Decreasing Time-to-Market via Synchrotron Utilization to Discover Stable Formulation

Focus on Finding a Solid Form that will Increase Exposure

Improved Pharma

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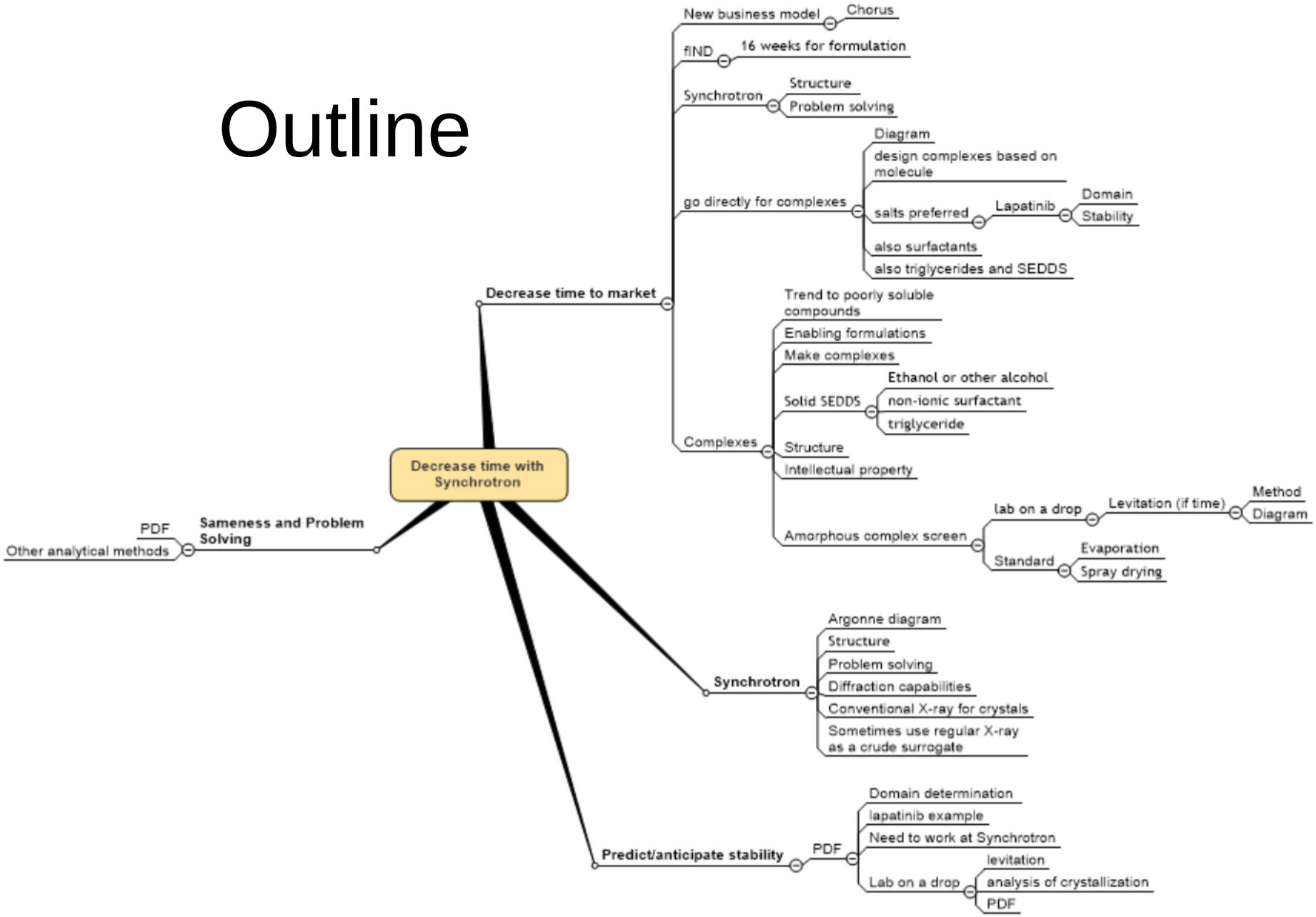
Outline



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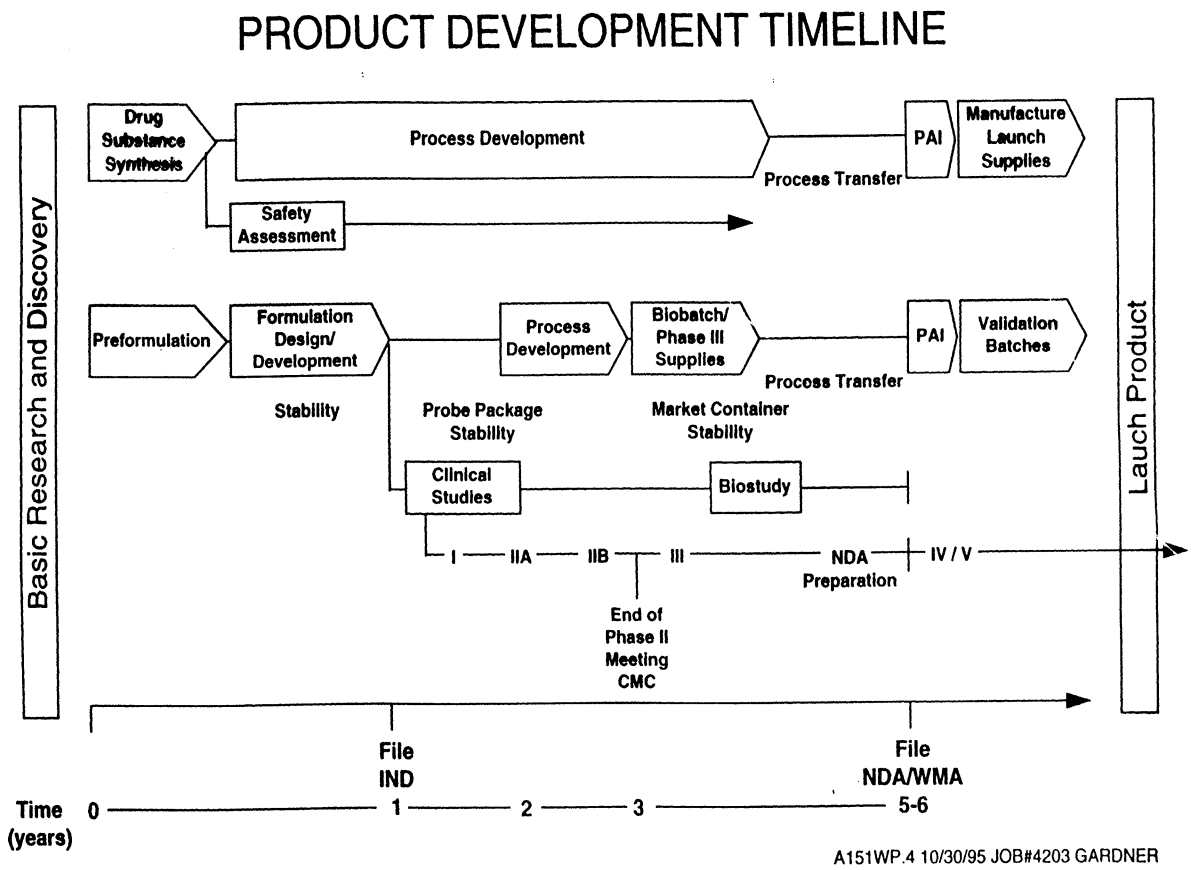
Outline

- Decrease time to market
  - fIND
  - Synchrotron
  - Amorphous complexes
- Predict/anticipate stability
  - Synchrotron
- Sameness and problem solving
  - Synchrotron

DECREASE TIME TO MARKET

Classical New Drug R&D



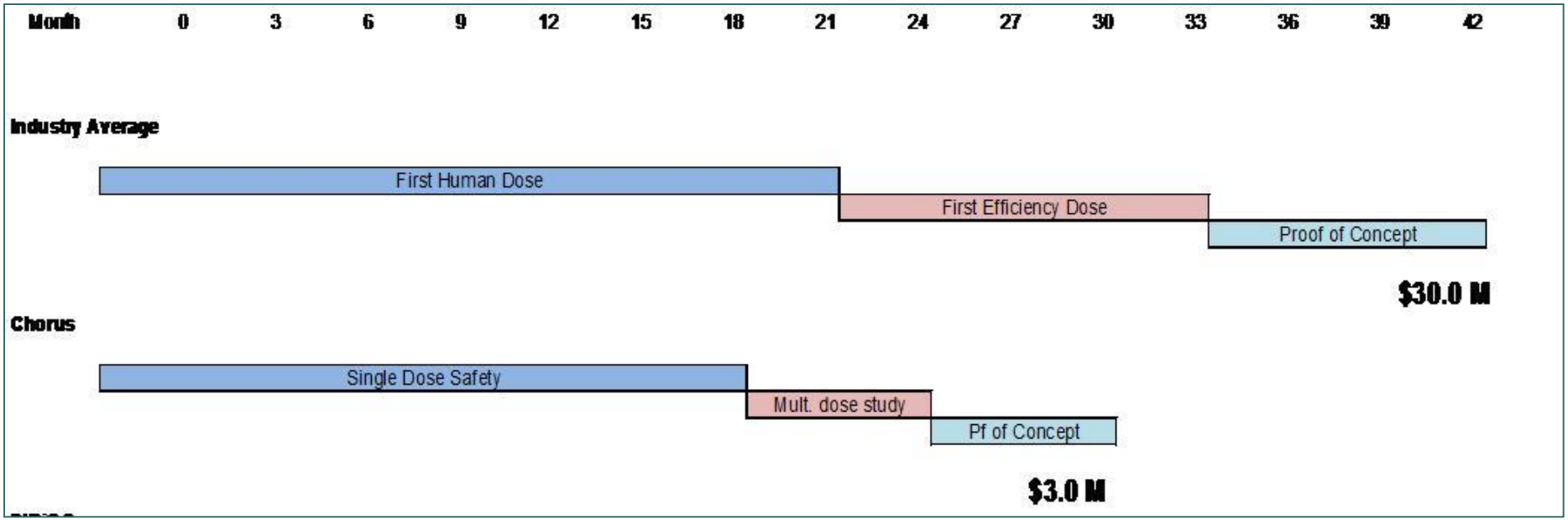
Expensive, long, risky, highly regulated

8-10 years development

Billion dollar development cost for a new drug

Chorus Timeframe & Costs

- Timeframe (Chorus)
  - Ind. Av.: 42 mo.
  - Chorus: 30 mo.
- Costs (Chorus)
  - Ind. Av.: $30M
  - Chorus: $3M



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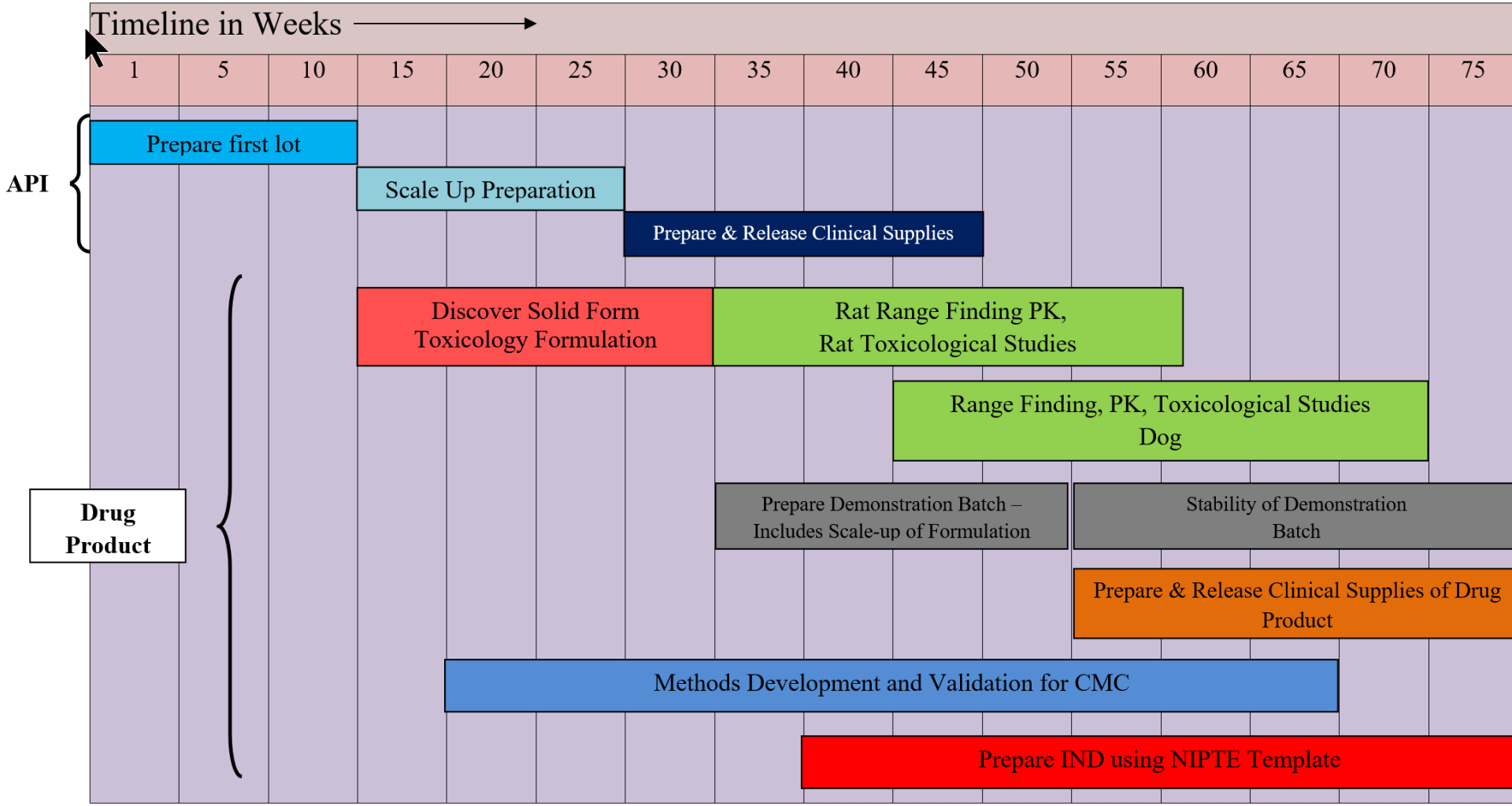
New Business Model

- Accelerating Proof-of-Concept Study
  Phase I and Phase IIa
- Make amorphous complexes of most candidates for accelerated toxicology and early animal studies
- Faster turnaround, more opportunities

fIND Strategy – Improved Pharma



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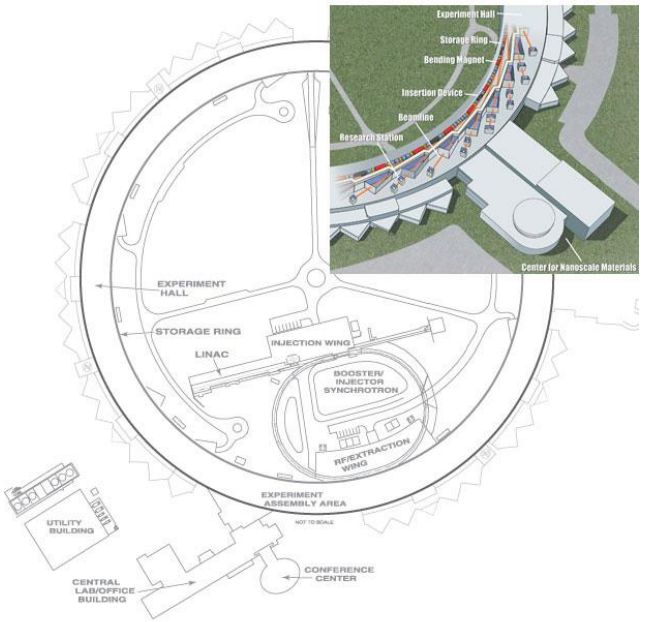
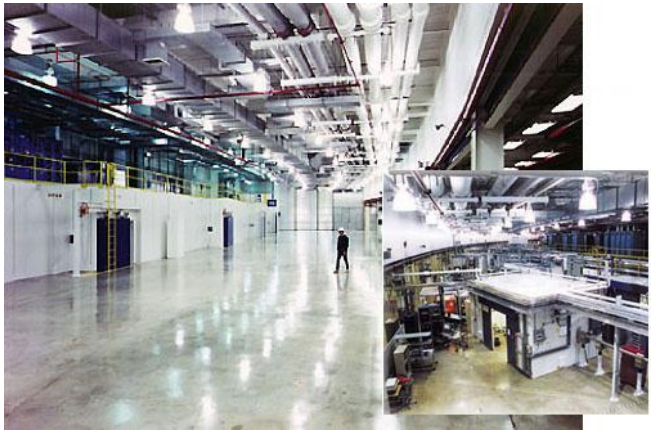
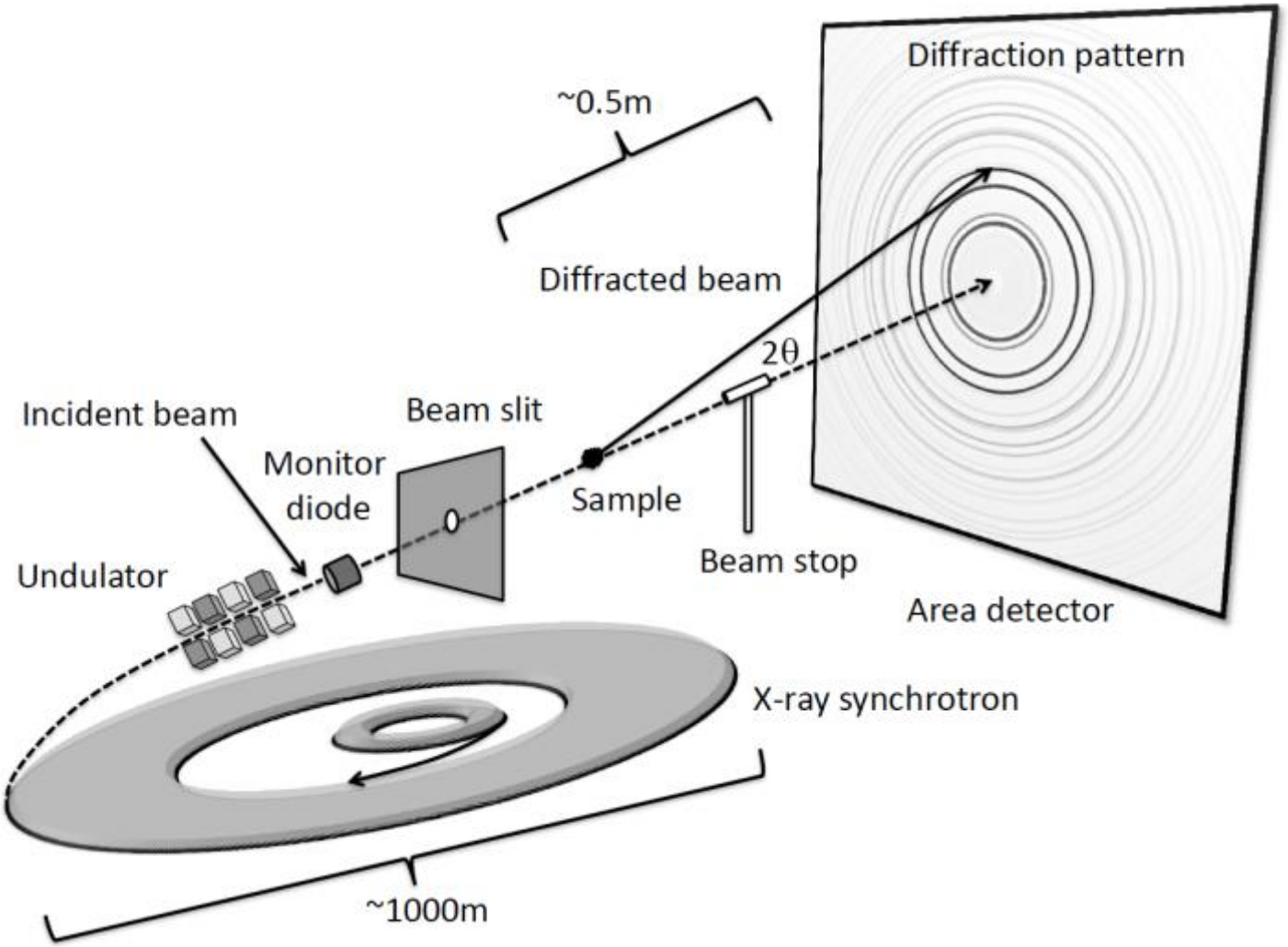
SYNCHROTRON

The Advanced Photon Source





Synchrotron high energy x-ray experiment



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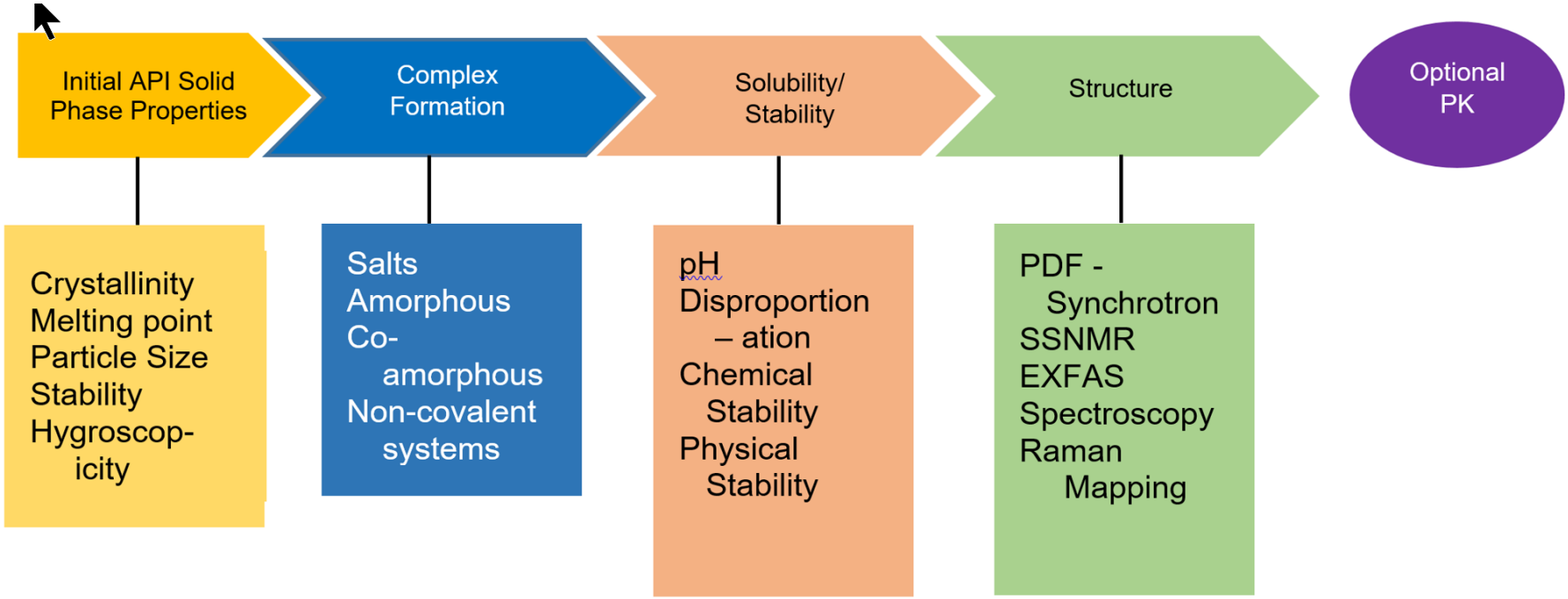
Resources

- Advanced Photon Source (Argonne)
  - Chris Benmore
- National Synchrotron Light Source (Brookhaven)
  - Simon Billinge
- Swiss Light Source (Paul Scherrer Institute)
  - Excelsus Structural Solutions

GO DIRECTLY TO COMPLEXES

Amorphous Complex Strategy



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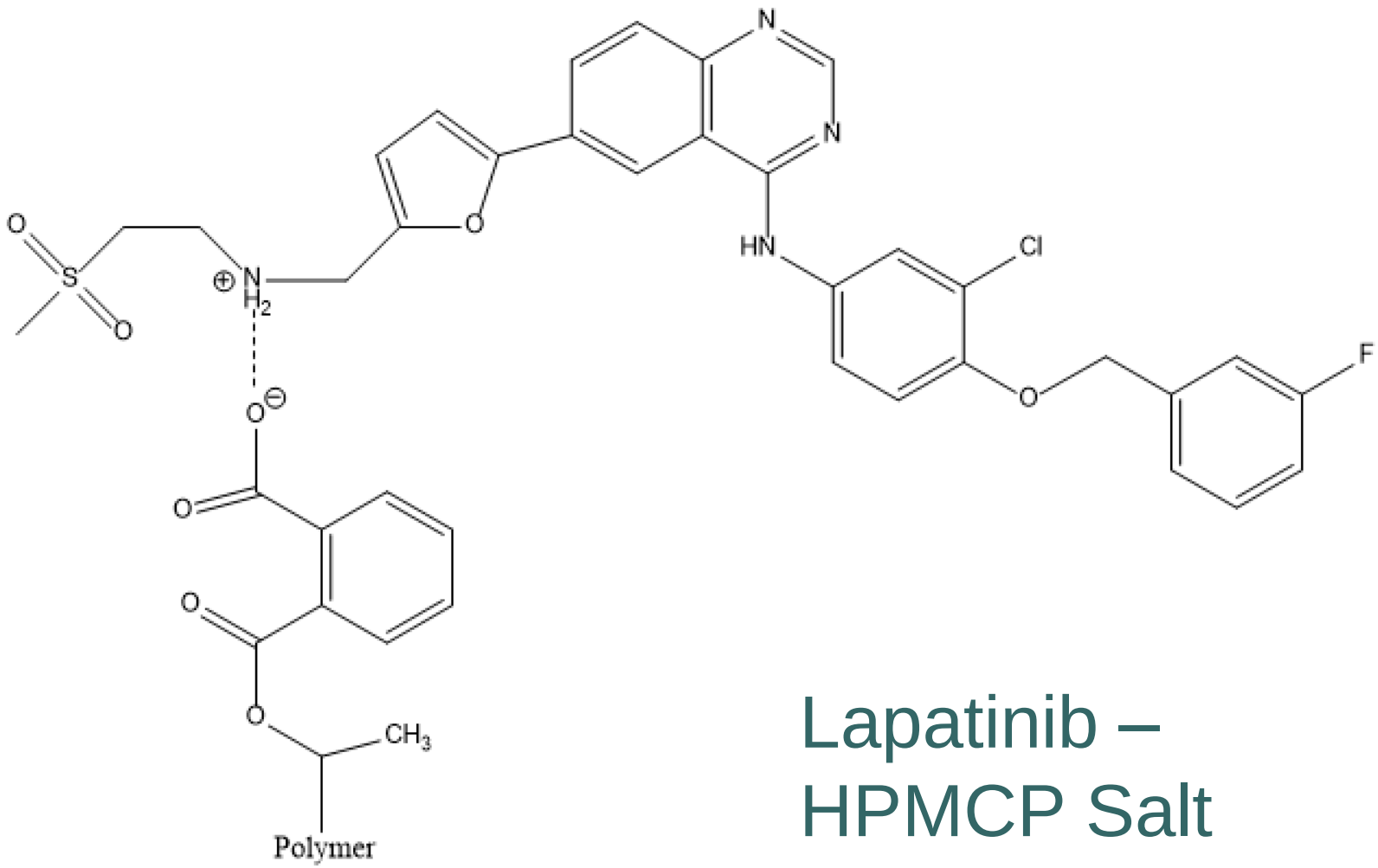

Lapatinib – HPMCP Salt Complex

Solid SEDDS-like Formulation

- Drug
- Alcohol
- Non-ionic surfactant
- Triglyceride
- Example - Ritonavir

Ritonavir + surfactants + polymers

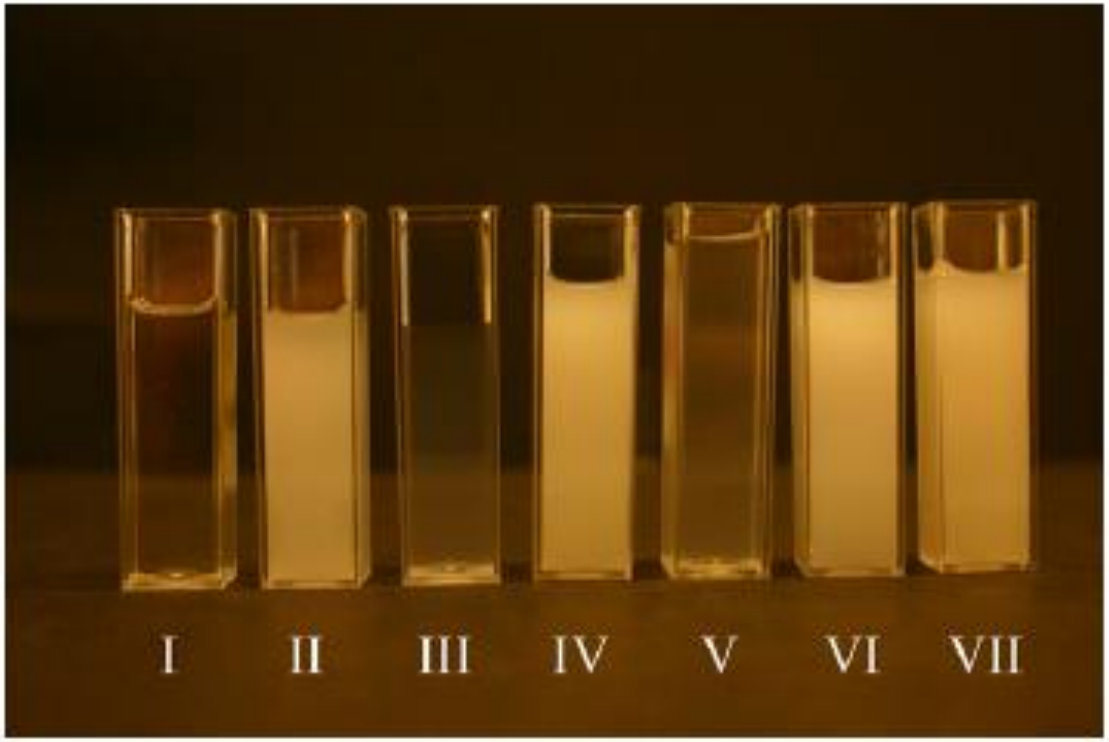

Fig. 5. Turbidity of dispersions of components in ritonavir extrudate; concentrations corresponding to ritonavir extrudate equal to 0.5 mg/mL ritonavir in water at pH 7. I, copovidone; II, sorbitan monolaurate; III, fumed silica; IV, copovidone + sorbitan monolaurate; V, copovidone + fumed silica; VI, sorbitan monolaurate + fumed silica; VII, copovidone + sorbitan monolaurate + fumed silica.

Only the complexes give a nano-suspension

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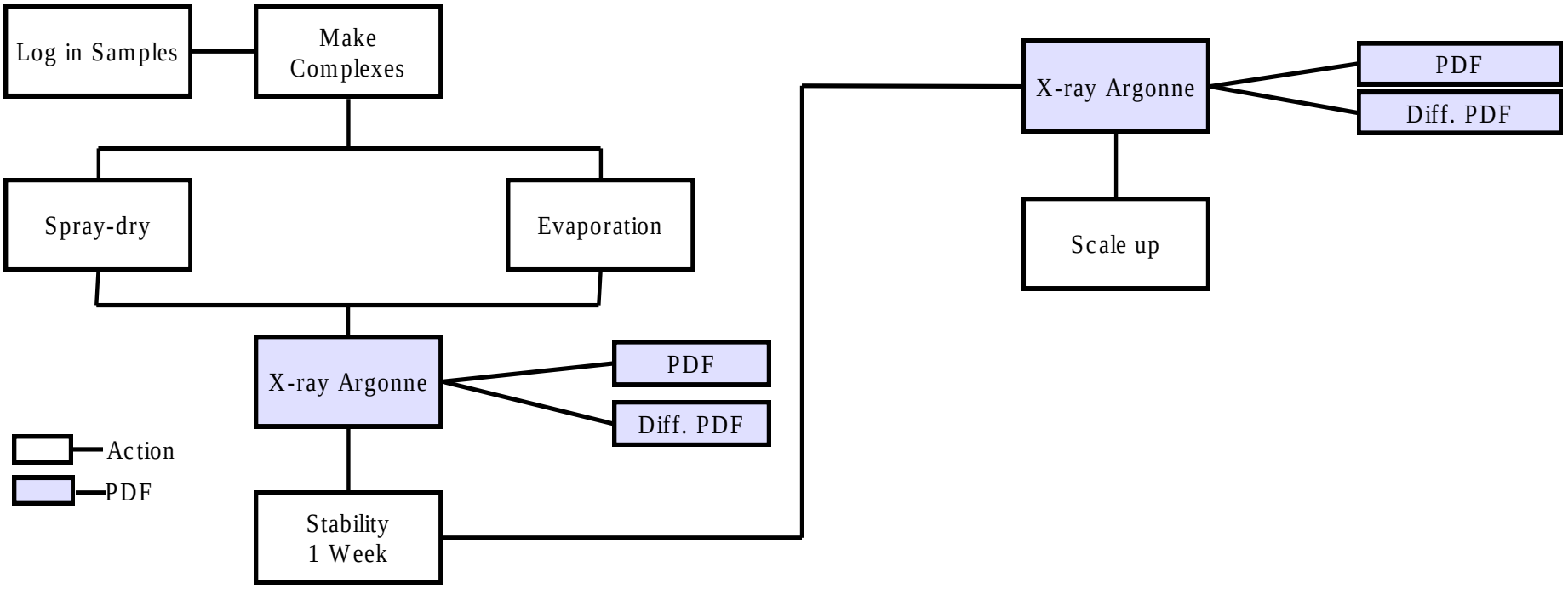
I. Tho et al. / European Journal of Pharmaceutical Sciences *40 (2010) 25–32*

Amorphous Complexes



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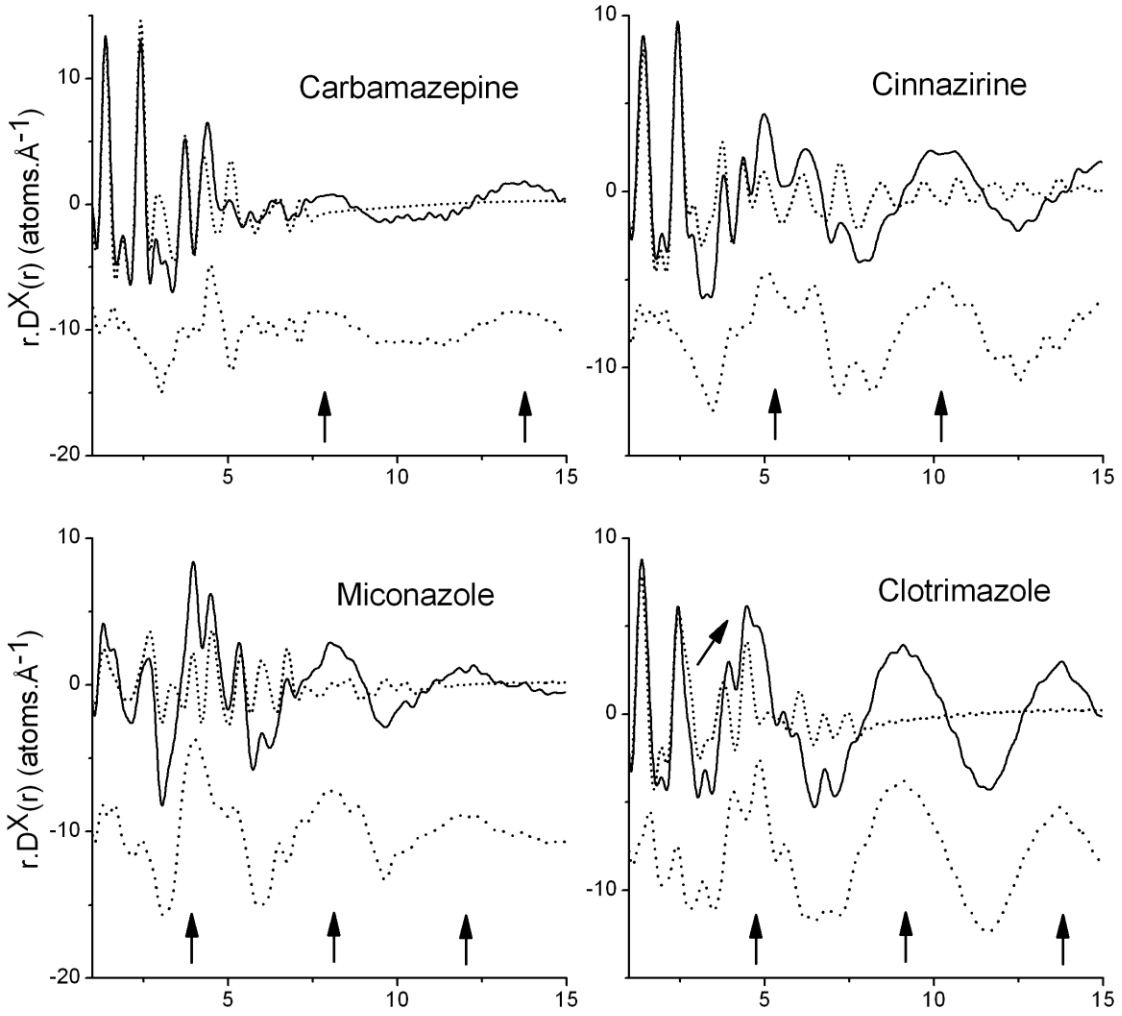
Design Complexes

- Utilize structural knowledge of drug and excipients
- Utilize literature on solid SEDDs formulations
- Utilize literature on hydrogen bonding
- Utilize solution NMR to test association and chemical shift changes

SYNCHROTRON

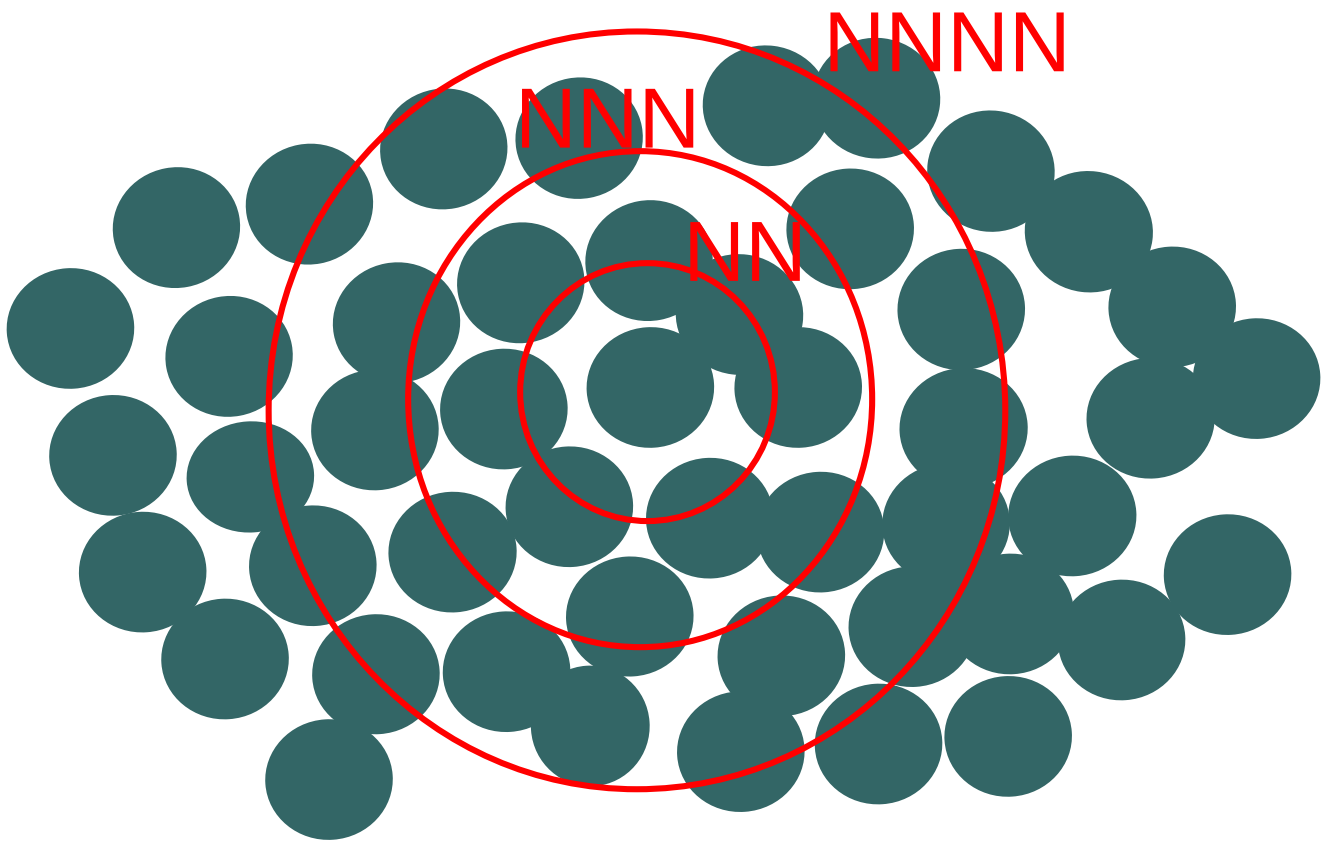
PDF Structure Analysis – Domains in Drug Amorphous Preparations



Arrows Represent Nearest Neighbor (NN) and NNN and NNNN Contacts

Benmore, Byrn, et a., Journal of Pharmaceutical Sciences (2013), 102(4), 1290-1300.

Neighbors in Amorphous Systems



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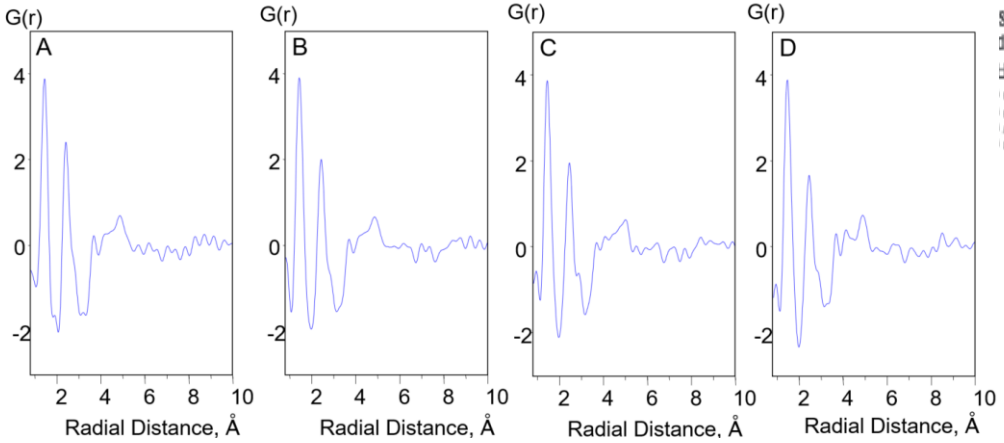
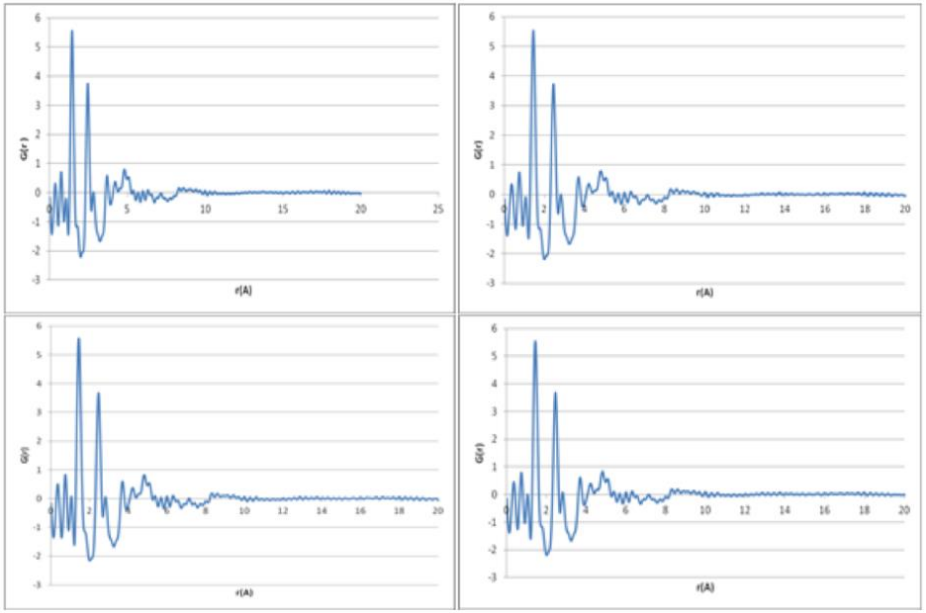
Need to Work at a Synchrotron for PDF



Stability and comparability of an amorphous drug prepared by different spray drying processes: atomic Pair-wise distribution functions (PDF) using conventional X-ray diffraction versus high energy synchrotron radiation

Hector Novoa de Armas[1], Marcus Brewster[1], Detlef Beckers[2], Milen Gateshki[2], Chris Benmore[3], Stephen Byrn[4]

[1] Pharmaceutical and Material Sciences, Johnson & Johnson Pharmaceutical Research & Development, a division of Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse, Belgium
[2] PANalytical B.V. Lelyweg 1 (7602 EA) PO Box 13, 7600 AA, Almelo, The Netherlands
[3] Argonne National Laboratory, 9700 S. Cass Ave, Argonne, IL 60439, USA
[4] Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA



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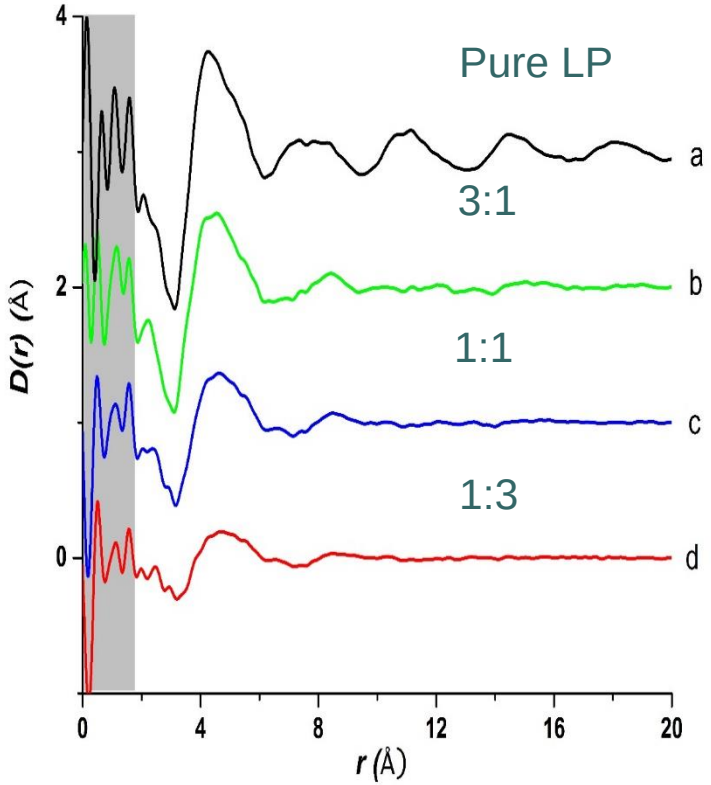
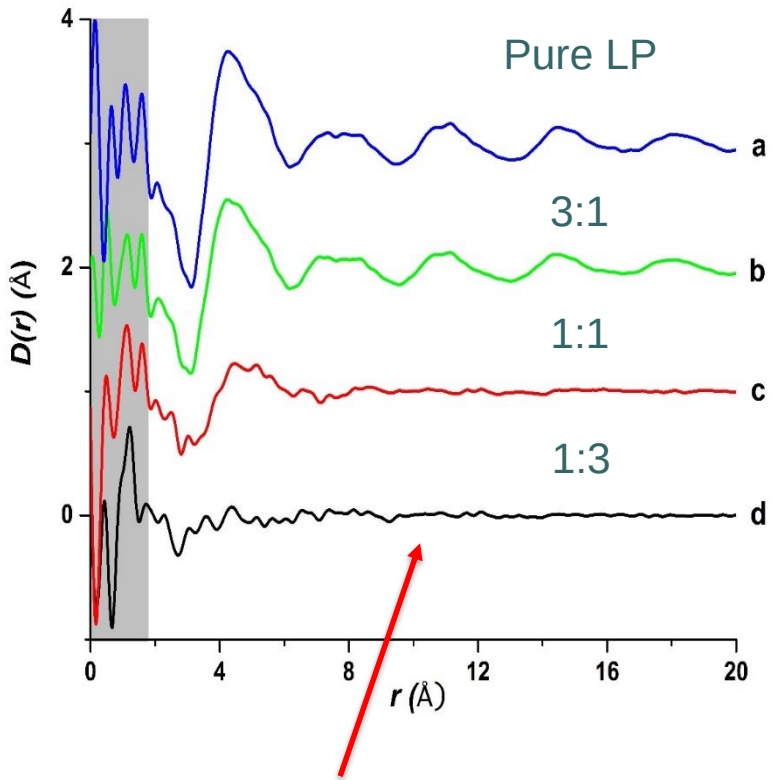
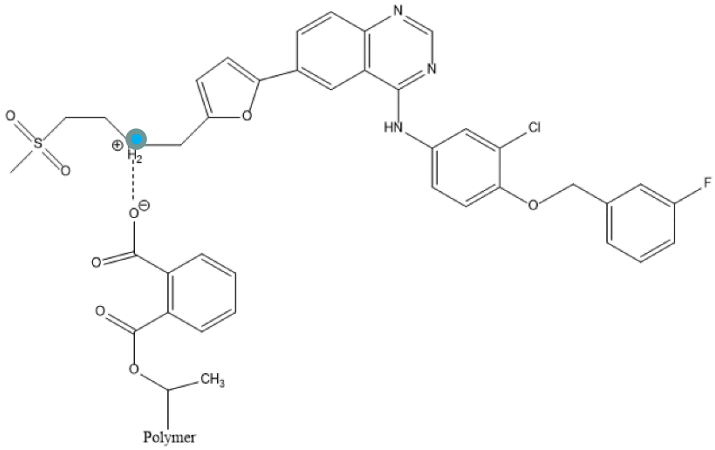
Lapatinib PDF – Left HPMC, Right HPMCP - Differential PDFs are Shown

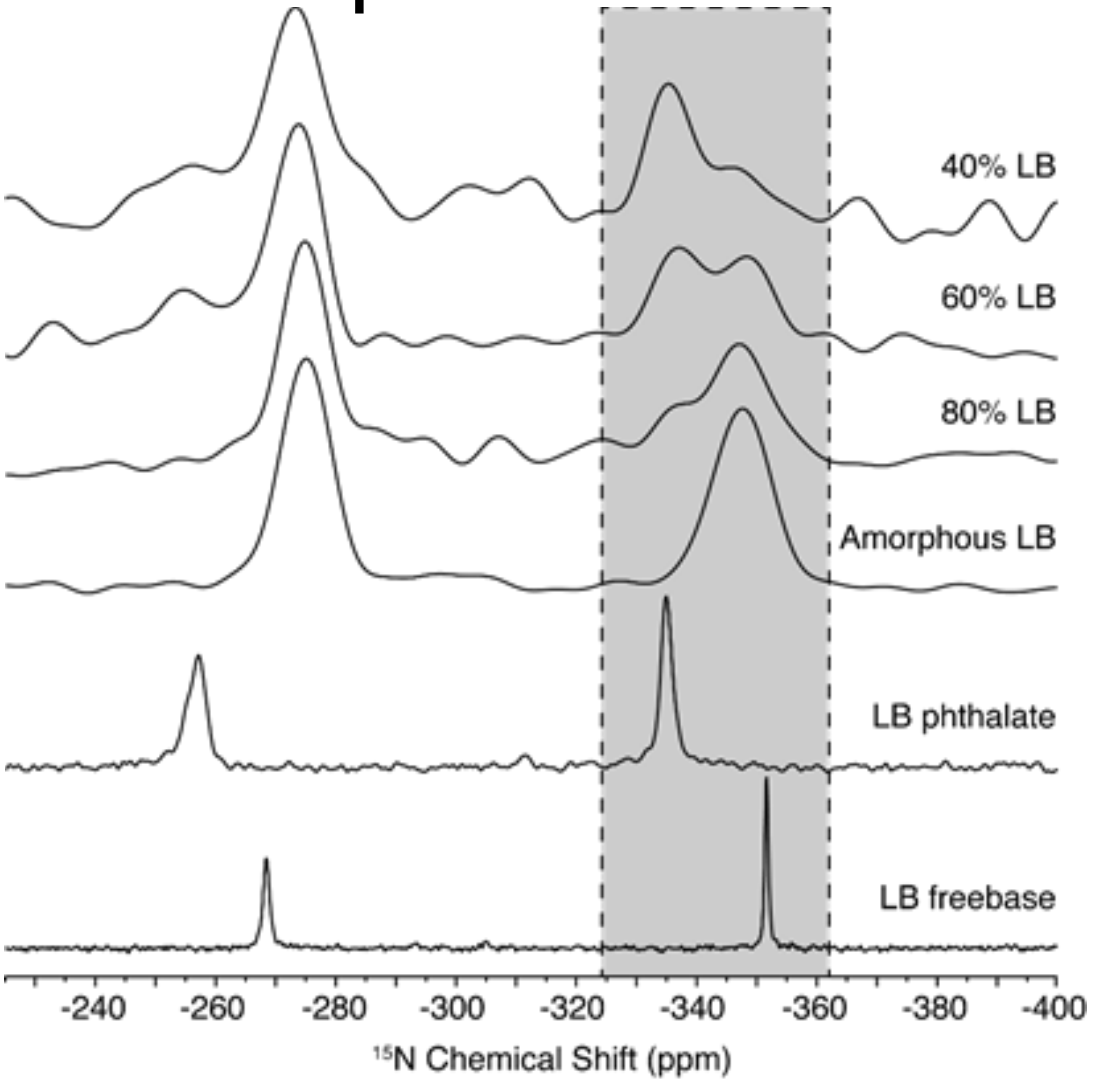




This is the only dispersion lacking domains

N-15 SSNMR of Lapatinib with HPMCP





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SYNCHROTRON “LAB ON A DROP” TO SAVE MATERIAL

Levitation Equipment

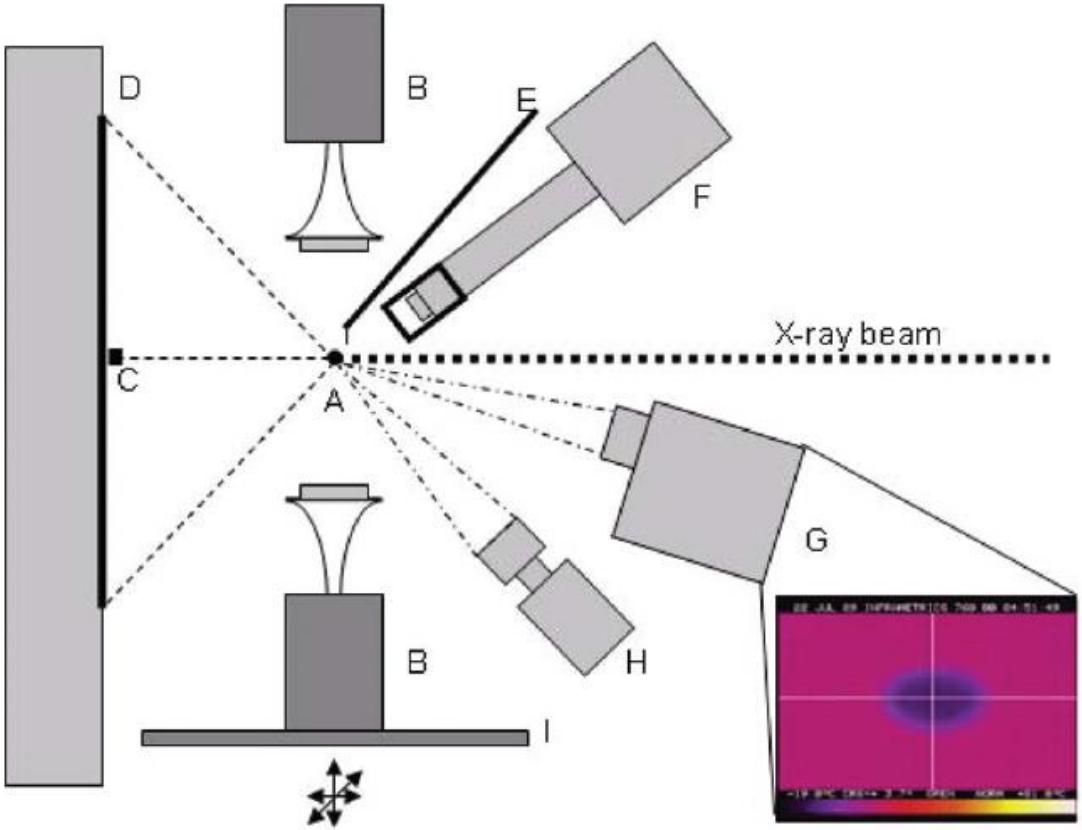
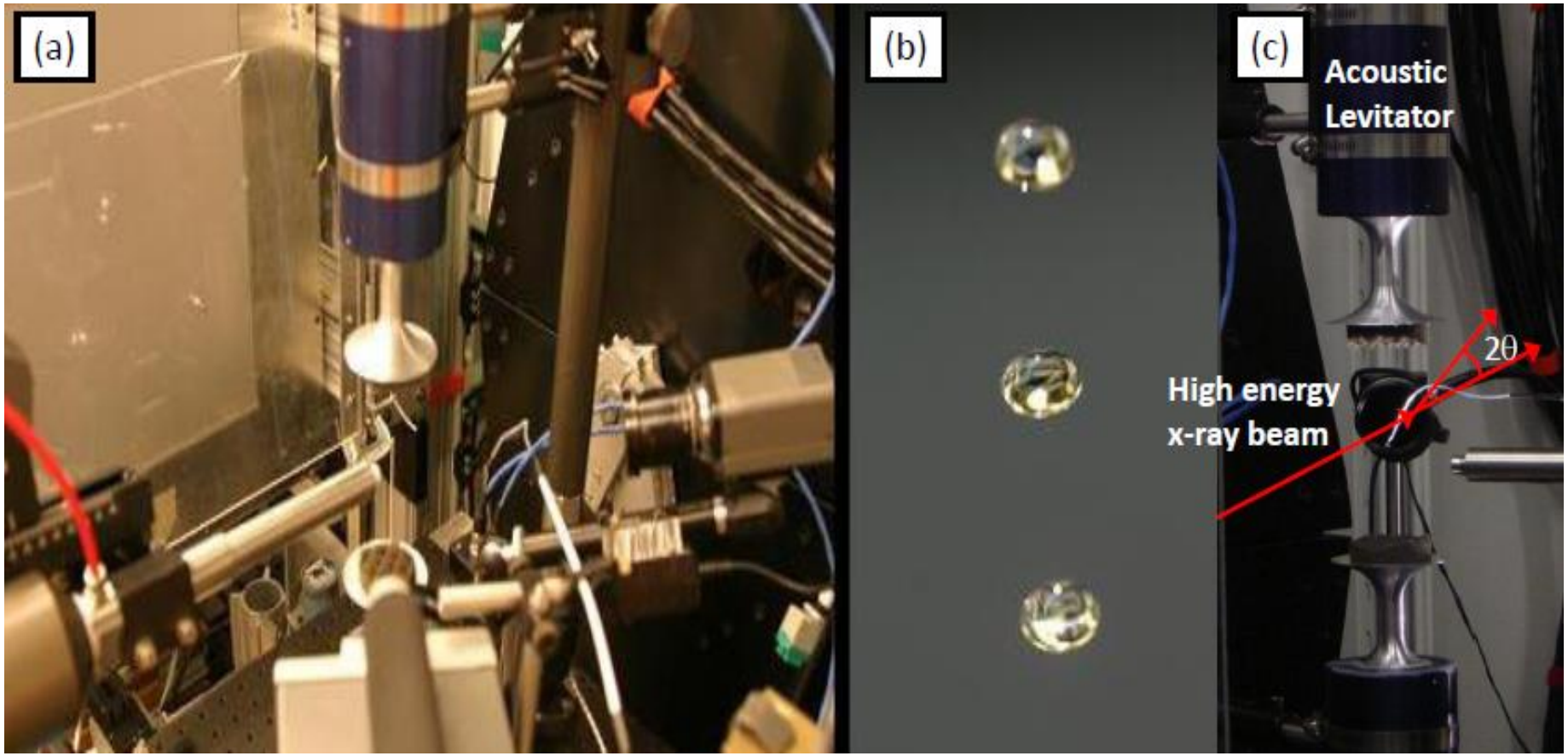


Figure 1. Schematic setup. A, sample; B, transducer (two); C, tungsten X-ray beam stop; D, Perkin-Elmer X-ray area detector; E, thermocouple; F, modified Cryostream plus with additional gas heater; G, infrared thermal imaging camera (insert: typical image); H, video camera; I, base plate mounted on a precision motor-driven $X-Y-Z$ translation stage.

Amorphous Screen Using Levitated Drops

http://www.youtube.com/watch?v=669AcEBpdsY

Levitation Equipment on Beamline 11-ID-C



Each drop contains about 0.1 mg of drug

(assuming solubility = 10 mg/mL)

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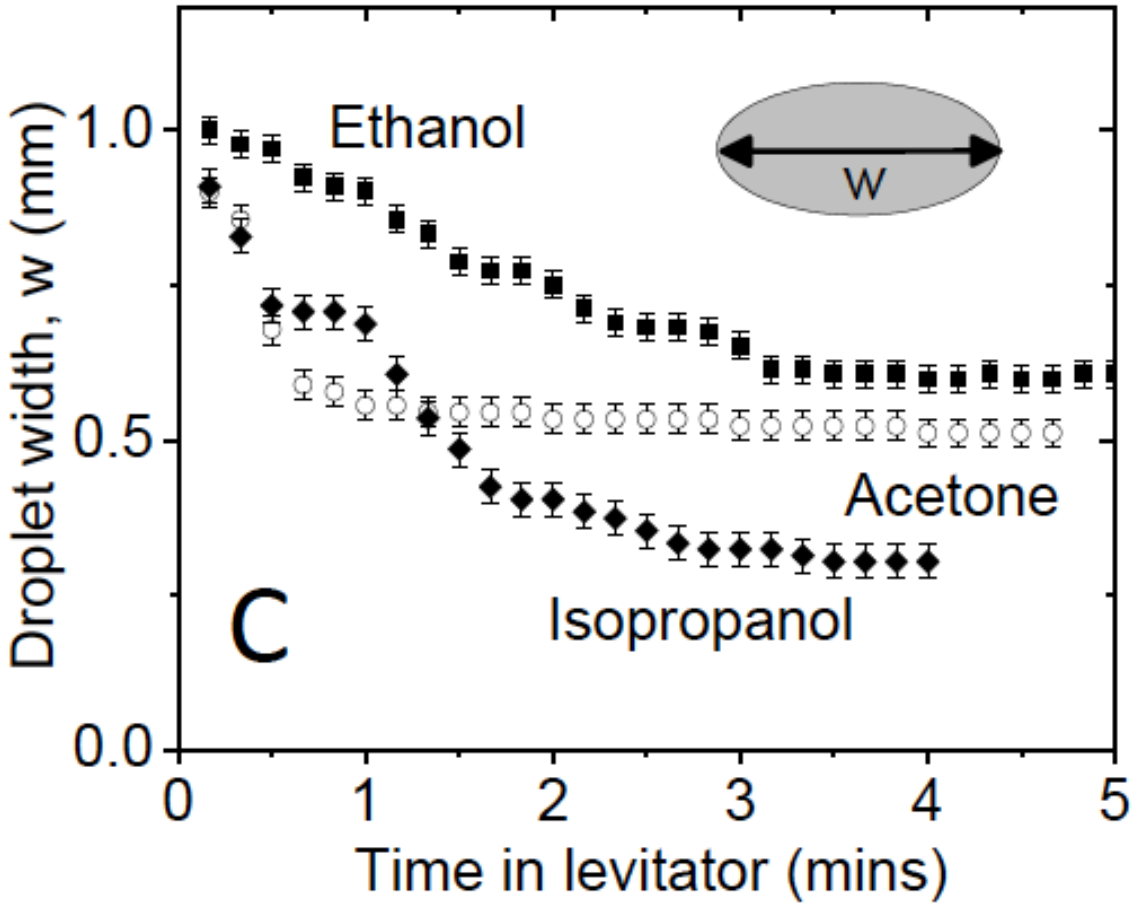
Fast Evaporation in Levitator



Complete evaporation takes about 16 min

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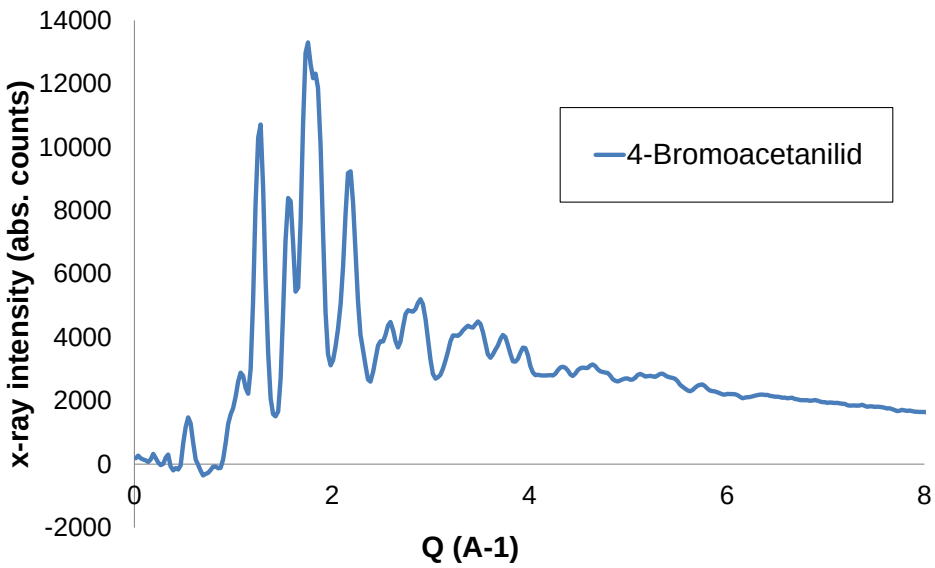
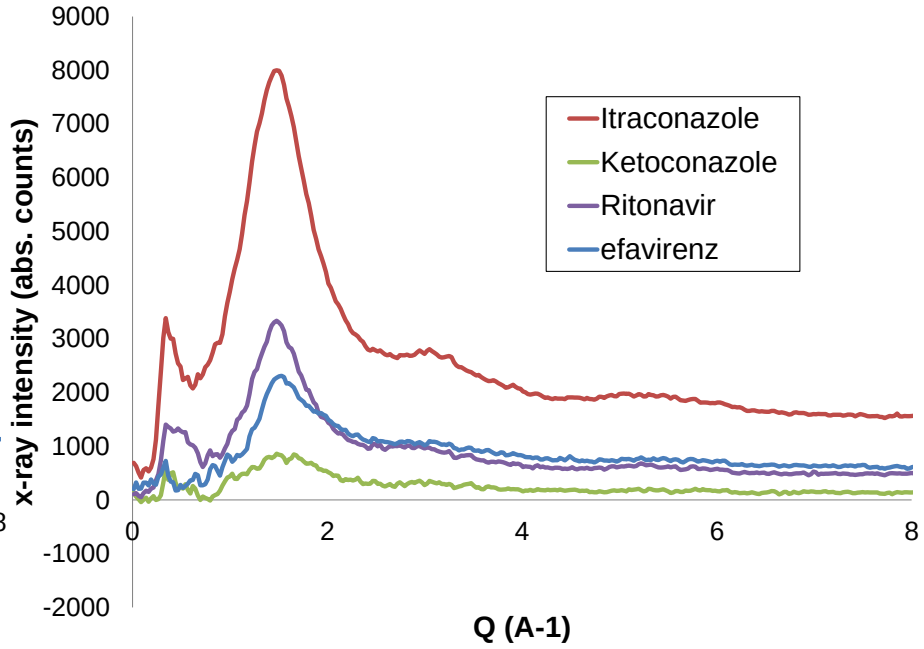
X-ray Patterns from Levitation Experiments





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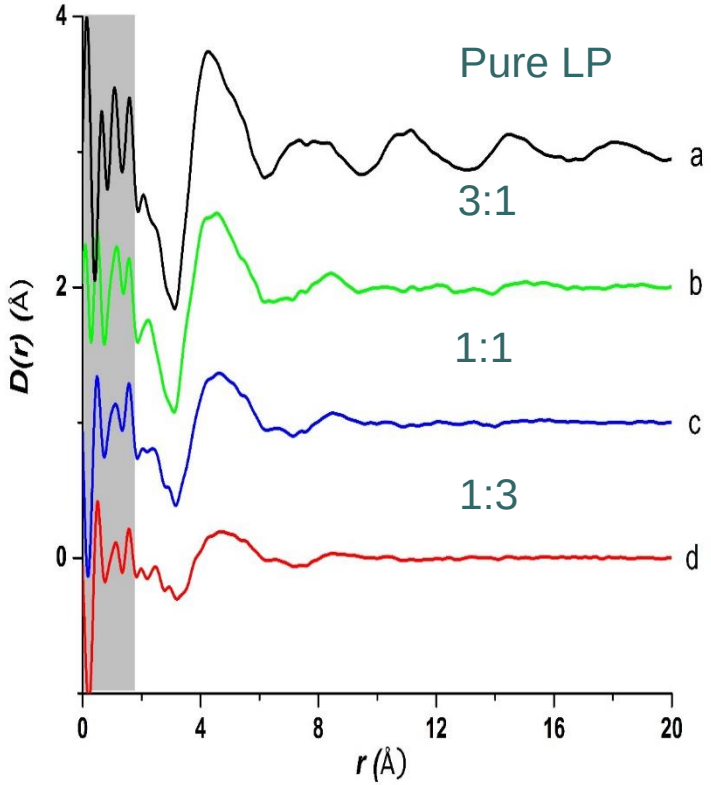
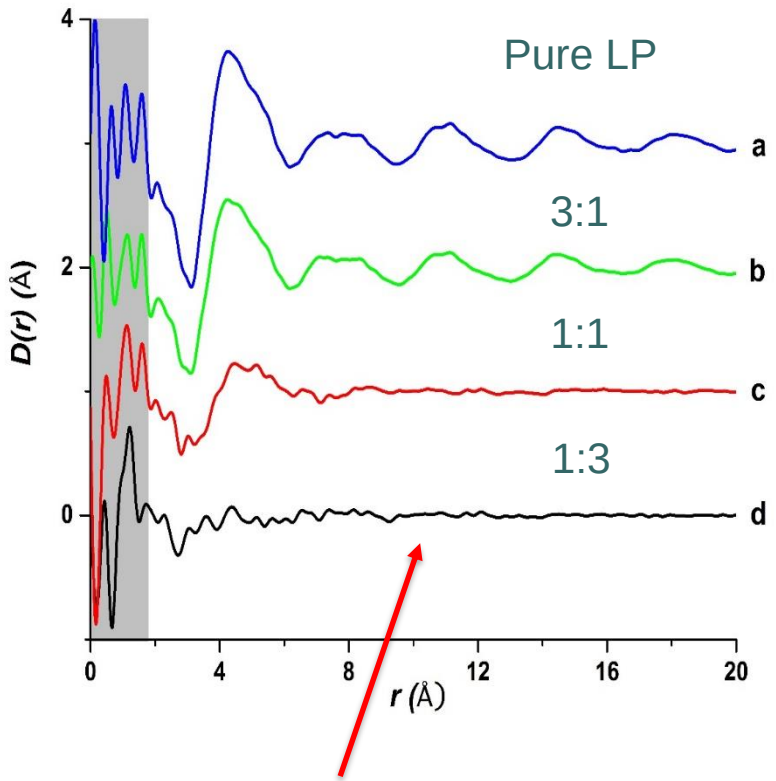
Acoustic Levitation – A First Step in Finding the Right Formulation

- Avoids need for large quantities of API required in standard amorphous screens
- Avoids crystallization induced by containers
- Is much faster than standard screens
- Allows detection of domains in amorphous screens – predicts stability
- Simulates spray-drying
- Finds the best formulation

PREDICT/ANTICIPATE STABILITY

Lapatinib PDF – Left HPMC, Right HPMCP - Differential PDFs are Shown





This is the only stable dispersion – a lapatinib-HPMC salt complex

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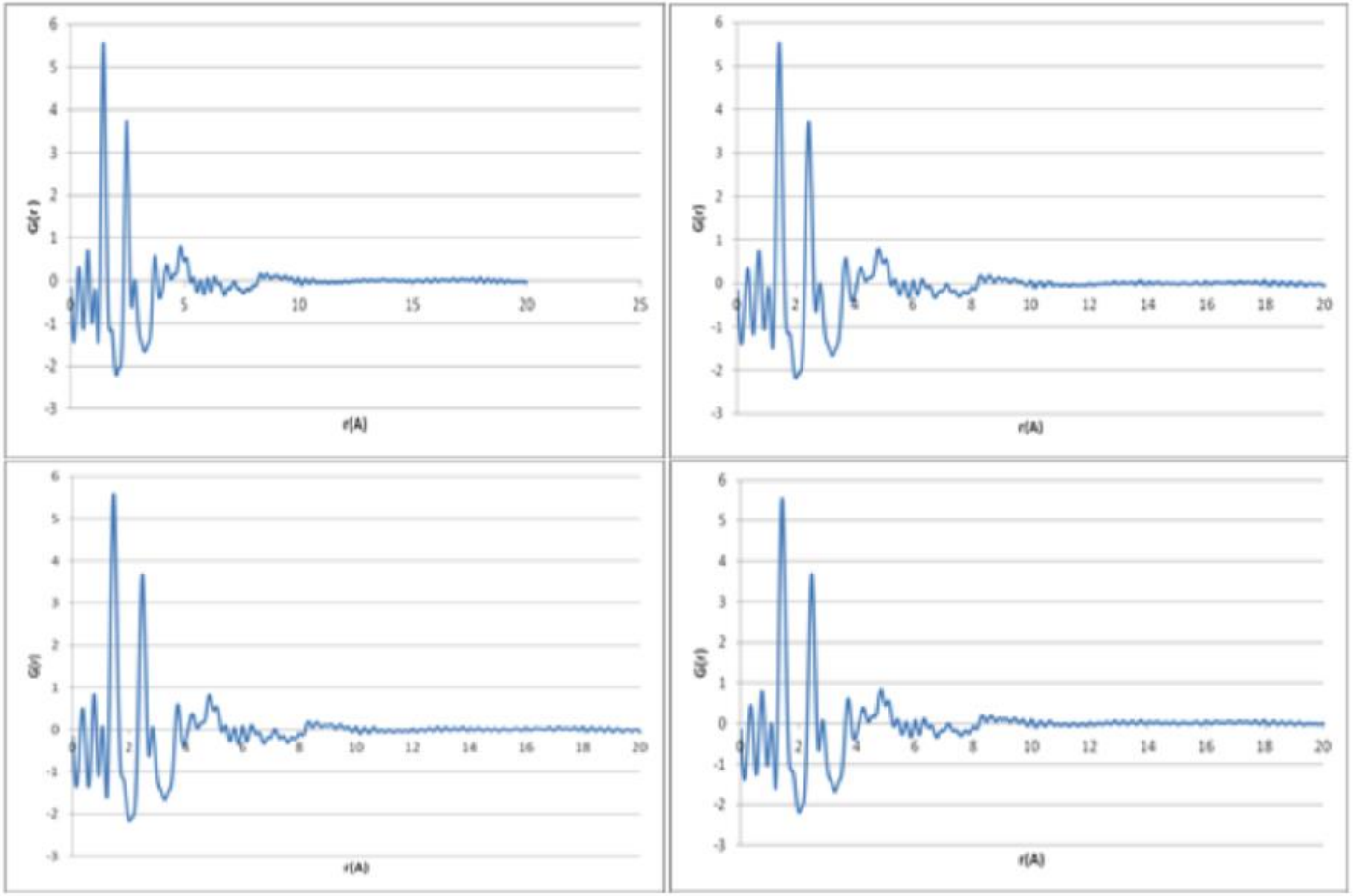
SAMENESS OF CLINICAL SUPPLIES AND PROBLEM SOLVING

Sameness Analysis



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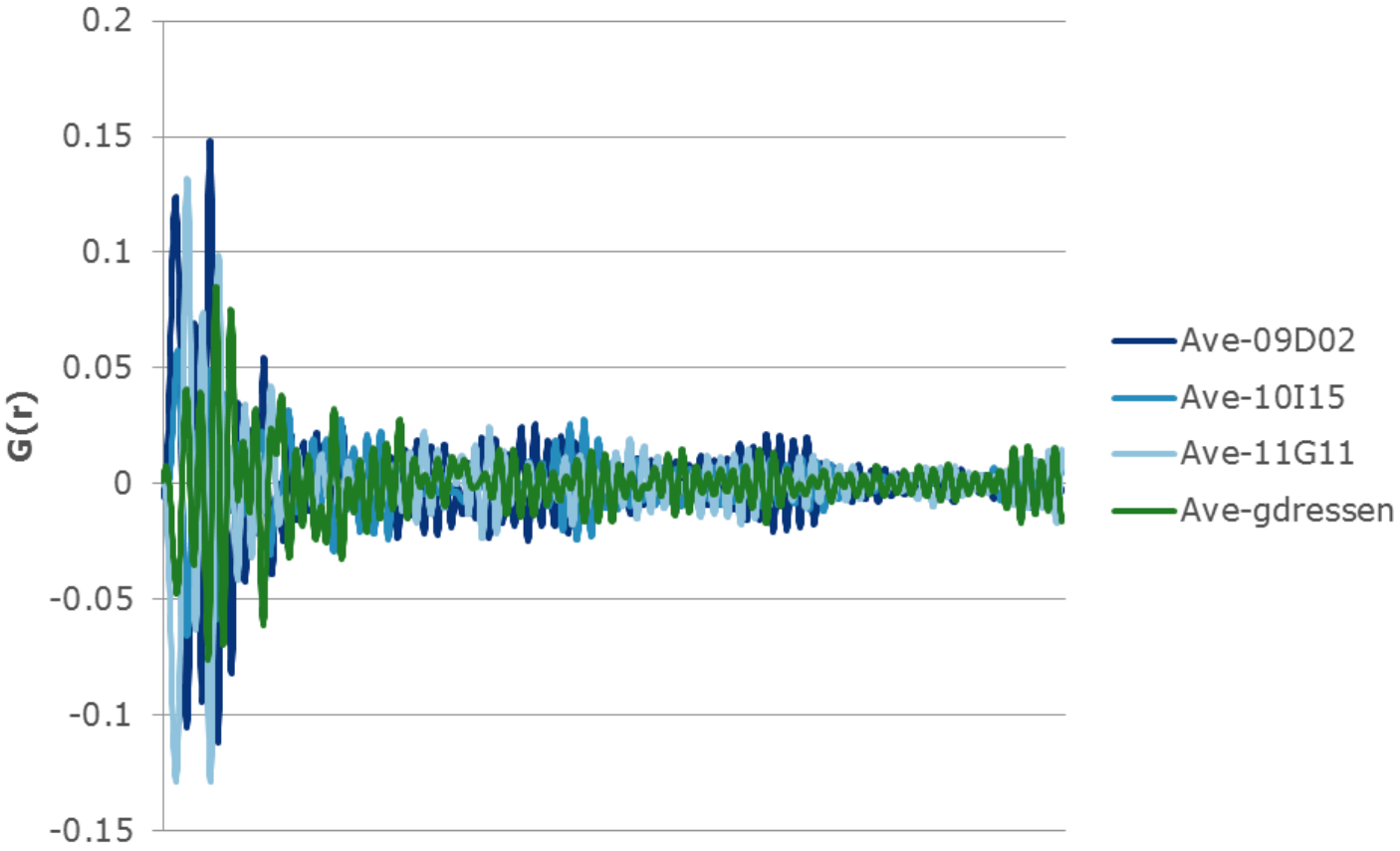
Sameness Study - Noise



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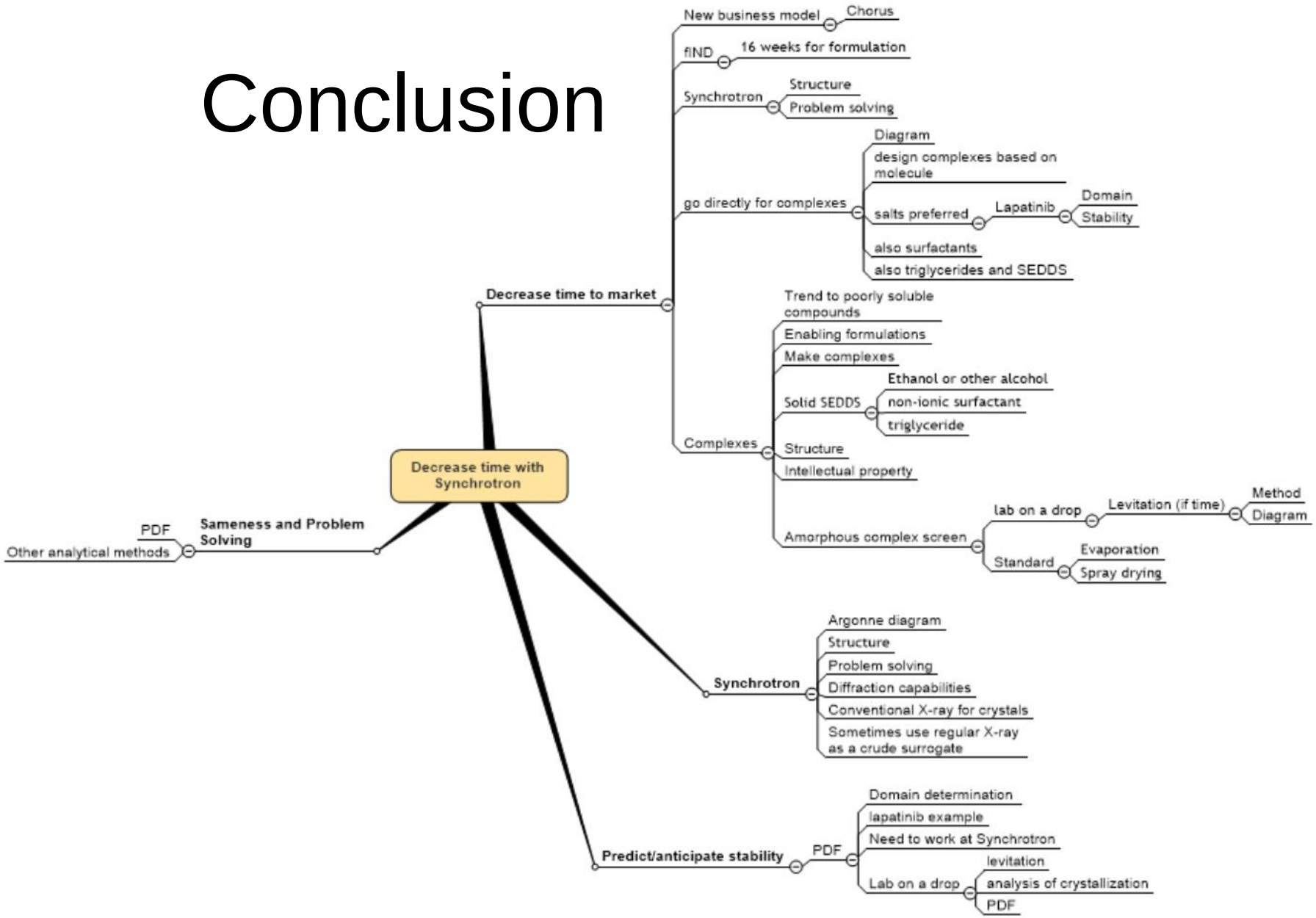
Conclusion



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