ADD6 JANUARY 2026

AMORPHOUS PHARMACEUTICALS

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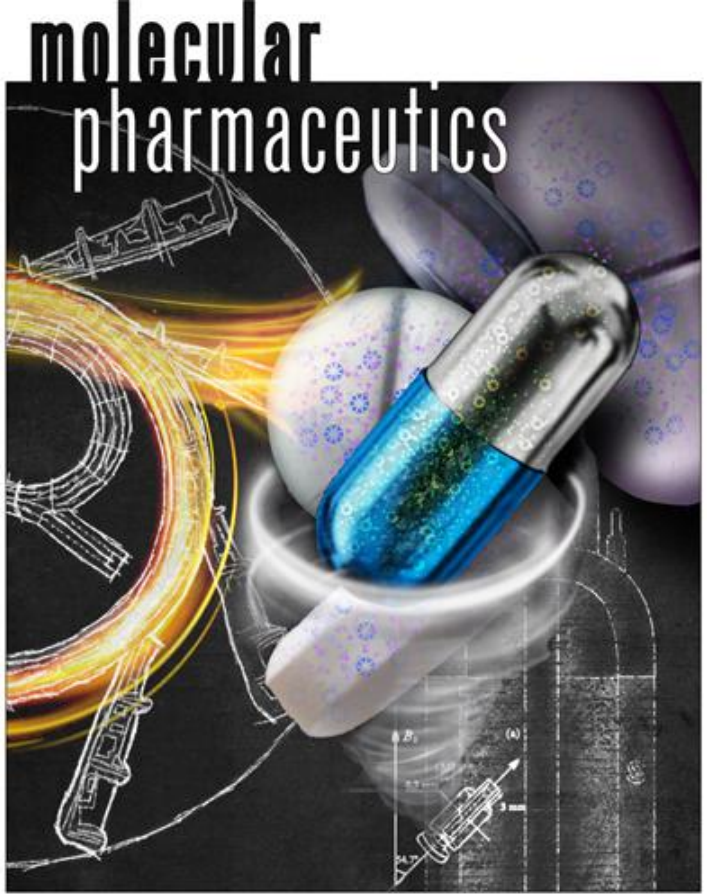

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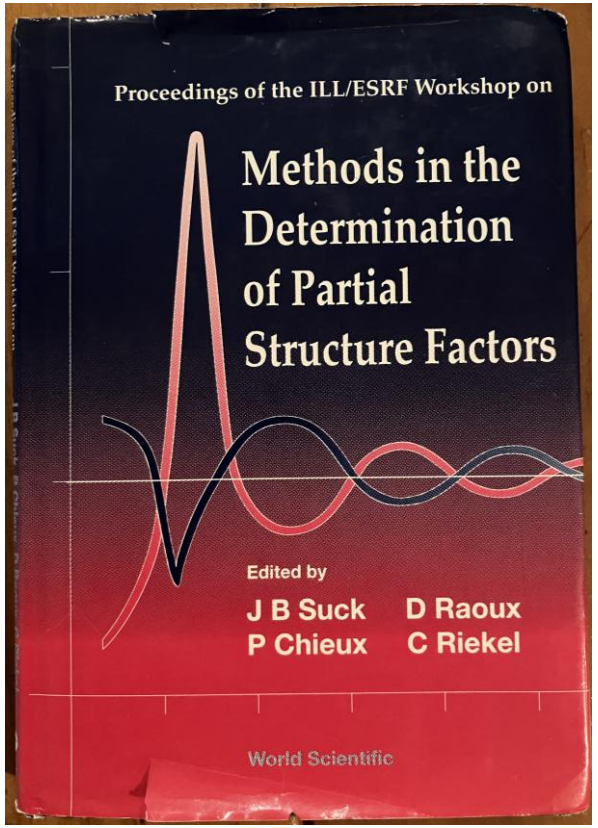
ILL/ESRF PARTIAL STRUCTURE FACTORS WORKSHOP 1992



COLLABORATORS & ACKNOWLEDGEMENTS

Improved Pharma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Jeffery Yarger

MDI Instruments for Innovation®


Rick Weber & Stephen Wilke

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- National Institutes of Health, R44GM117701.
- U.S. DOE Office of Science, DE-AC02-06CH11357
- Argonne, LDRD

SPS-XRPD WORKSHOP

2018 Purdue University, USA
2019 PSI, Switzerland
2023 Purdue University, USA
2024 Novartis, Basel, Switzerland
2025 APS, Argonne, USA
2026 Novartis, Basel, Switzerland

EXCELSUS STRUCTURAL SOLUTIONS

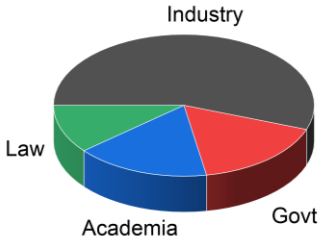


Fabia Gozzo, Thibaud Stoll & Mathilde Reinle-Schmitt

NOVARTIS

Arnaud Grandeury

SPS-XRPD 2025 attendees



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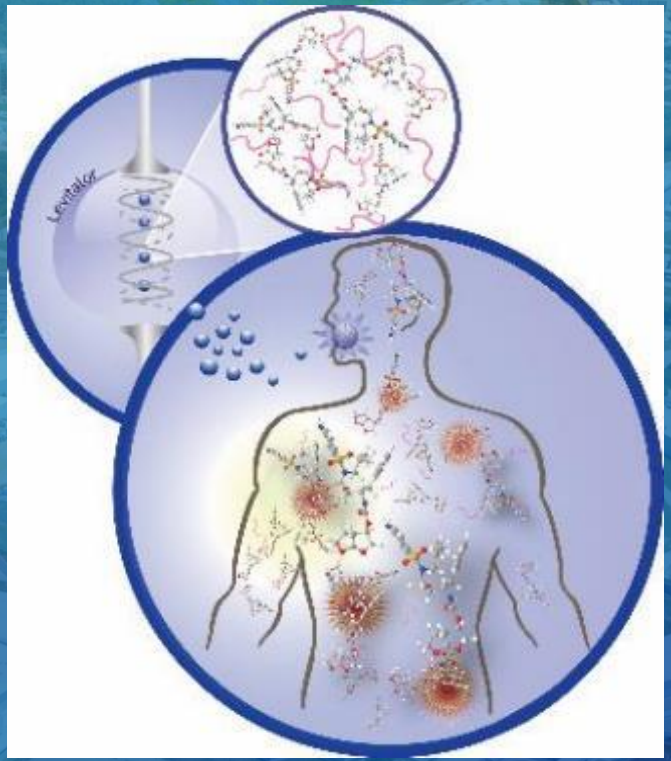
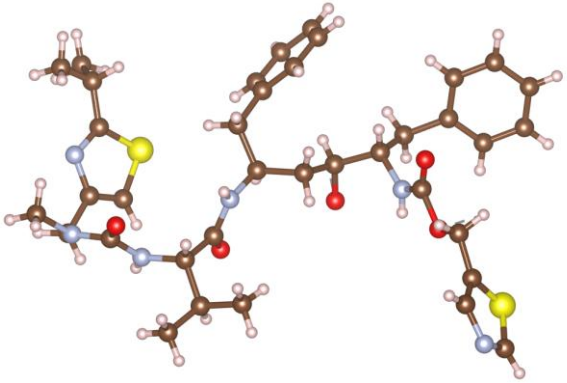
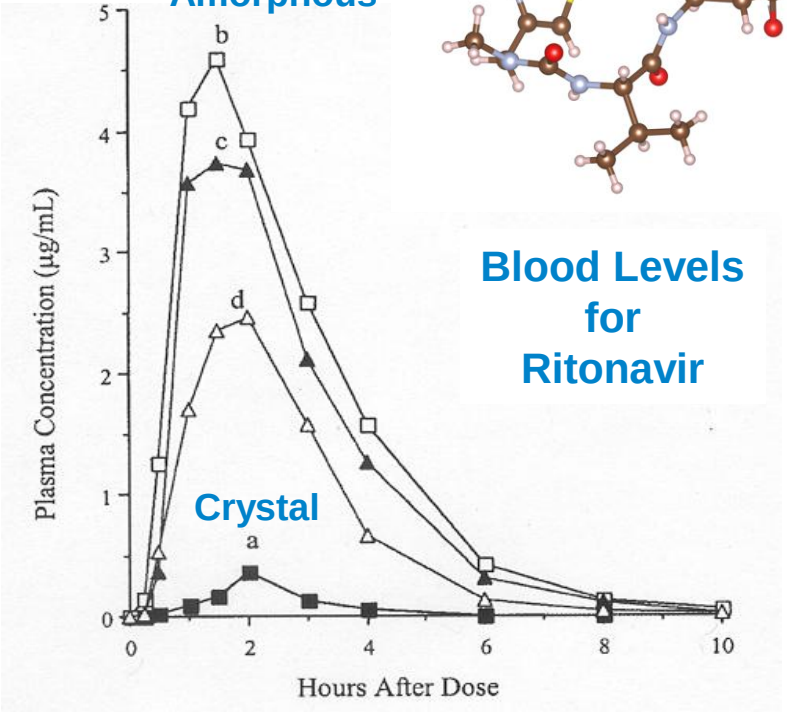
SOLUBILITY, BIOAVAILABILITY, & FORMULATION



RITONAVIR

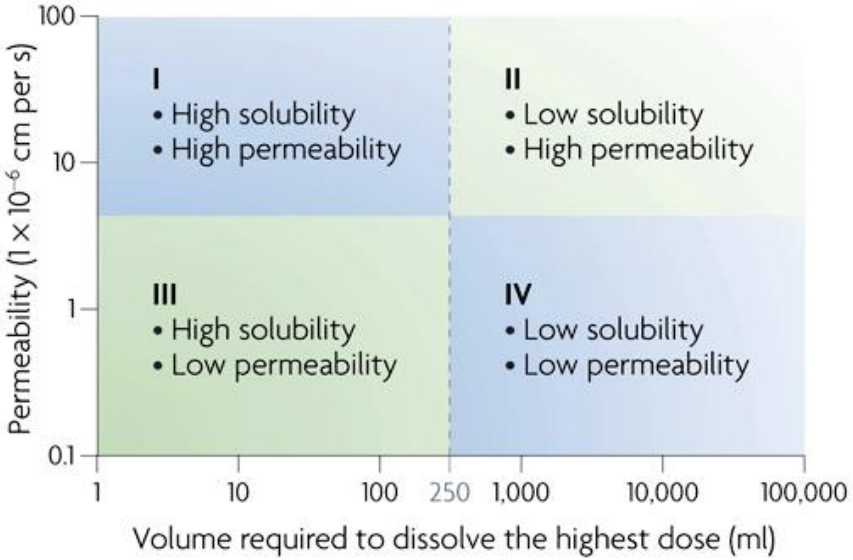




Law *et al.*, J. Pharm. Sci. 93 (2004) 563

- Originally dispensed in 1996 in crystalline form I (monoclinic)
- HIV deaths in US fell by 64% following FDA approval of Ritonavir
- Two years later a lower energy more stable form II appeared (orthorhombic)
- Form II was much less soluble and had lower bioavailability
- Caused the removal of formulation from the market (cost Abbvie ~US$240M)
- Re-formulated as amorphous form in 2000 with higher solubility.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

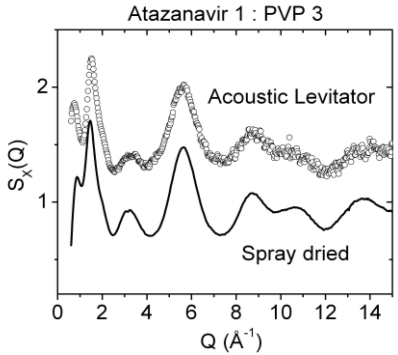


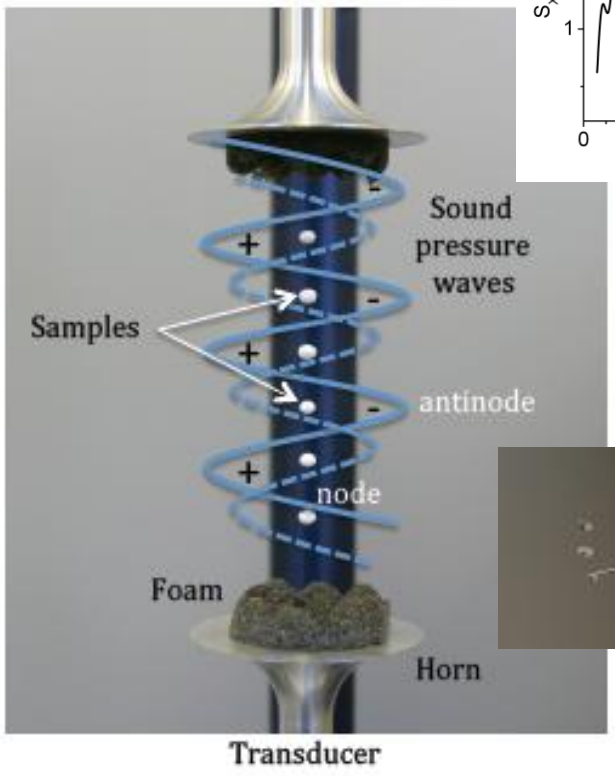
- Low aqueous solubility is the major problem encountered with formulation development.
- More than 40% of new drugs developed in the pharmaceutical industry are practically insoluble in water.
- Solubility, permeability, polymorphism and stability are key issues in pharmaceutical formulations
- Class II pharmaceuticals: Posaconazole, Itraconazole, Carbamazepine, Nifedipine, Felodipine, Ketoprofen

ACOUSTIC LEVITATION

A LABORATORY MODEL FOR SPRAY DRYING

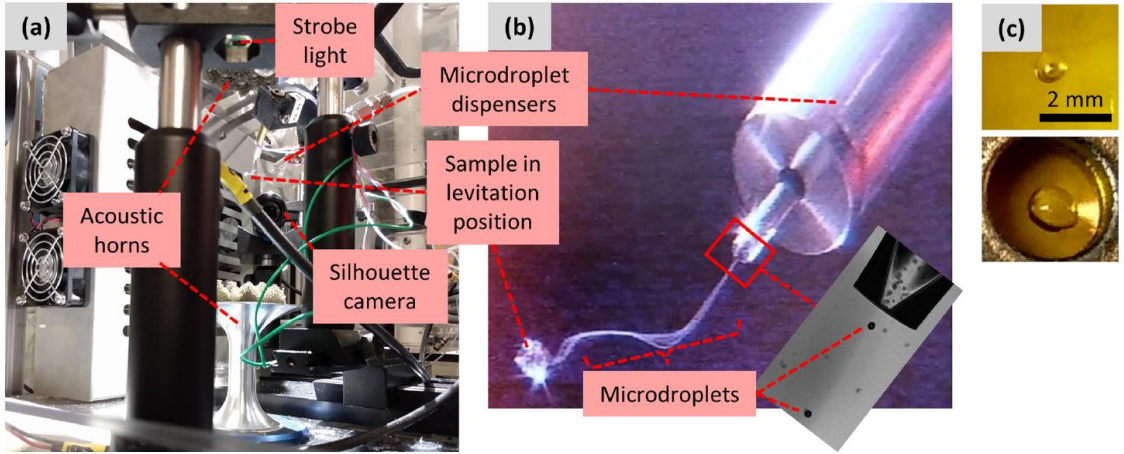
- Spray drying produces dry powder from liquid by rapid drying with hot gas
- Spray nozzle disperses droplets in typically in 100-300 micron size range
- Commonly used method for producing amorphous pharmaceuticals.
- Acoustic Levitator operates at 22 kHz
- Nodes are 7mm apart, so sample size is limited up to 3mm in diameter
- Surface tension ultimately determines droplet diameter

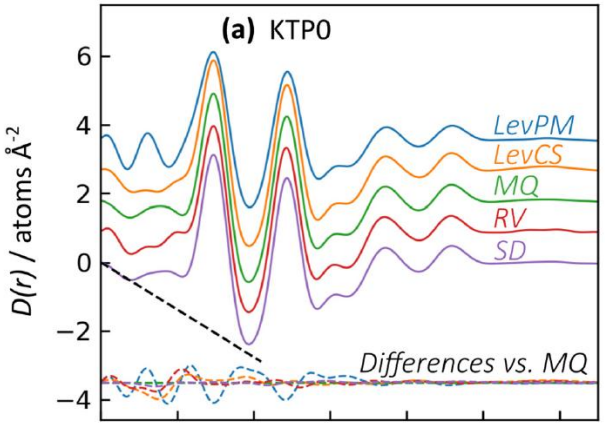




C.J. Benmore and J.K.R. Weber *Containerless synthesis of amorphous and nanophase organic materials.* U.S. Patent 9327264B2 (2016)

AMORPHOUS SOLID DISPERSIONS PREPARED BY DIFFERENT METHODS



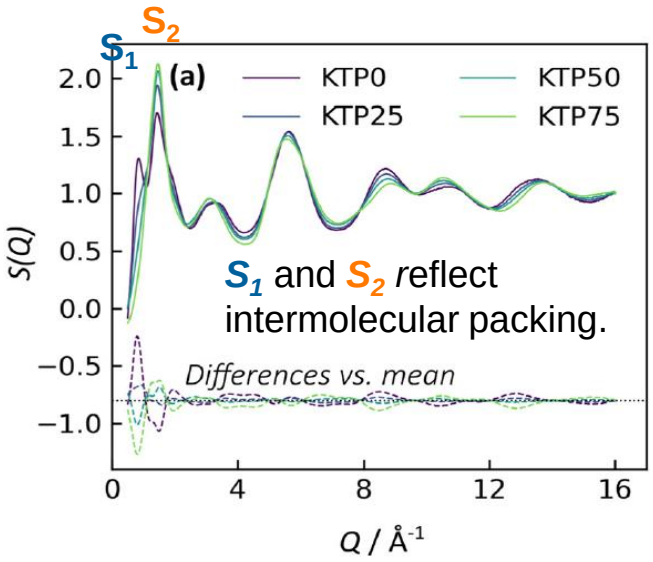


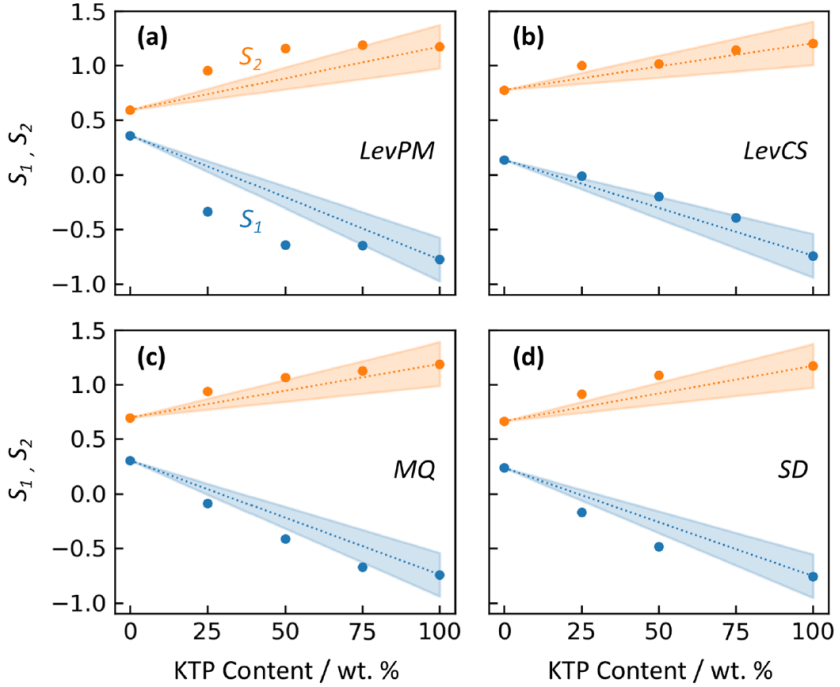
- Amorphous Solid Dispersions are used to increase the solubility of oral medicines by stabilizing the more soluble amorphous phase
- Ketoprofen (KTP) – Polyvinylpyrrolidone (PVP) mixtures made by different methods – how can PDF help ?

LevPM - premix levitation
LevCS - co-spray levitation
MQ - melt quenching
RV - rotary evaporation
SD - spray drying

S.K. Wilke *et al. Pharmaceutics 1,* 2024, 121

PHASE SEPARATION IN KTP-PVP ASD'S

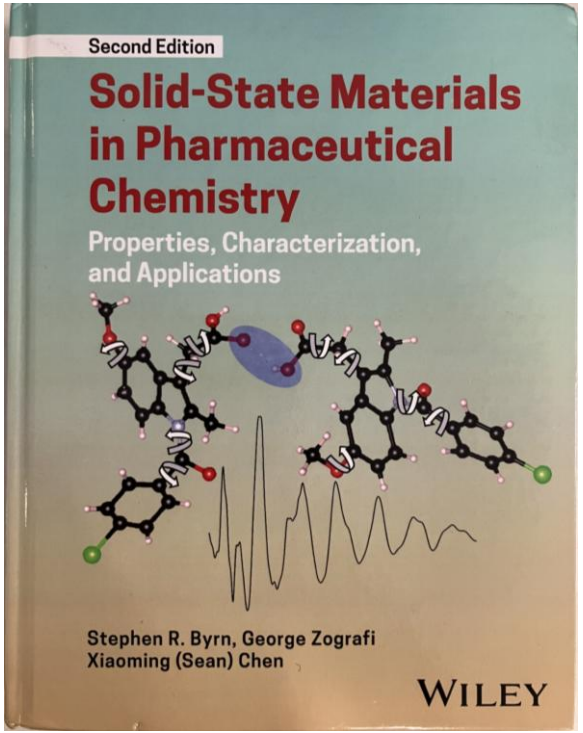




- Variability in the extent of molecular mixing using different amorphization routes - a direct indication of their relative stability against crystallization.

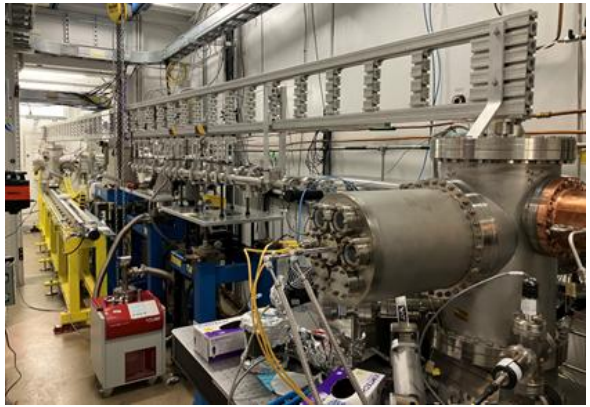
- MQ, SD & LevPM solutions exhibit some degree of molecular mixing. LevCS close to KTP/PVP physical mixtures

EPSR MODELING OF ACTIVE PHARMACEUTICAL INGREDIENTS (API)



HIGH ENERGY X-RAY DIFFRACTION

- 6-ID-D at the Advanced Photon Source has a High Energy Bent Double Laue Monochromator
- Si 311 (50-95keV) Si 331 (70-125keV)
- Undulator 13th harmonic is at 90.88keV @ 9mm gap
- Calibrate to Bi K-edge 90.54 keV
- Data reduction for liquids problem: not all x-ray PDF software are the same.



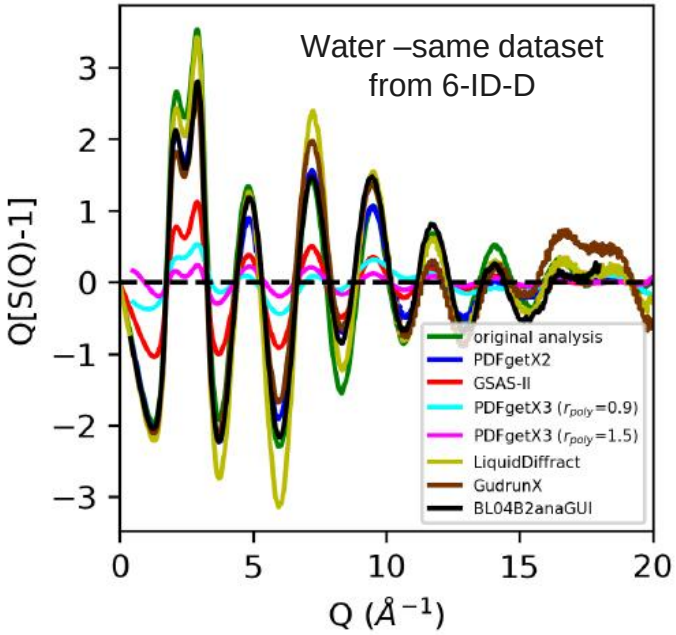
quantum beam science

Quantum Beam Sci. **2023**, *7*, 20.

Review

Review of Current Software for Analyzing Total X-ray Scattering Data from Liquids

Leighanne C. Gallington [1], Stephen K. Wilke [1], Shinji Kohara [2] and Chris J. Benmore [1,*]



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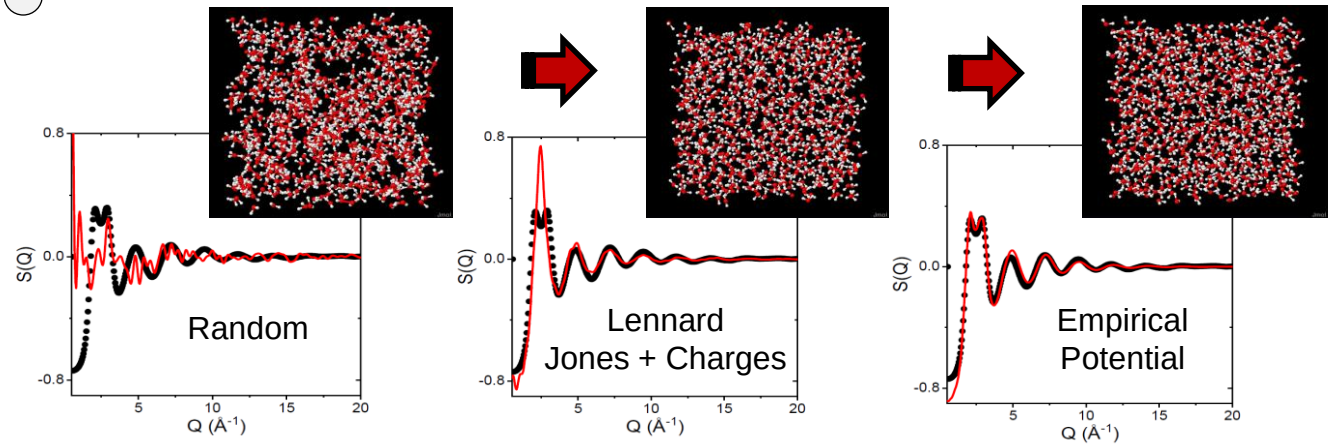
EMPIRICAL POTENTIAL STRUCTURE REFINEMENT

- EPSR is a RMC approach: a fitting tool analogous to Rietveld refinement for liquids
  - Uses a reference LJ potential & atomic charges PLUS an Empirical Potential
    - Empirical Potential altered until model and diffraction (PDF) data agree

$$U_{\alpha\beta}(r) = 4\epsilon_{\alpha\beta}\left[\left(\frac{\sigma_{\alpha\beta}}{r}\right)^{12} - \left(\frac{\sigma_{\alpha\beta}}{r}\right)^{6}\right] + \frac{q_\alpha q_\beta}{4\pi\epsilon_0 r} + C_{\alpha\beta}exp\left[\frac{1}{\gamma}(r_{\alpha\beta} - r)\right]$$

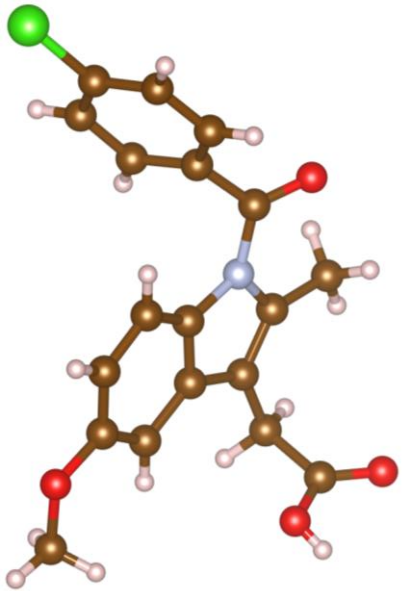
Intermolecular potential energy — **LJ potential** — **Coulomb** — **Empirical potential**



A.K.Soper *Chem. Phys.* **202** 295 (1996); A.K.Soper *Phys Rev B**72*** 104204 (2005);
A.K. Soper & C.J. Benmore *Phys Rev Lett*. 101 (2008) 065502

MODELING PROCEDURE - EPSR

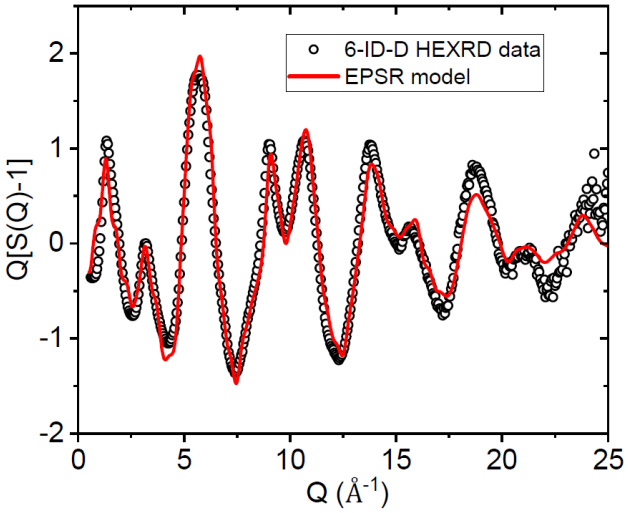
- Use LJ starting parameters from Optimized Potentials for Liquid Simulations (OPLS). Listed by chemical group (W.L. Jorgensen)
- Partial Charges taken from MD simulations or DFT calculations
- Define torsional angle rotations of specific bonds from NMR or polymorphs of specific chemical groups
- General strategy – Test a range of models. Focus on simplest models that provide a “good” fit to S(Q).
- Try different starting molecular conformations
- Typically 60-100 molecules in a cubic ~30Å^3 box
- Collect over 10,000 configurations – typically 12 hours

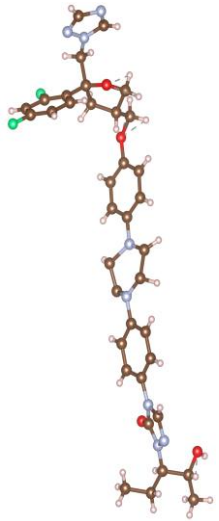


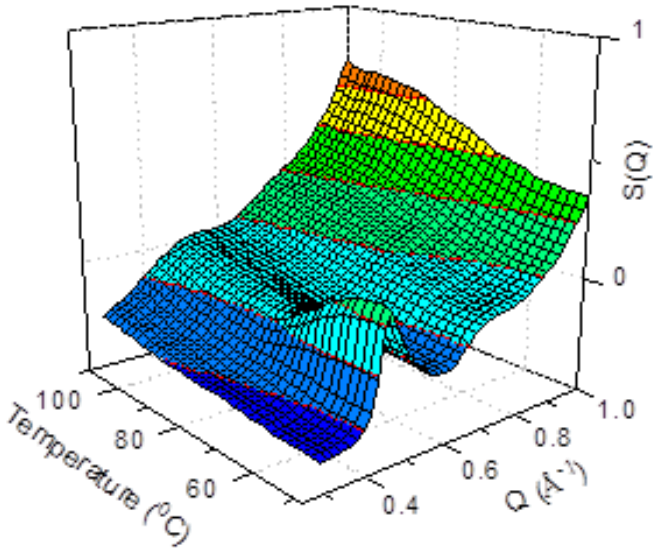
RIGID, ROD-LIKE MOLECULES

Define Posaconazole molecule in EPSR

Atom types (chem groups): 26
Angles (3 atoms): 90
Dihedral angles (4 atoms): 249
Rotations specified: 13 tried – rigid works well
Standard LJ parameters: changing has little effect

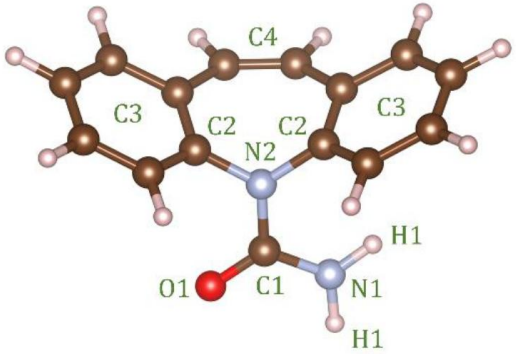


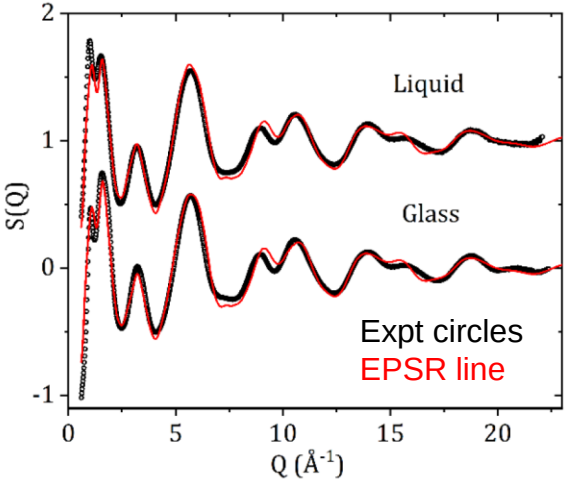




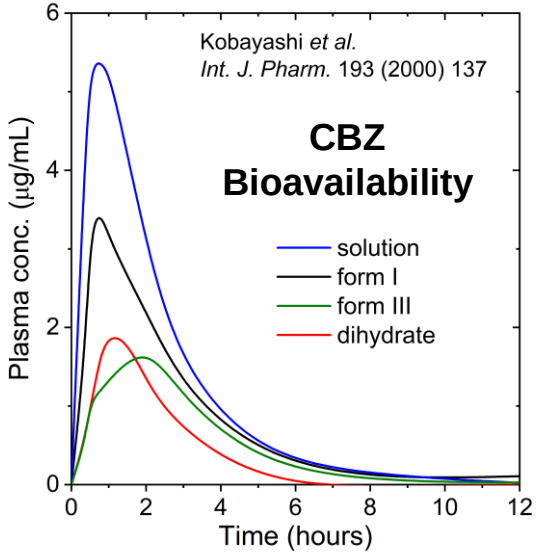
A SAXS-WAXS study of the endothermic transitions in amorphous and supercooled liquid ***Itraconazole.***
C.J. Benmore *et al.*
Thermochimica Acta 644 (2016) 1

RIGID MOLECULES - CARBAMAZEPINE





- Carbamazepine (CBZ) used to treat epilepsy
- Liquid & Amorphous CBZ has a much higher oral solubility than crystal forms
- Stability is an issue. In 1998, 70 million tablets of CBZ were withdrawn – dihydrate formed

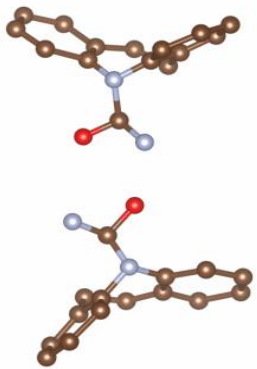


- N1-O1 Hydrogen bonding. C3-C3 ring interactions
- Liquid and glass models show structures not present in the crystalline forms that vary with temperature

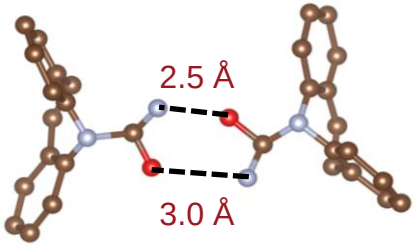
C.J. Benmore *et al. Quantum Beam Sci*. 6 (2022) 31

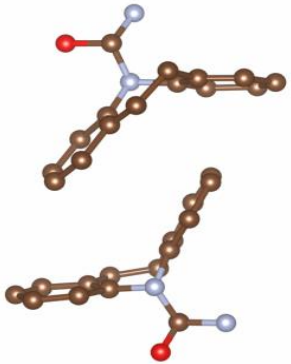
CARBAMZEPINE

CBZ HYDROGEN BONDING & AROMATIC INTERACTIONS

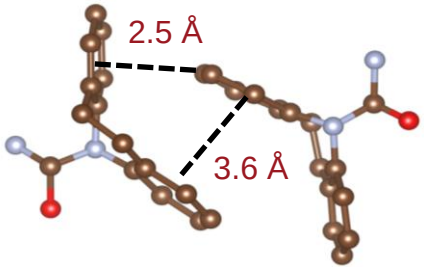


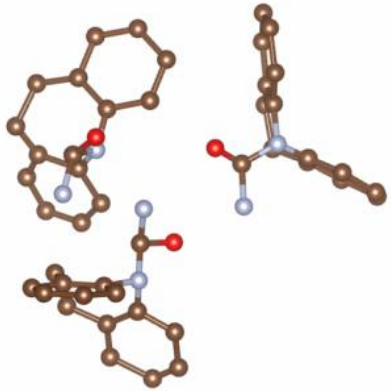
Double HB dimers in crystal → mainly single HB bond in liquid/glass



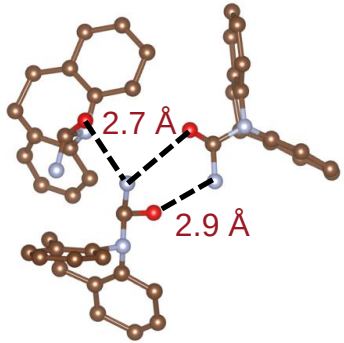


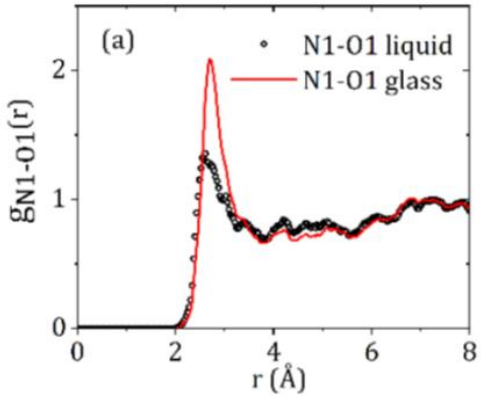
More aromatic ring interactions in liquid than glass

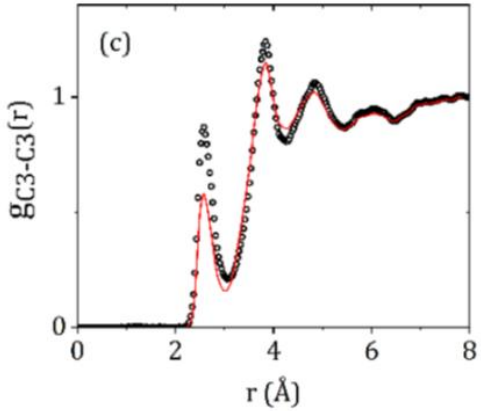




More HB trimers and tetramers in liquid than glass

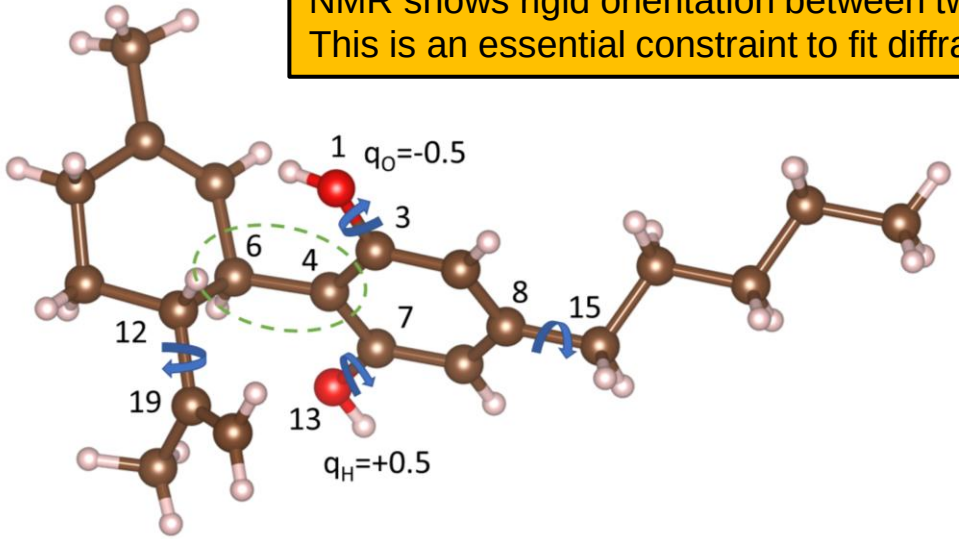


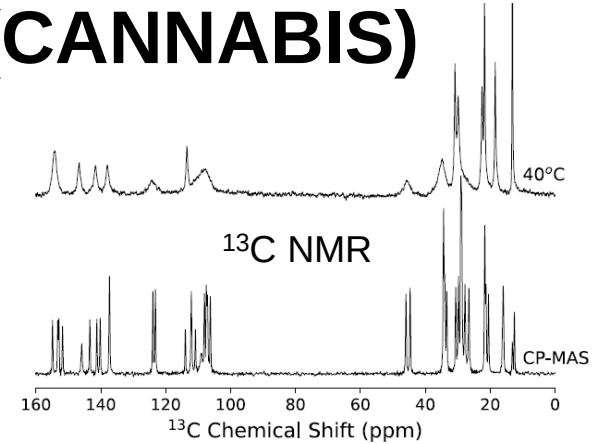


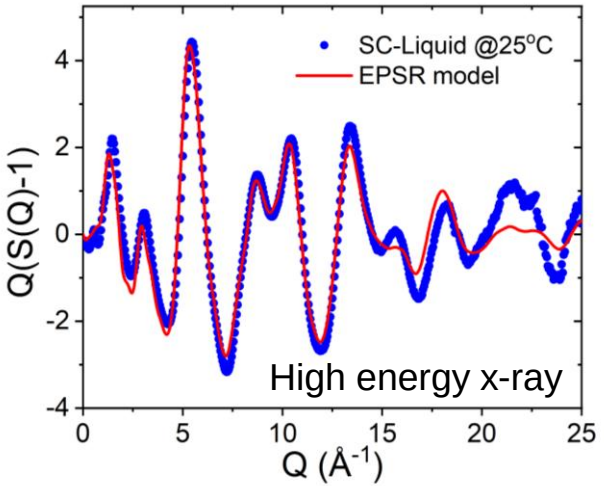


ROTATIONS MATTER – CBD (CANNABIS)

NMR shows rigid orientation between two rings 6-4
This is an essential constraint to fit diffraction data





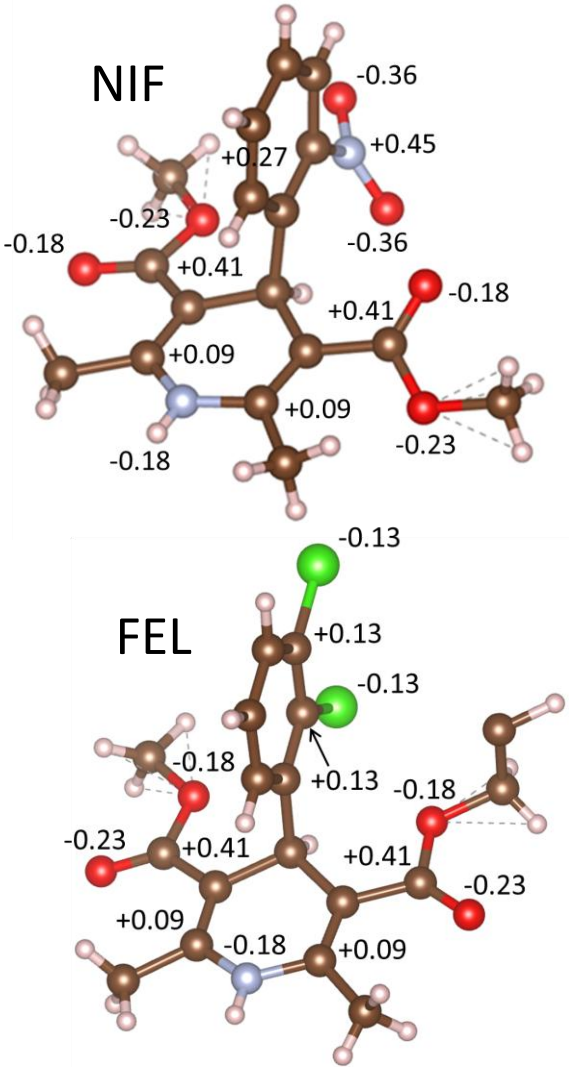


- Systematic inclusion of rotations to observe effect on EPSR fit
- 8-15 has two different conformations in crystal
- Need to allow 12-19 rotation to reproduce FSDP
- Sparse HB from H1O. H13 partially blocked by side group

Shrader, Davidowski, Benmore, Kauffman, Richert & Yarger, submitted.

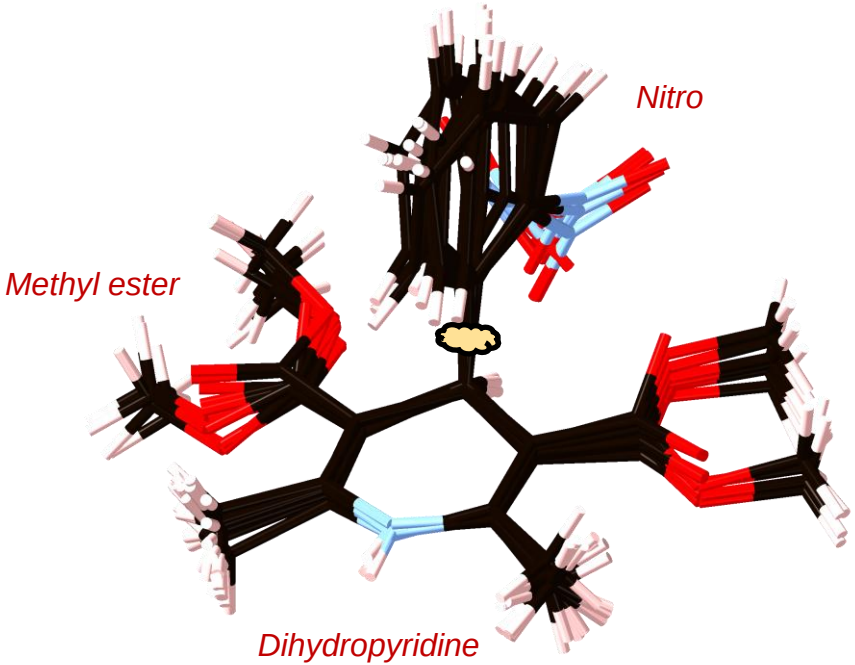
NIFEDIPINE & FELOPIDINE

- Nifedipine (NIF) and Felodipine (FEL) are both calcium channel blockers - strong cardiac medicines for hypertension
- NIF has a nitro group. FEL contains a dichlorophenyl group.
- NIF crystallizes faster than FEL. Questions regarding relative strengths of hydrogen bonds.
- Partial charges were assigned based on MD simulations. Gupta & Kothekar, *J. Biosci*. 22 (1997) 177.
- Charge balance on each chemical group to probe chemical group swap.
- Full rotations and partial rotations (wobble) introduced (no dihedrals defined but no rotations enabled)

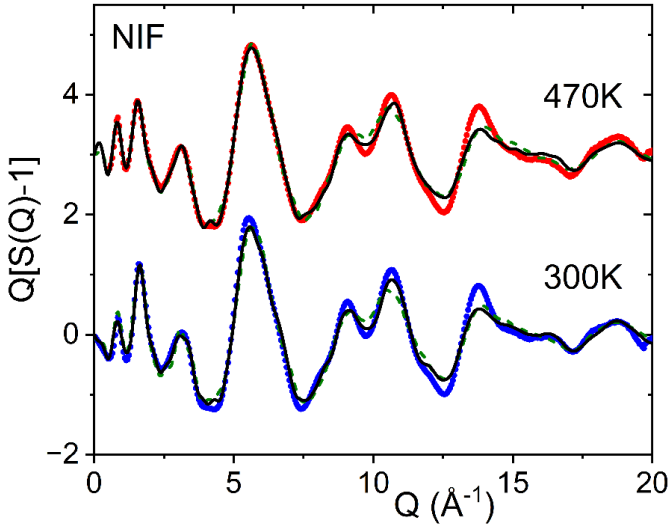


NIF POLYMORPHS

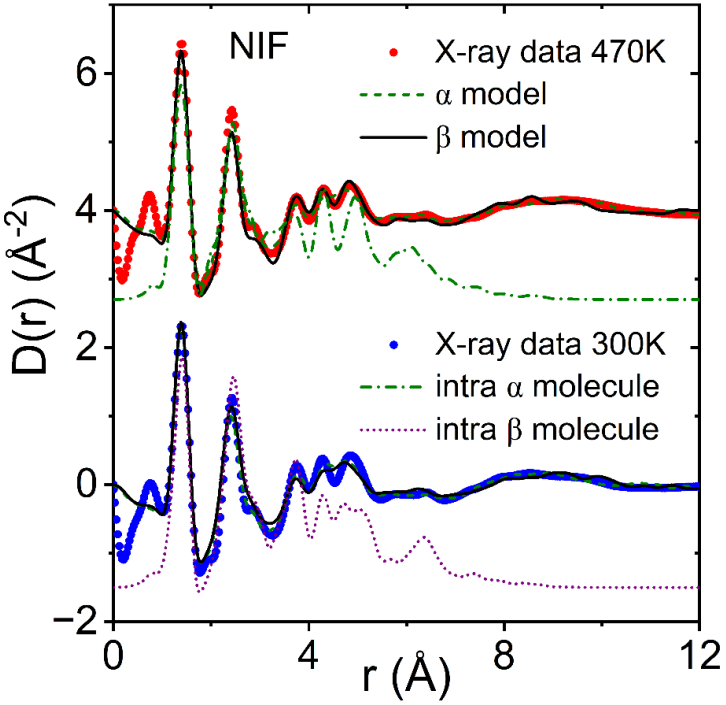
GLASSY NIFEDIPINE



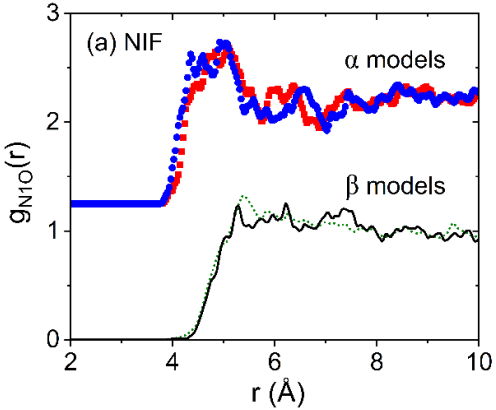
- CCD show NIF has six polymorphs. 10 conformers
- α-phase is the most stable and grows >120 °C
- <42°C liquid NIF turns to glass and its crystallizes to the β phase
- Models with α & β form conformations

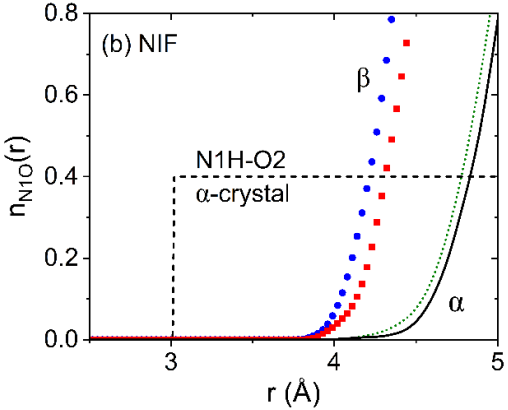


α & β NIF MODELS



- Better fits <6Å for β-conformation -consistent with DFT - predicts most crystal conformers have similar energies.
- Weak inter-molecular hydrogen bonds of the type N−H···O in both the α and β NIF polymorphs.

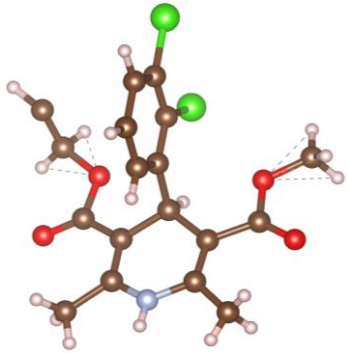




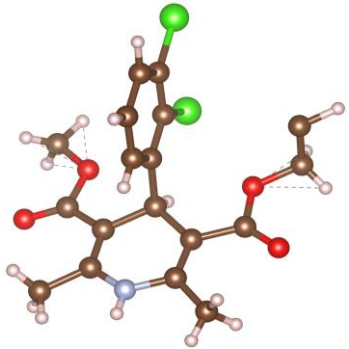
FELODIPINE (FEL) POLYMORPHS

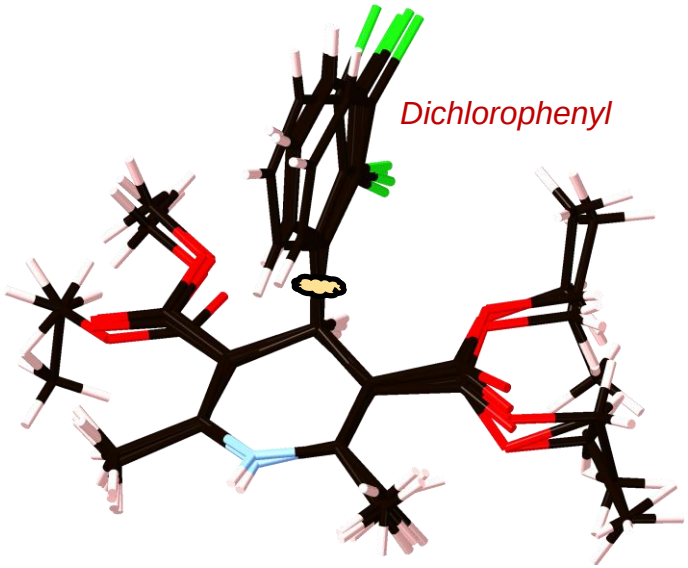
- FEL is a chiral drug with two enantiomers: R- & S-
- The R-enantiomer of FEL is more likely to cause adverse reactions than the S-enantiomer
- Form I is the most stable. Form II is metastable, has the highest solubility & dissolution rate. Both are racemic

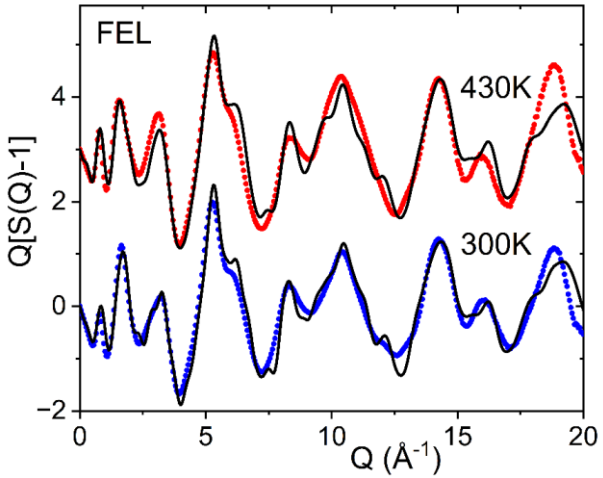
R-enantiomer (form I)



S-enantiomer (form II)

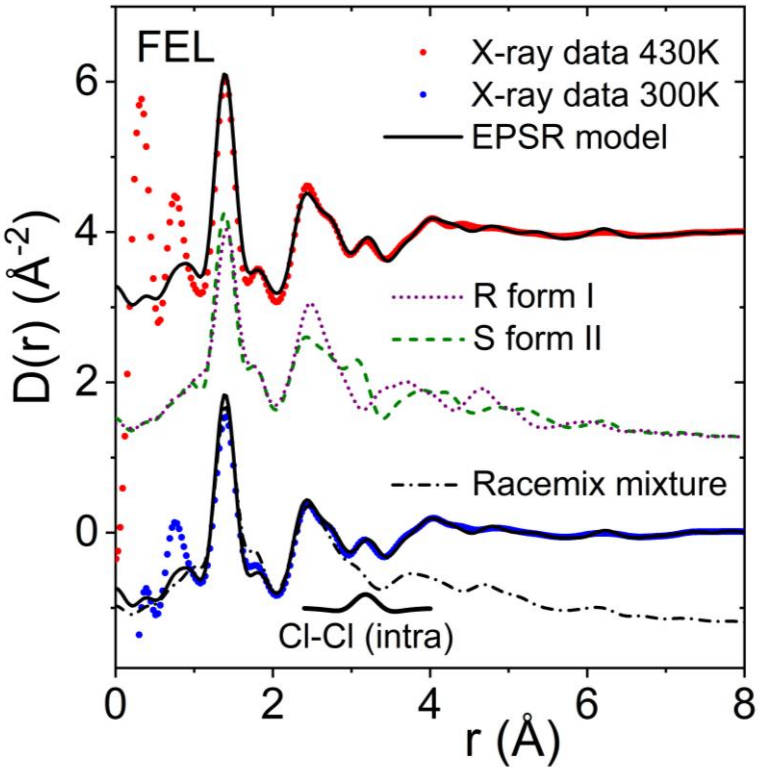




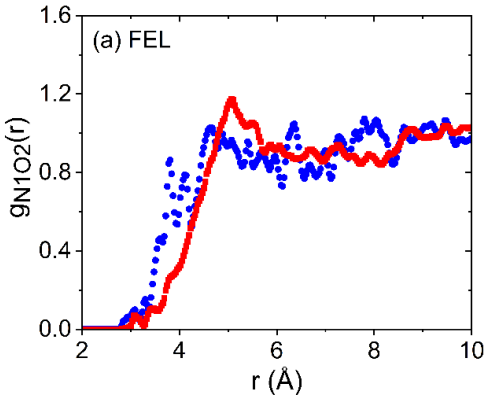


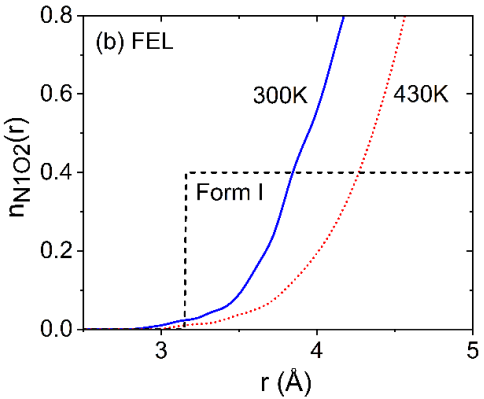
- Five polymorphs
- Use racemic mixture of R & S based on form I conformation
- T_m~417K & T_g=318K

RACEMIC FEL MODEL

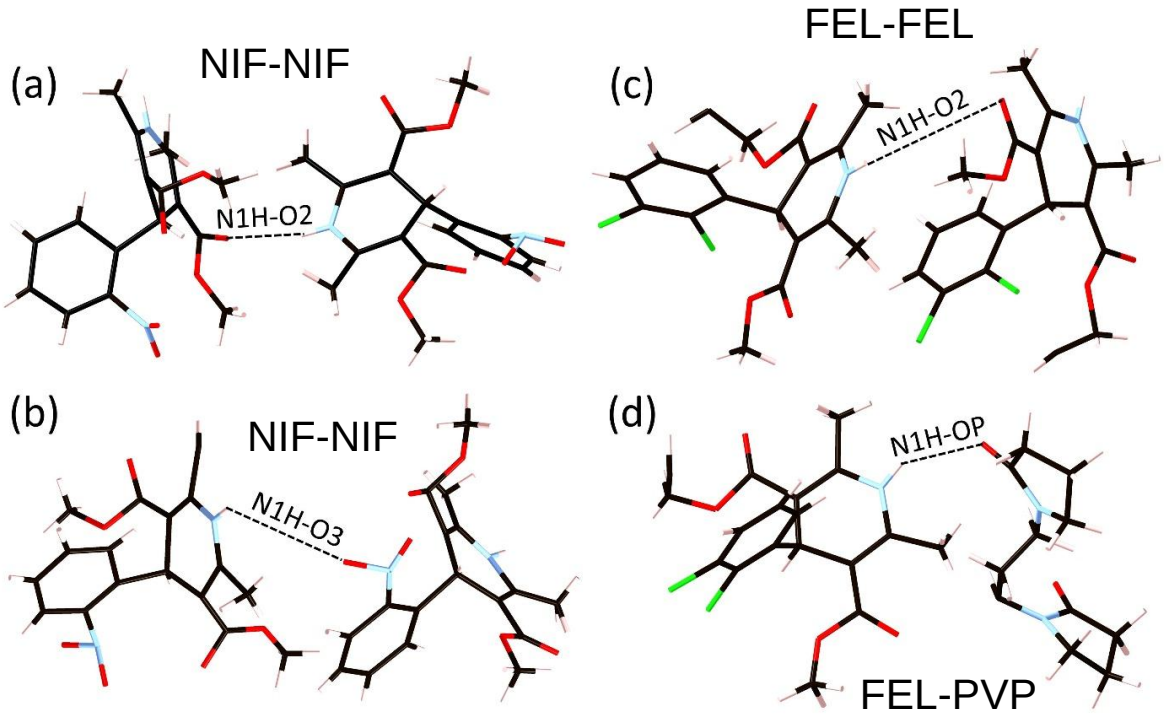


- Disorder in side chains between form I and form II reflected between enantiomers in 2nd peak in D(r)
- Previous X-ray PDF and DFT suggest extra intra-molecular alkoxy–Cl correlations at 3.0Å. Geddes *et al. Chem. Commun.*, 2019,55, 13346.
- Our EPSR shows 3.0Å distance corresponds primarily to *intra-molecular Cl-Cl pairs.*
- Slight shift corresponds to 4º change in ∠CCCl angle within the dichlorophenyl ring



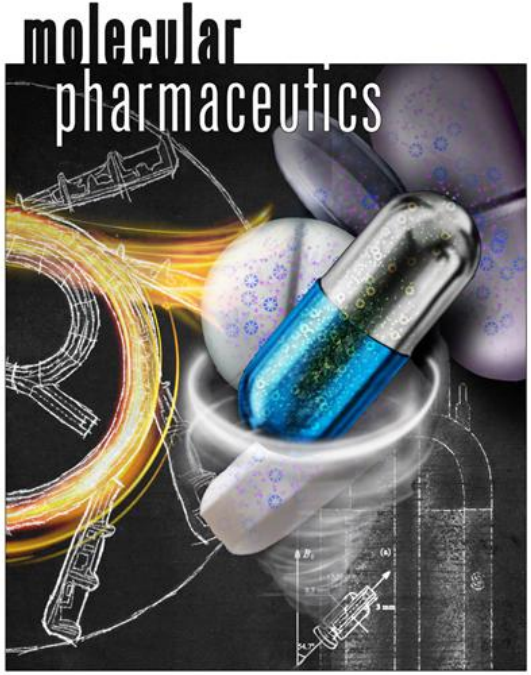


BONDING IN GLASSY NIF & FEL



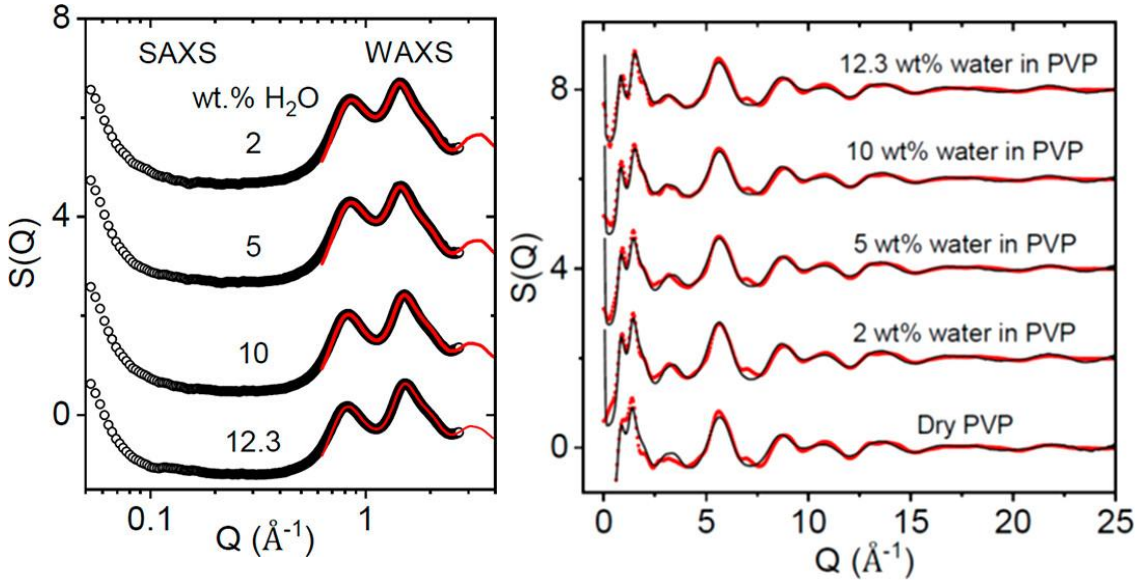
- Liquid and glassy NIF & FEL both have N1H-O2 hydrogen bonds
- **NIF also has similar number of N1H-O3 (nitro) hydrogen bonds – an interaction not observed in the crystal forms**
- FT-IR has previously suggested hydrogen bonding in the amorphous form of FEL is stronger than in crystal. Marsac *et al. Pharm Res*. 23 (2006) 2306.
- Not supported by EPSR
- Based on our EPSR models we suggest a peak re-assignment to “free” (non-hydrogen bonded) N-H stretching groups

AMORPHOUS SOLID DISPERSIONS

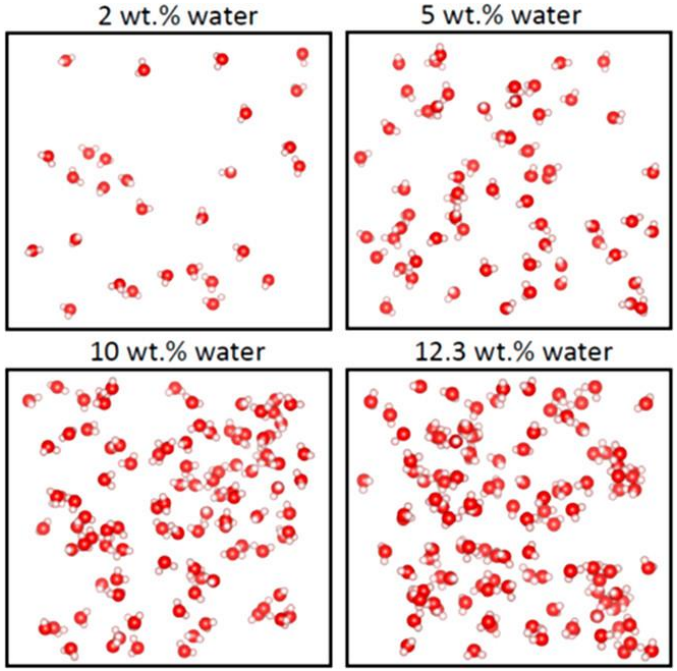


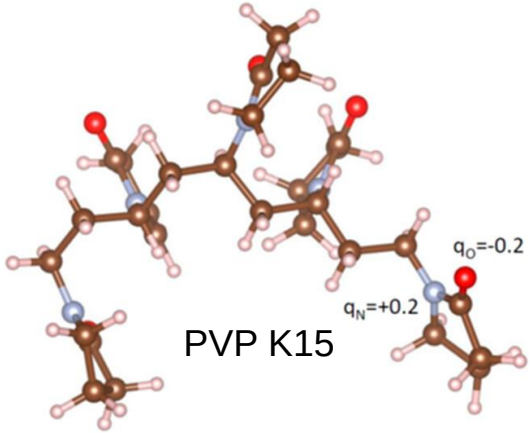
POLYMER “EXCIPIENT”

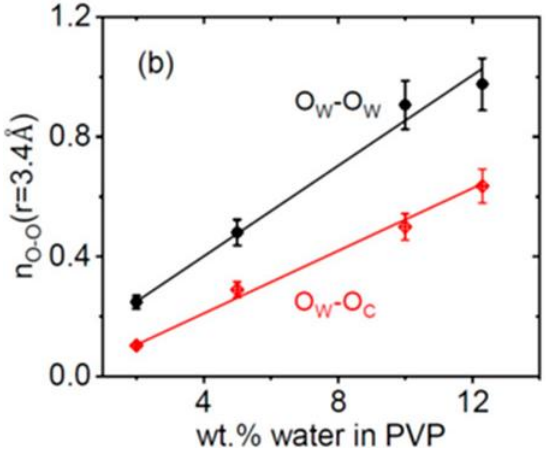
- PVP is a ***hydrophilic*** polymer commonly used as an excipient (inactive ingredient) in formulations
- In Amorphous Solid Dispersions, excipients inhibit crystallization (increase shelf life) and promote stability. Effectiveness depends on Tg, molecular mobility & API-polymer bonds
- Hydrogen bonding interactions between the API & excipient are often the main cause of the dissolution enhancement in the bloodstream



WATER IN PVP







- Water uptake depends on temperature and humidity. Don't store in the bathroom!
- EPSR shows linear relations between the water-water and water-polymer CN's versus water content in PVP.
- A stronger preference for water−water hydrogen bonding over water-polymer hydrogen bonding is found.

C.J. Benmore *et al. Mol. Pharmaceutics* 2023, 20, 7, 3645–3652

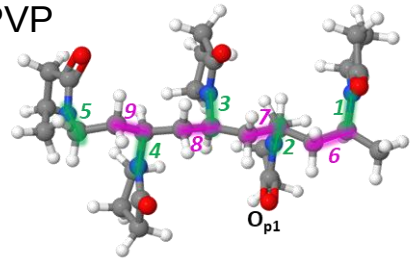
EPSR SENSITIVITY TO INPUT PARAMETERS

KETOPROFEN-PVP

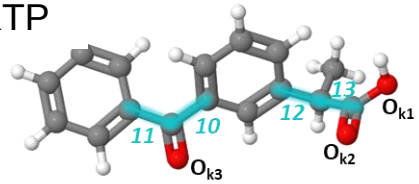
- Assess EPSR sensitivity to:
- Intramolecular bond rotations
- PVP molecule length
- PVP tacticity

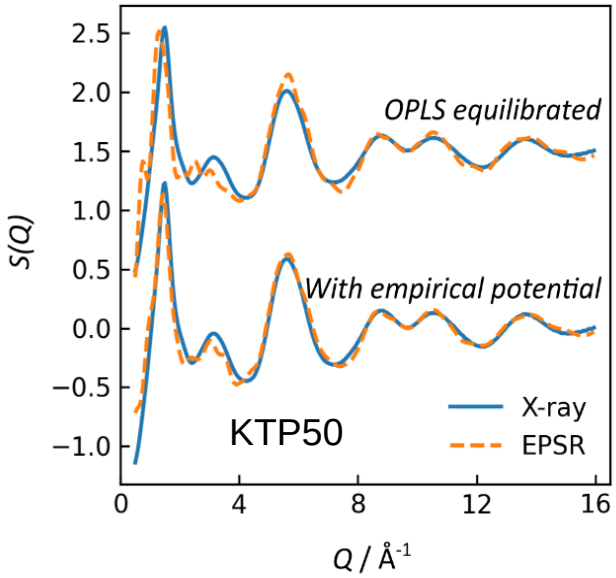
Simulation	Intramolecular rotations*	PVP length (# monomers)	PVP tacticity
A	none	5	syndio
B	2, 5, 8, 11, 12	5	syndio
C	1-5, 6, 8, 10-13	5	syndio
D	none	3	syndio
E	none	10	syndio
F	none	5	iso

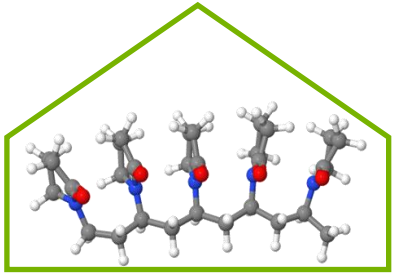
PVP



KTP

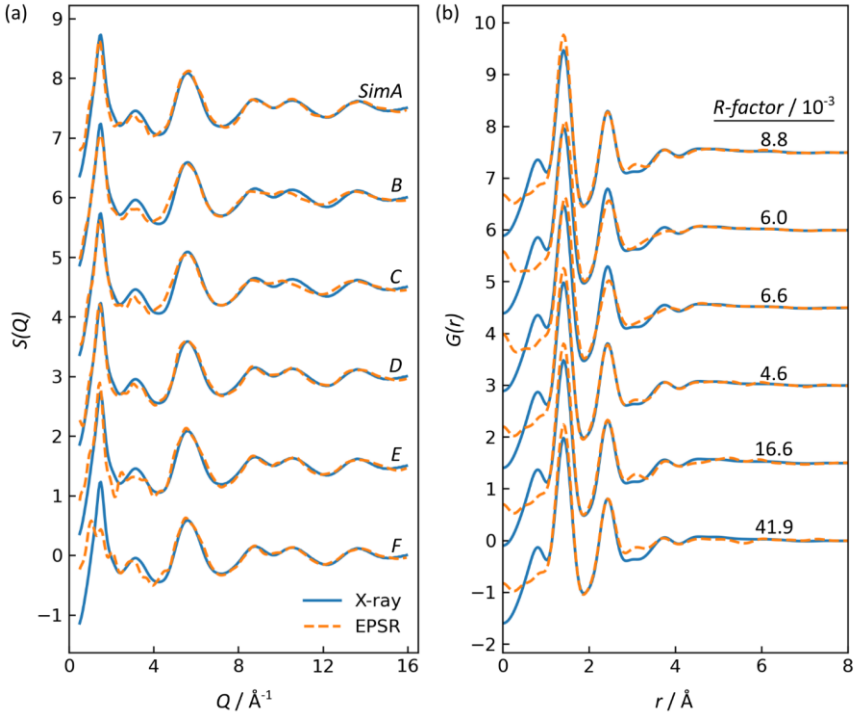






- Six simulations used to probe EPSR's sensitivity to different molecular inputs
- Includes 9.4 wt.% water

GOODNESS-OF-FIT COMPARISONS



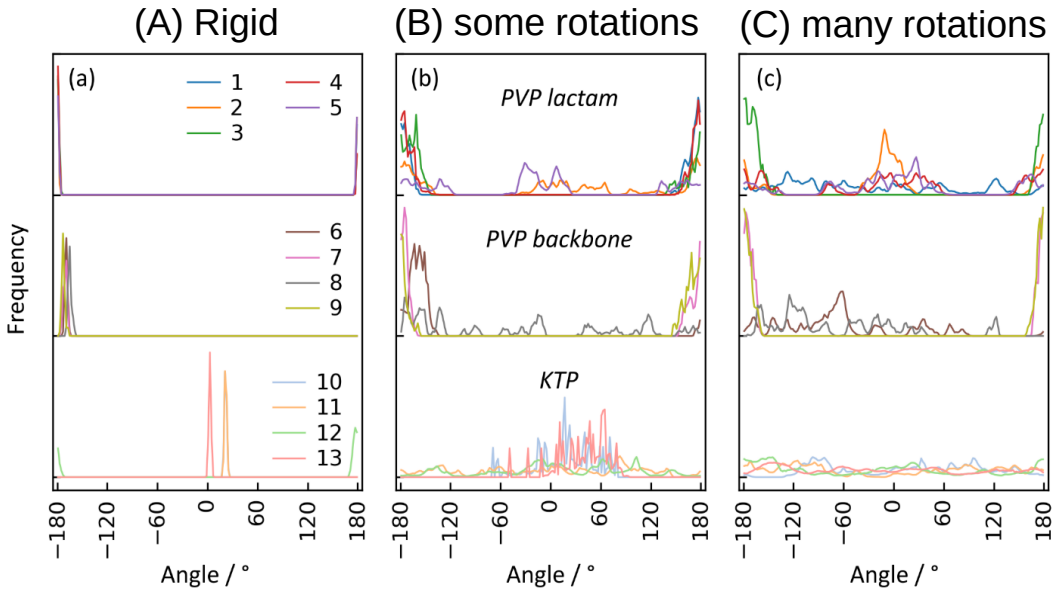
- *R-factors* indicate better goodness-of-fit in real space

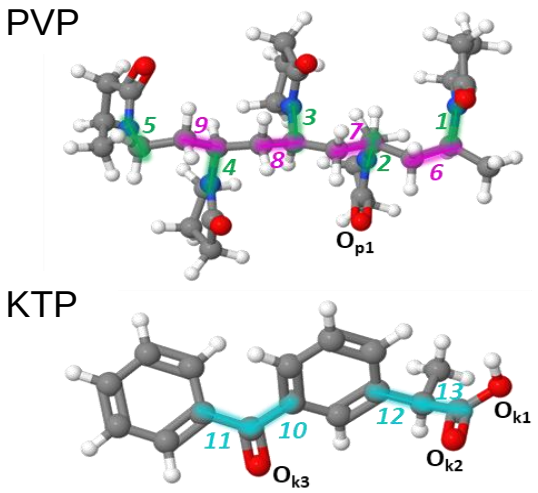
- A, B & C explore **bond rotations**:
- A has rigid molecules – good fit
- B & C have increasing numbers of bonds rotations – worse at high-Q (intra-molecular problems in PDF)

- A(5), D(3) & E(10) explored the effect of **PVP molecule length** – all rigid.
- *R-factors* decrease as the polymer length decreases.

- Pre-peak Q=0.85Å^{-1} from the PVP chain.
- First diffraction peak in *S(Q)* is best matched to (D) 3-monomer PVP
- F used rigid, 5-monomer, **isotactic PVP**, which yielded the worst match to X-ray data.

BOND DIHEDRAL ANGLE DISTRIBUTIONS

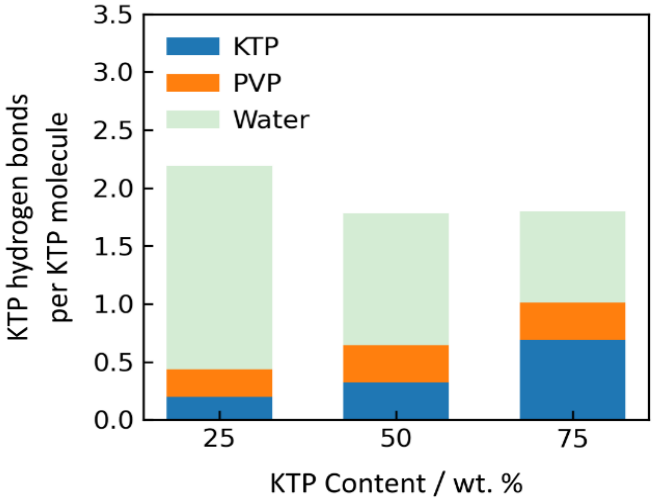


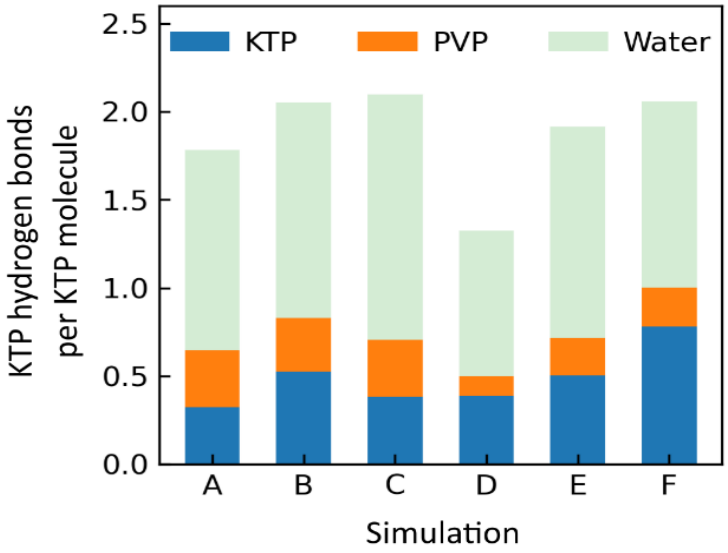


- EPSR allows a few degrees of bond rotation to simulate thermal motion.
- narrow dihedral angle distributions in A.
- Bond rotations enabled in B & C but interatomic potentials prevent intra-molecular overlap.
- When bonds rotate, either a few distinct angles are adopted due to steric hinderance e.g. purple 5 in B, or a nearly random distribution occurs e.g. blue 10 in C.

HYDROGEN BONDING INVOLVING KTP

- Hydrogen bonds are distinguished by the second molecule : KTP molecule, PVP, or water.
- (A) KTP molecule has 1.78 hydrogen bonds –majority are water bonds.
- All six simulations similar except (D) 3-PVP monomers





- The number of KTP-KTP hydrogen bonds increases (0.20 to 0.69) with drug loading.
- KTP-PVP hydrogen bonding is similar with composition – indicates reported instability of high drug loading ASDs likely due to a decrease in PVP's steric hinderance of the KTP molecules

Wilke *et al.* *Mol. Pharmaceutics* 2024, 21, 8, 3967–3978

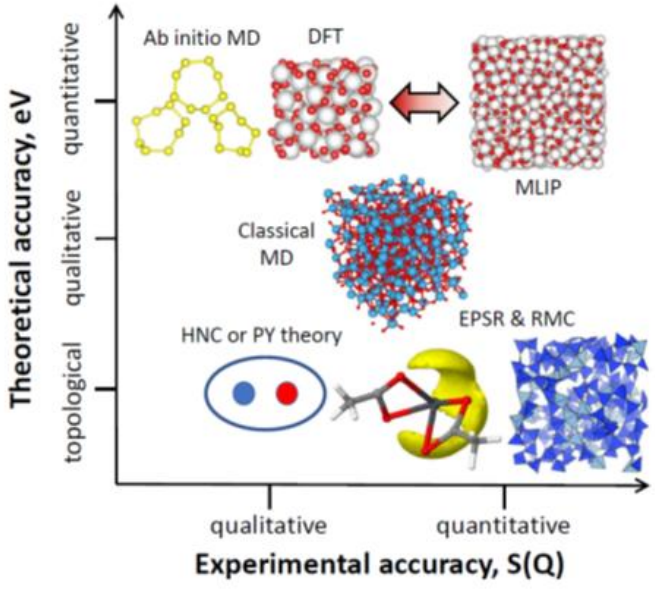
FUTURE DEVELOPMENTS

PROS & CONS

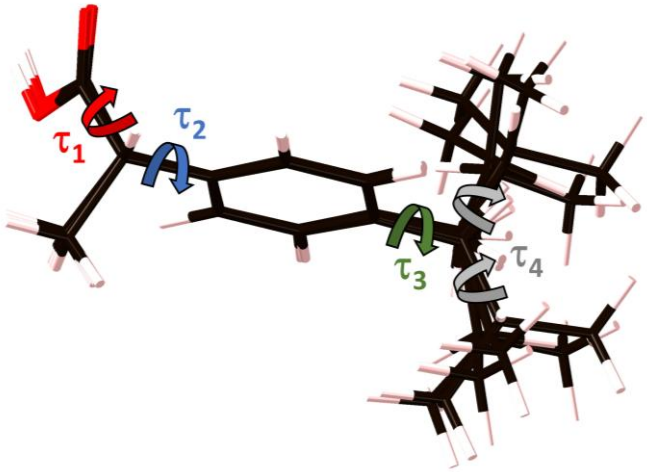
- EPSR is a powerful technique for investigating disordered structures – input knowledge from known polymorphs, NMR, vibrational spectroscopy and DFT calculations
- EPSR is not unique but ideal for testing different molecular conformation/bonding scenarios
- Main drawback is it's classical by nature- no quantum mechanics are included
- Both scientific and legal implications to this work. How to patent an Amorphous Solid Dispersion ?

- Ibuprofen is a flexible molecule with two polymorphs. Form I was discovered in 1974 and form II in 2010
- "Blind test" predicted form II crystal structure (6th)
- Francia *et al.* (2021) studied 555 possible crystal structures, optimizing both the molecular conformation and crystal structure, and found 205 viable structures!

FUTURE DIRECTIONS – MACHINE LEARNING



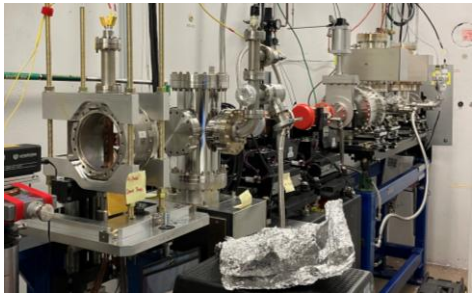
- *Deciphering diffuse scattering with machine learning…* G. Sivaraman & C.J. Benmore *J. Phys. Condens. Matt.* 36 (2024) 381501
- Experimentally Driven Automated Machine-Learned Interatomic Potential for a Refractory Oxide. Sivaraman… C.J. Benmore. *Phys. Rev. Lett.* 126 (2001) 156002



- Tested different combinations of torsional angles of rotation, τ_n, within the Ibuprofen molecule.
- Quantum chemical calculations based on machine learning interatomic potentials (Rowan software) were performed on the Ibuprofen molecule and found six likely conformers – EPSR input
- Rowan tools do not possess long range forces needed for polymer reactivity, complex melts.


Argonne
NATIONAL LABORATORY
Advanced
Photon Source

High Energy Bent Double Laue Monochromator

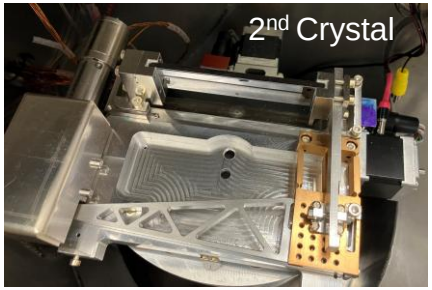


White beam slits

Canted undulators
~35m upstream

2mm CVD
diamond
4mm Al filters

1st Crystal in
liquid bath of
Ga-In-Sn

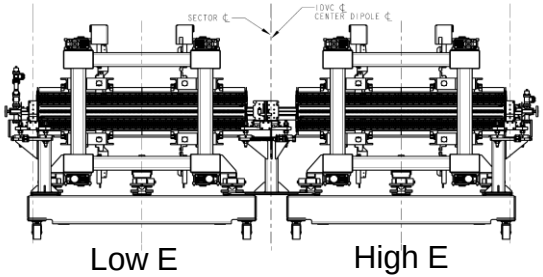


311 (50-95keV)
331 (70-125keV)

600 mm Horiz.

6-ID-B,C (3-30 keV)

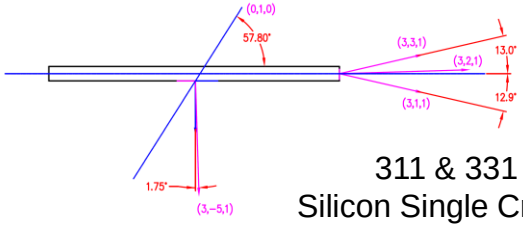
25mm Vert.



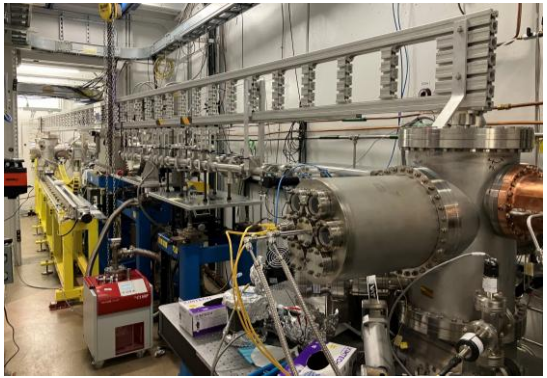
Low E High E

6-ID-B,C
Bragg Monochromator

6-ID-D
Laue-Laue Monochromator



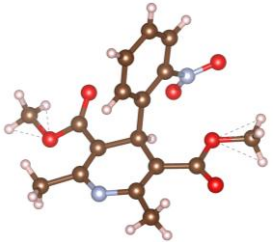
311 & 331
Silicon Single Crystal



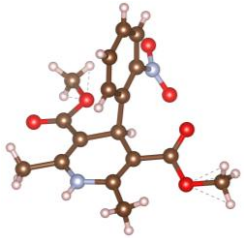
NIFEDIPINE (NIF) POLYMORPHS

- CCD shows NIF has six polymorphs. α-phase is the most stable and grows >120 °C
- <42°C liquid NIF turns to glass and its crystallizes to the β phase

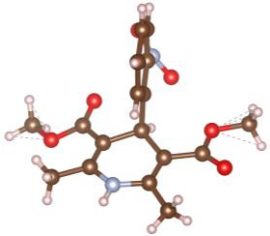
β 100K
BICCIZ02



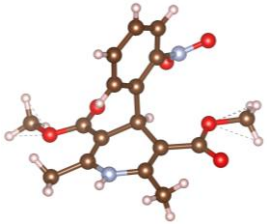
β 296K
BICCIZ03



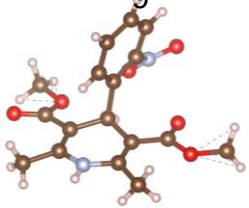
α 297K
BICCIZ07



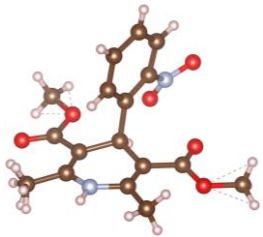
β' 338K
BICCIZ08



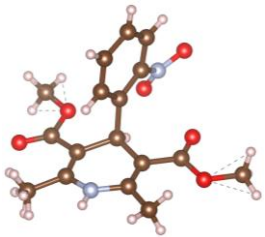
γ 100K
BICCIZ0
9



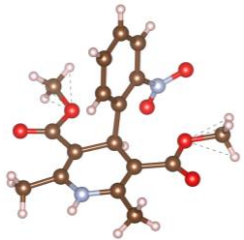
γ' 296K
BICCIZ10



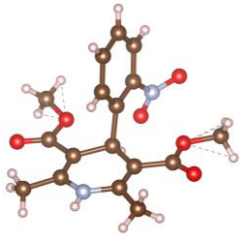
γ' 250K
BICCIZ11



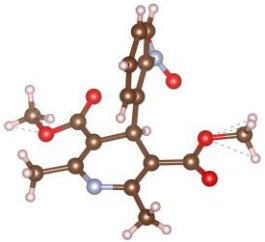
δ 100K
BICCIZ12



δ 293K
BICCIZ13



α 100K
BICCIZ14

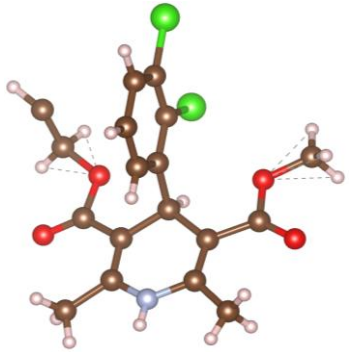


Gui *et al. Cryst. Growth Des*. 2022, 22, 1365.

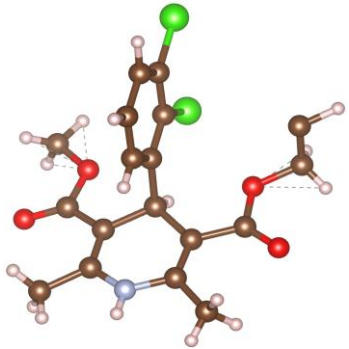
FELODIPINE (FEL) POLYMORPHS

- FEL is a chiral drug with two enantiomers: R- & S-
- The R-enantiomer of FEL is more likely to cause adverse reactions than the S-enantiomer
- Interchange of the methyl and ethyl chains inverts the chirality of the molecule
- Form I is the most stable and racemic
- Form II is metastable, has the highest solubility & dissolution rate

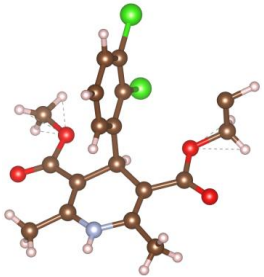
R-enantiomer



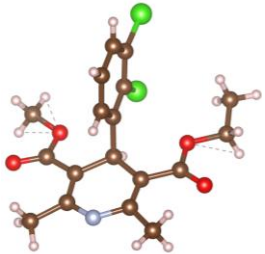
S-enantiomer



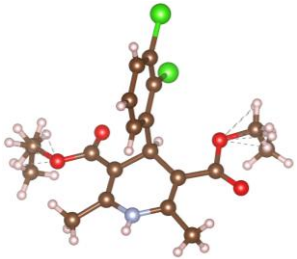
Form I
DONTIJ



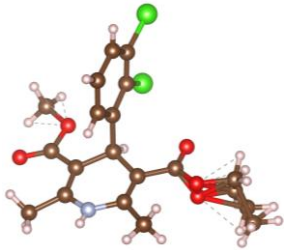
Form II
DONTIJ01



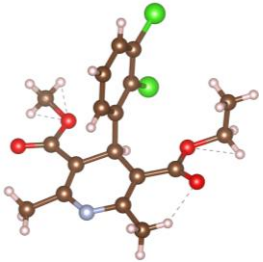
Form III
DONTIJ02



Form IV
DONTIJ11



Form V
DONTIJ06



Surov *et al. Cryst. Growth Des*. 2012, 12, 4022.