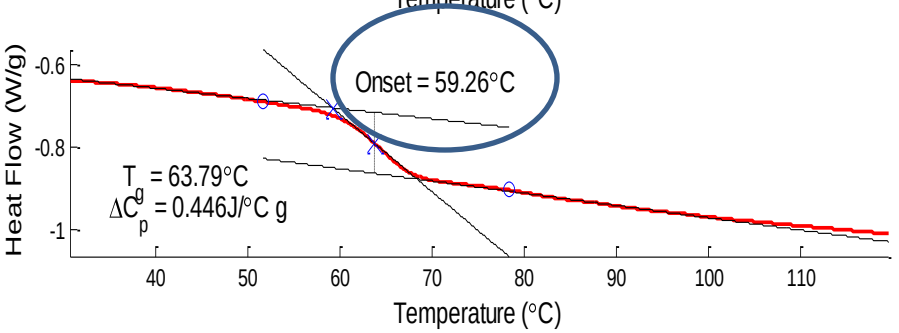
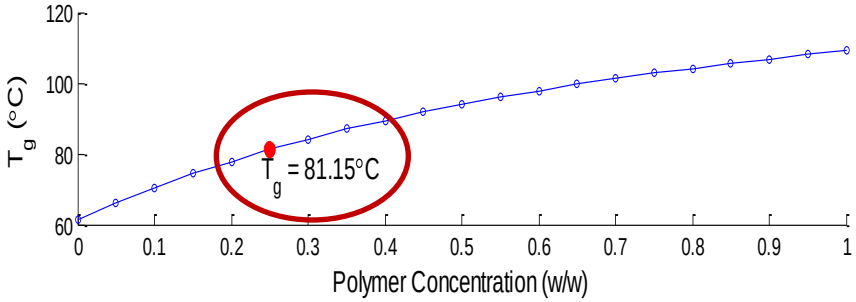
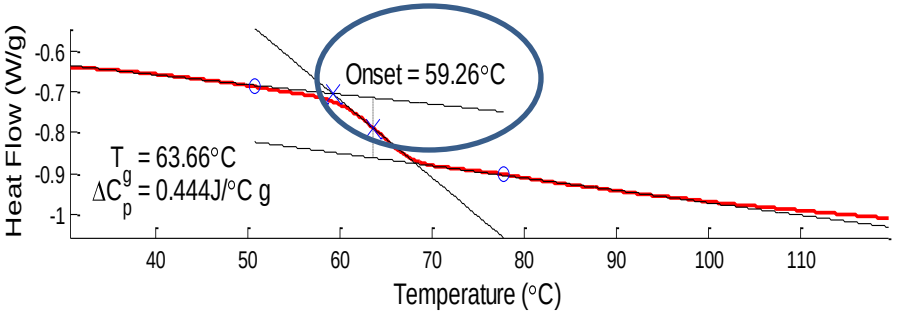








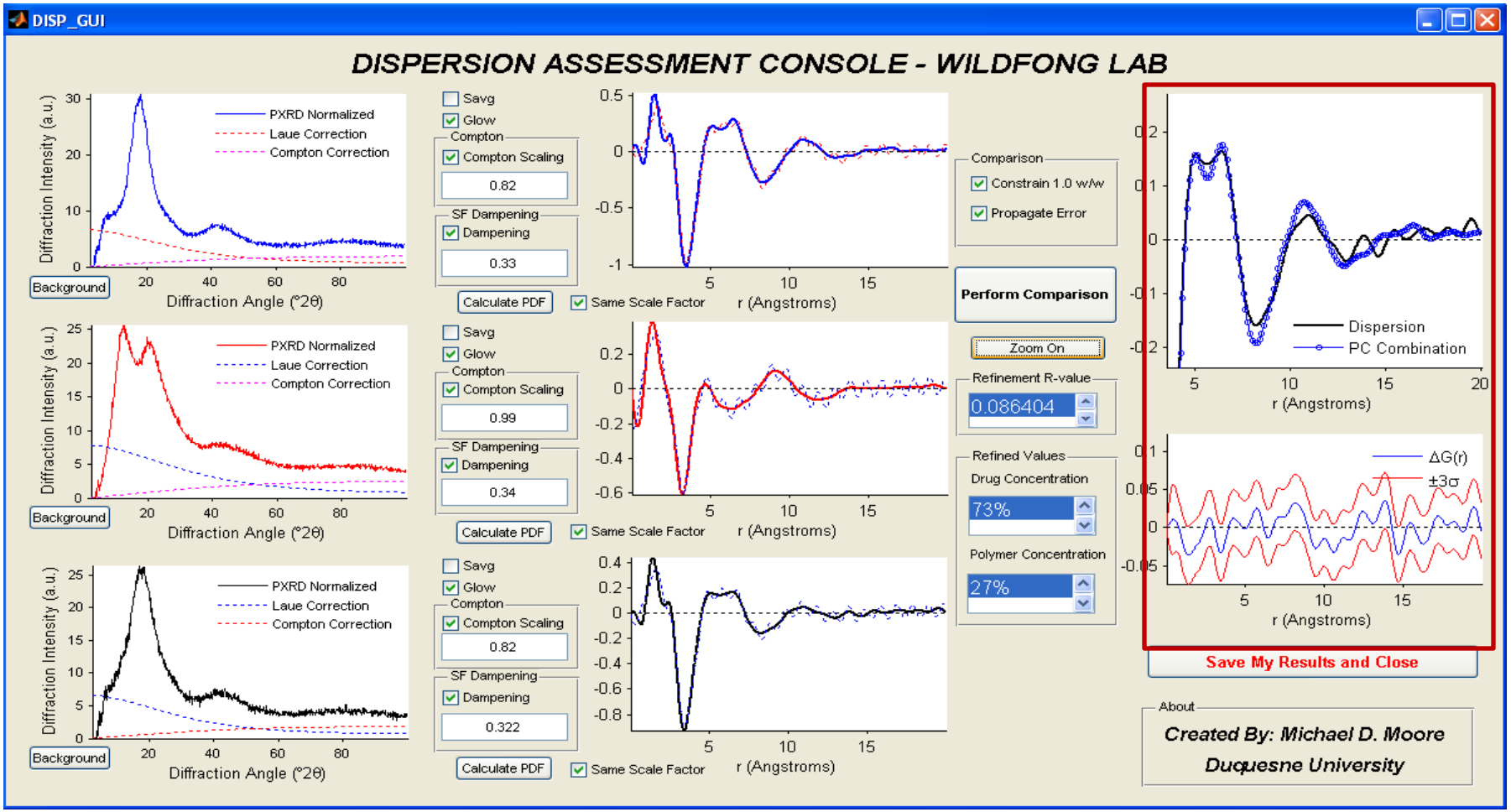




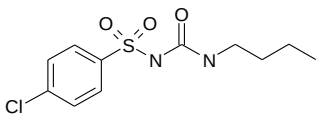
Predicted T_g = 81.15 °C

Measured T_g = 59.2 °C

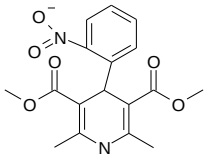
Terfenadine: PVPva 75:25 w/w



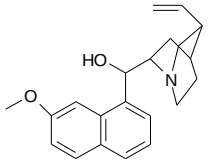
Compound Library



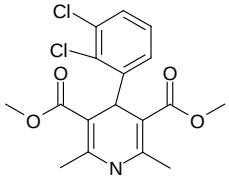
Chlorpropamide
BEDMIG02
Model



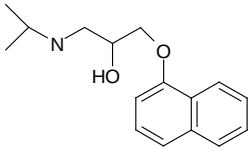
Nifedipine
BICCIZ
Model



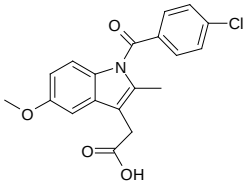
Quinidine
BOMDUC
Model



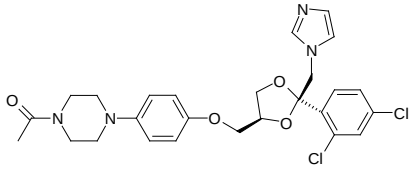
Felodipine
DONTIJ
Model



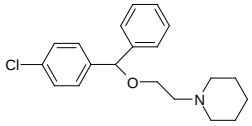
Propranolol
FIDGAB
Model



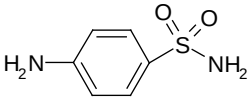
Indomethacin
INDMET03
Model



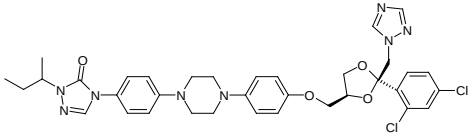
Ketoconazole
KCONAZ
Model



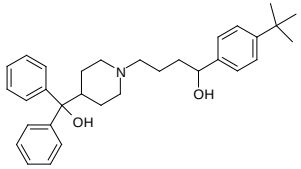
Cloperastine
QAWNAD
Model



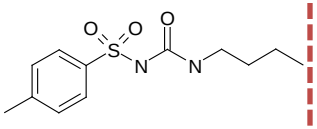
Sulfanilamide
SULAMD06
Model



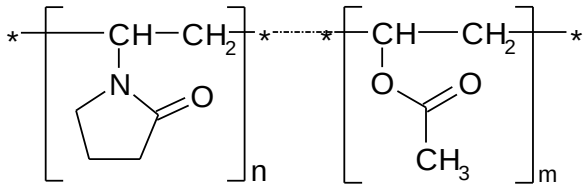
Itraconazole
TEHZIP
Model



Terfenadine
XUHTID
Model



Tolbutamide
ZZZPUS02
Model



PVPva

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Compound Library Results (n=3)

Compound	Forms Dispersion?
Felodipine	YES
Indomethacin	YES
Ketoconazole	YES
Itraconazole	YES
Tolbutamide	YES
Chlorpropamide	YES
Nifedipine	NO
Quinidine	NO
Propranolol	NO
Cloperastine	NO
Terfenadine	NO
Sulfanilamide	NO

Library was balanced with respect to phenomenological dichotomy

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Molecular Descriptors

- **Over 1600 available descriptors from EDRAGON**
  - 17 categories
- **Crystallographic structure solution required**
  - The three dimensional coordinates (*.xyz) are converted to the sybyl (*.mol2) format
    - Single molecule; not including H_2O, salts, *etc.*

Compound	CSD Ref Code
Chlorpropamide	BEDMIG02
Nifedipine	BICCIZ
Quinidine	BOMDUC
Felodipine	DONTIJ
Propranolol	FIDGAB
Indomethacin	INDMET03
Ketoconazole	KCONAZ
Cloperastine	QAWNAD
Sulfanilamide	SULAMD06
Itraconazole	TEHZIP
Terfenadine	XUHTID
Tolbutamide	ZZZPUS02
Cimetidine	CIMETD
Melatonin	MELATN01
Bicalutamide	JAYCES

Model Compounds

Test Compounds

Univariate Significance

- Log-likelihood values were calculated for each individual molecular descriptor against a model created from the mean
- Variables were kept if their signficance (χ^2) was ≥0.999

Rank (by LL ratio)	Molecular Descriptor	Regression Equation	p-value	Deviance	Ln likelyhood ratio	LOO Crosval
7	'T(O..Cl)'	logit P(Y) = -1.927 + 0.208**T(O…Cl)**	0.0010	6.513	10.86	0.3841
4	'SEigZ'	logit P(Y) = -12.33 + 7.37**SEigZ**	0.0004	4.889	12.49	0.4208
3	'SEigm'	logit P(Y) = 12.57 + 7.50**SEigm**	0.0004	4.813	12.56	0.4199
6	'H1m'	logit P(Y) = -17.78 + 12.31**H1m**	0.0009	6.314	11.06	0.3964
5	'HTm'	logit P(Y) = -13.25 + 1.14**HTm**	0.0007	5.992	11.39	0.3720
1	'R3m'	logit P(Y) = -88.54 + 135.18**R3m**	0.0000	0.039	17.34	0.0565
2	'R4m+'	logit P(Y) = -15.2 + 346.22**R4m+**	0.0002	3.253	14.12	0.2637

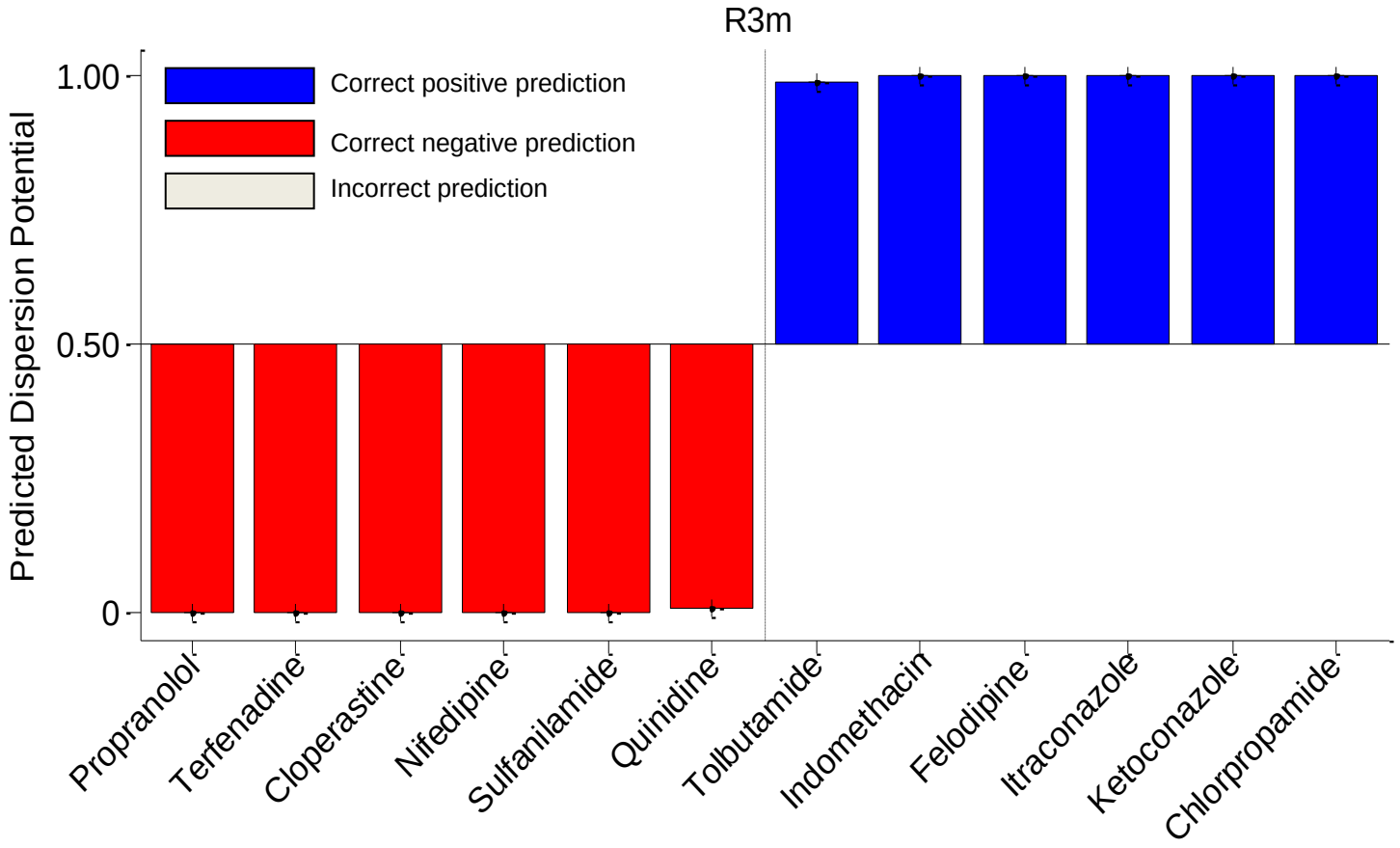
- Backward (fully saturated) and forward elimination multivariate screening was performed
- At a significance level of α = 0.2, R3m was only variable remaining

VCCLAB, Virtual Computational Chemistry Laboratory. http:\\www.vcclab.org.
D.G. Kleinbaum and M. Klein. Logistic Regression, Springer, 2002.
D.G. Kleinbaum, L.L. Kupper, K.E. Muller, and A. Nizam. Applied regression and other multivariable methods, Duxbury Press, 1998.

GETAWAY Indices

R autocorrelation of lag 3 weighted by atomic masses

Logit P(Y) = -88.536 + 135.18R3m



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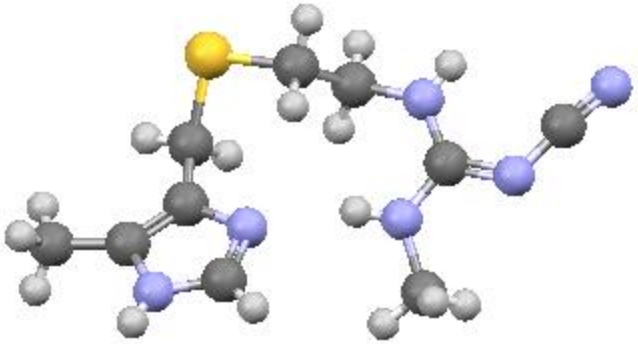
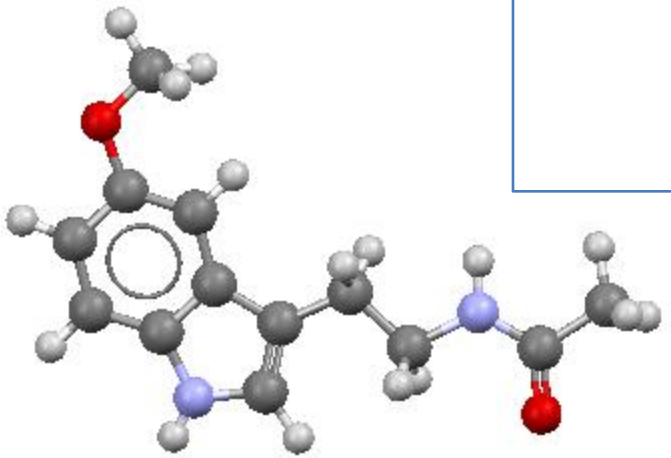
R3m Model "Challenge" Compounds

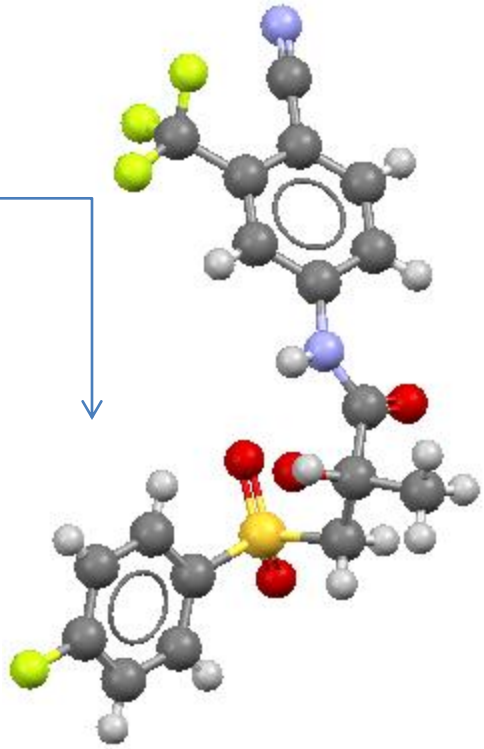
Prediction based on R3m codes to 1 (*i.e.*, will form dispersion)



Cimetidine
R3m = 0.436
P(Ŷ) = 1.3976e-013 ≈ 0



Melatonin
R3m = 0.408
P(Ŷ) = 3.1739e-015 ≈ 0



Bicalutamide
R3m = 1.008
P(Ŷ) = 1

Prediction based on R3m codes to 0 (*i.e.*, will not form dispersion)

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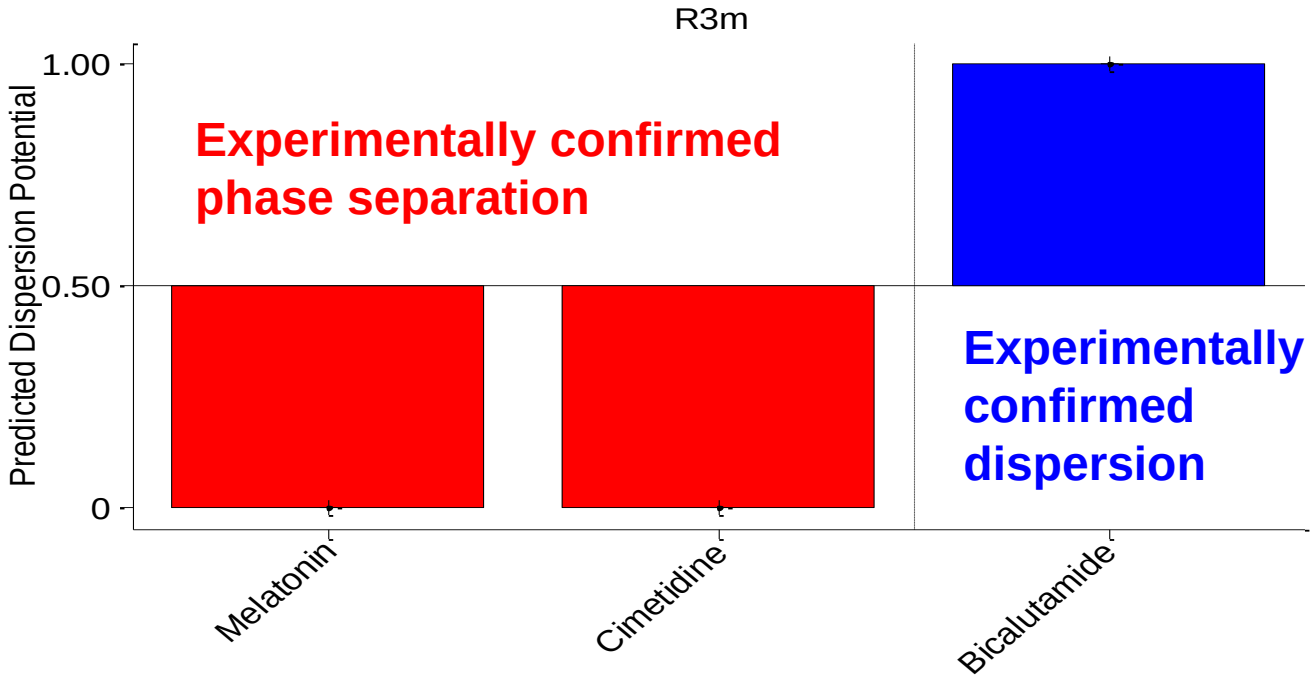
Results



- From model prediction, bicalutamide was the only compound capable of amorphous molecular solid dispersion formation
- Melatonin and cimetidine were identified as phase separated systems by PDF

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Future Directions

- **Library expansion**
  - 12 model API + 3 test API is a start (a small one, at that)
  - Expand using structural analogues
  - Expand structural diversity of model compounds
    - The predictive power becomes much greater as you increase the number of materials (and possibly descriptors)
- **Method expansion**
  - Melt-quench method limits polymer and API (viscosity)
  - Mechanical, solvent-based, spray-drying methods
- **Different polymer carriers**
  - PVPva used mainly in support of preparation method
  - PEGs, cellulosic polymers known to serve as good carriers
  - Optimize carrying capacity

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