TWO-DIMENSIONAL X-RAY DIFFRACTOMETRY IN PHARMACEUTICAL PRODUCT AND PROCESS DEVELOPMENT

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PPXRD-14
June 8, 2016

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Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd   ICDD Website - www.icdd.com

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- Dr. Gregory Stephenson (Eli Lilly & Co.)
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- Dr. Bob He (Bruker)
- Dr. Karl Jacob (Dow Chemical Co.)
- Characterization Facility (UMN)
- Argonne National Laboratory (Synchrotron)
- Eli Lily and Company
- Lilly Innovation Fellowship Award

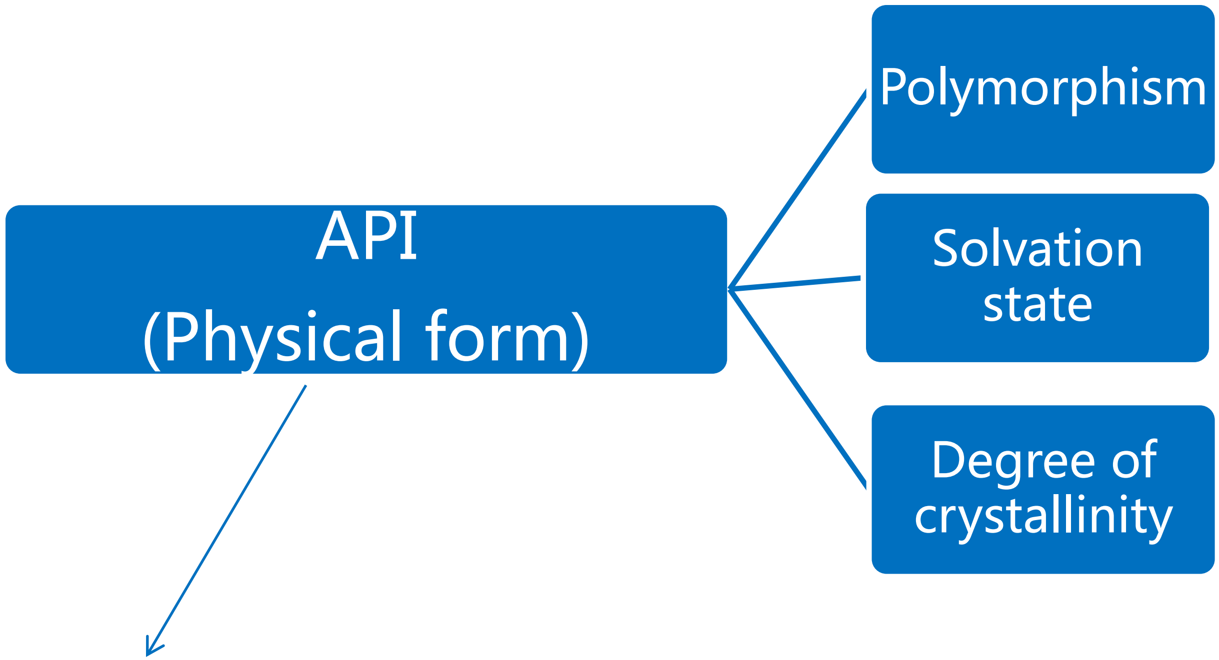
In situ Phase Transformation

Market Recall

- 2012: Market recall of nimodipine due to crystallization of nimodipine in soft gel capsules, that could adversely affect the product's bioavailabilty *
- April 2013, Apotex Corp. recall of 15 lots of Pipercillin and Tazobactum for injection (USP): showing crystallization/precipitation in I.V. bags*
- Dr. Reddy lab (June 2014) and Wockhardt (Sept 2014): Metoprolol succinate ***prolonged release tablet***, dissolution failure after **18** and **9** months of storage, respectively*

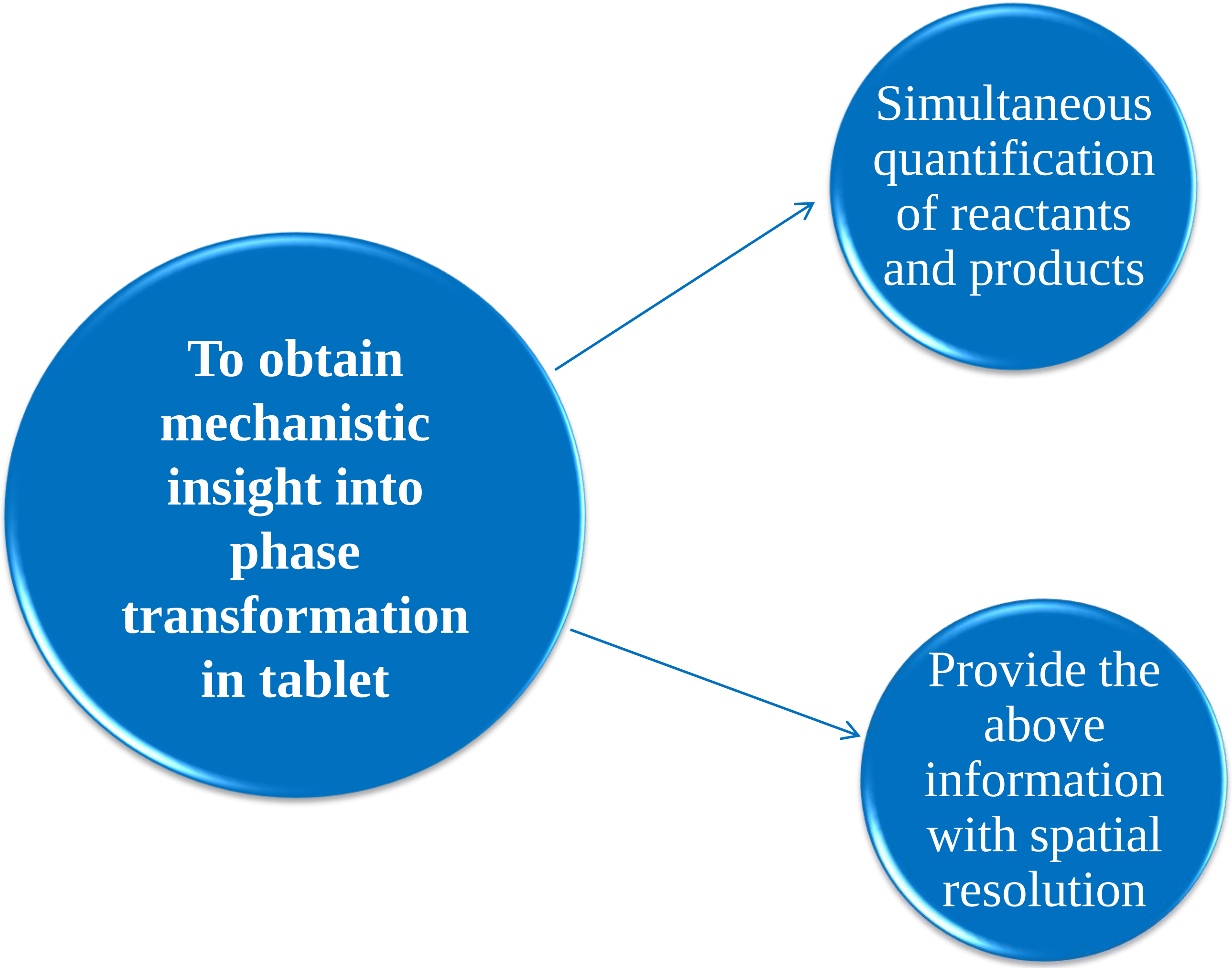
** USFDA*

Physical Stability



Final product performance in solid dosage forms

Mitigation Strategy



molecular pharmaceutics

Quantification, Mechanism, and Mitigation of Active Ingredient Phase Transformation in Tablets

Naveen K. Thakral, Vishard Ragoonanan, and Raj Suryanarayanan*
* Department of Pharmaceutics, College of Pharmacy, University of Minnesota, 9-177 WDH, 308 Harvard Street S.E., Minneapolis, Minnesota 55455, United States

Mol. Pharmaceutics, **2013**, *10* (8), pp 3128–3136
DOI: 10.1021/mp400180n
Publication Date (Web): July 22, 2013

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[*‡]
† Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, United States
‡ Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455, United States

Mol. Pharmaceutics, **2015**, *12* (1), pp 253–263
DOI: 10.1021/mp5005788

Spatial Distribution of Trehalose Dihydrate Crystallization in Tablets by X-ray Diffractometry

Naveen K. Thakral[†‡], Hiroyuki Yamada[§], Gregory A. Stephenson[†], and Raj Suryanarayanan[*‡]
† Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, United States
‡ Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455, United States
§ Mitsubishi Tanabe Pharma Co., 3-16-89 Kashima, Yodogawa-ku, Osaka 532-8505, Japan

Mol. Pharmaceutics, **2015**, *12* (10), pp 3766–3775
DOI: 10.1021/acs.molpharmaceut.5b00567

Compression induced phase transformation in amorphous API: A case study

Compression of amorphous API
Plan

- Introduction
- Analytical method development
- Proof of concept using amorphous trehalose tablets
- Case study: Compression of amorphous indomethacin
- Conclusion
- Other projects

Plan

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- Case study: Compression of amorphous indomethacin
- Conclusion
- Other projects

Effect of Compression on Amorphous Indomethacin

QTPP

Description	: Round flat tablet.
Size	: Diameter 8 mm.
Identity	: Positive for active ingredient.
Assay	: ± 5% weight.
Physical form	: Amorphous.
In vivo availability	: Immediate release determined by *in vitro* dissolution test.
Dose Uniformity	: Meet pharmacopoeial standard.
Packaging	: Unit dose, moisture protection.

Plan

- Introduction
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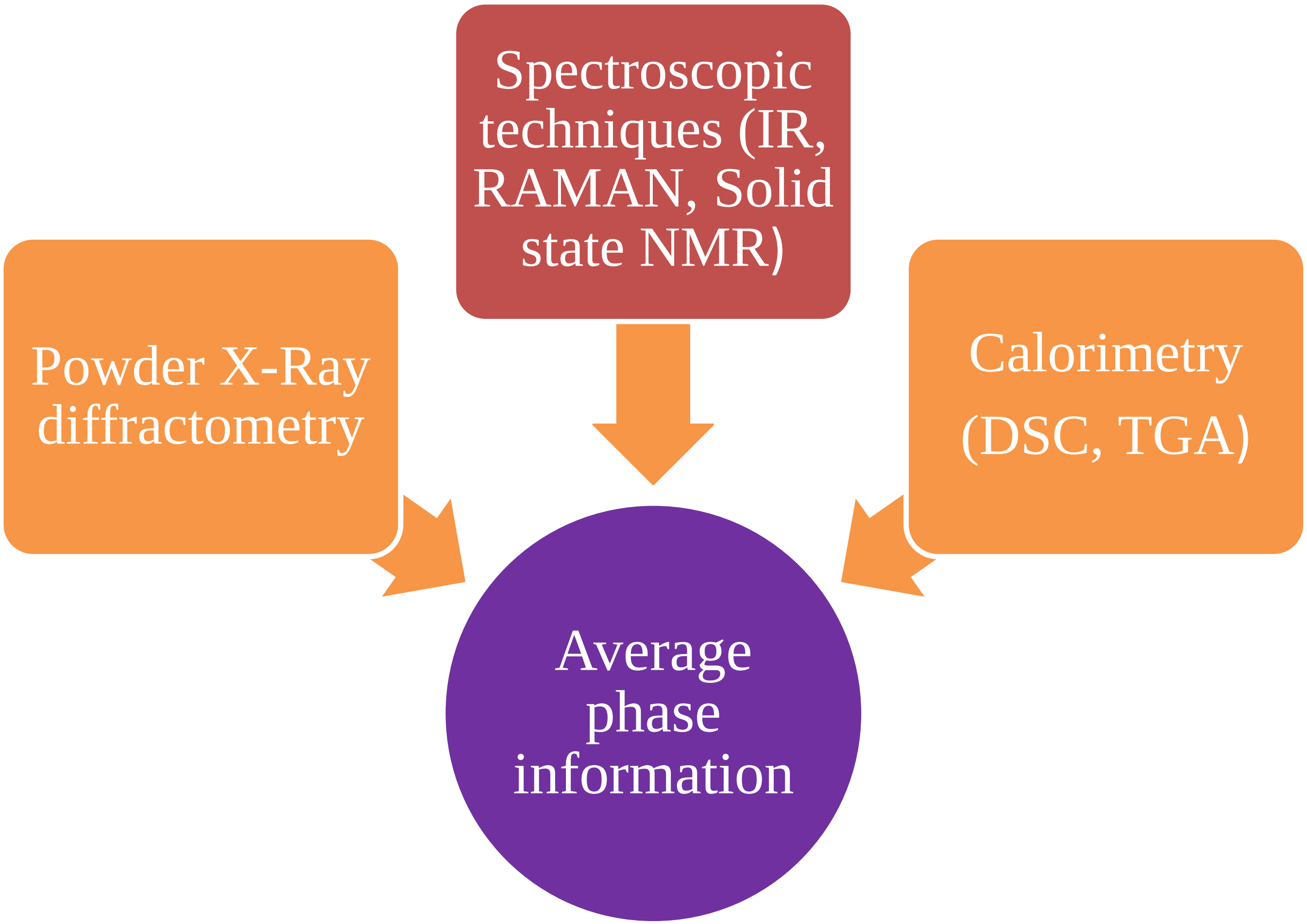
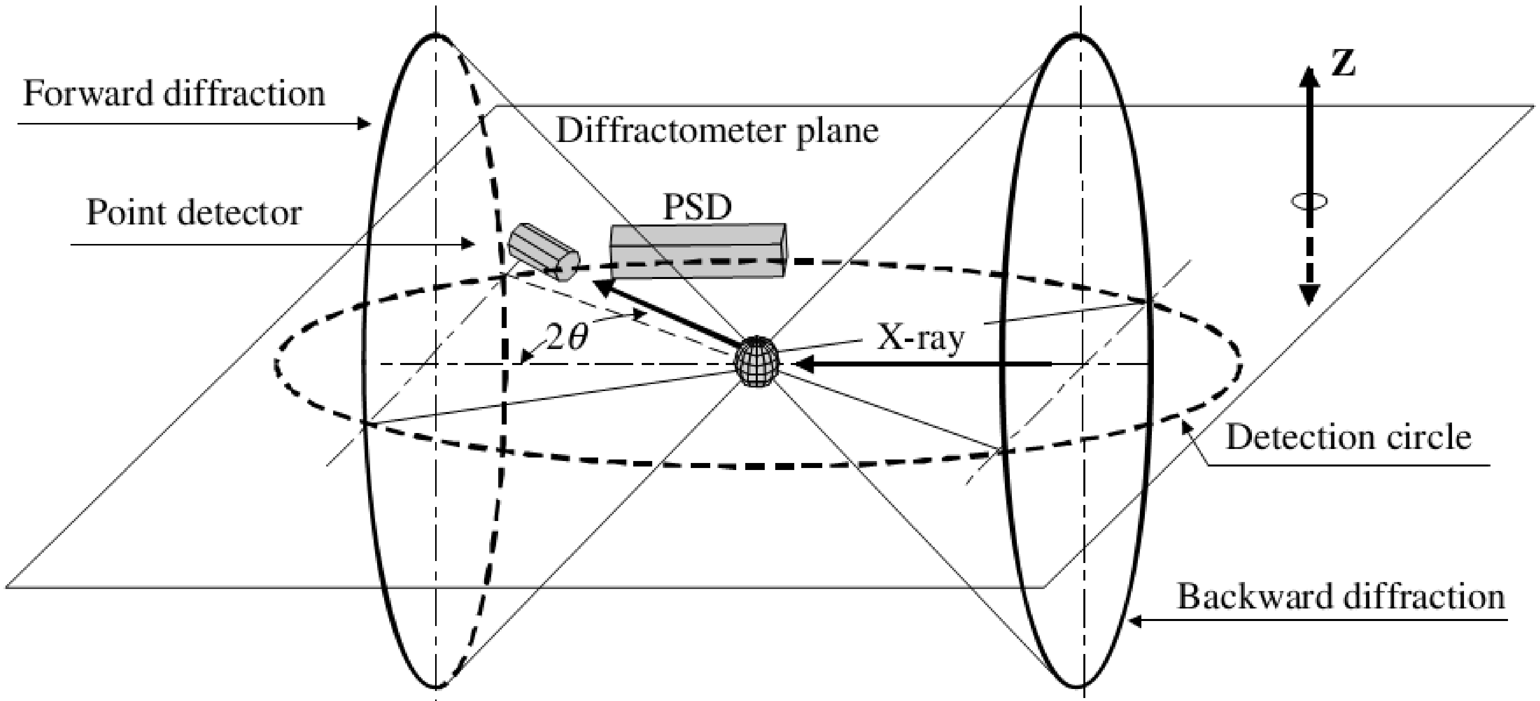
- Other projects

Analytical Methods

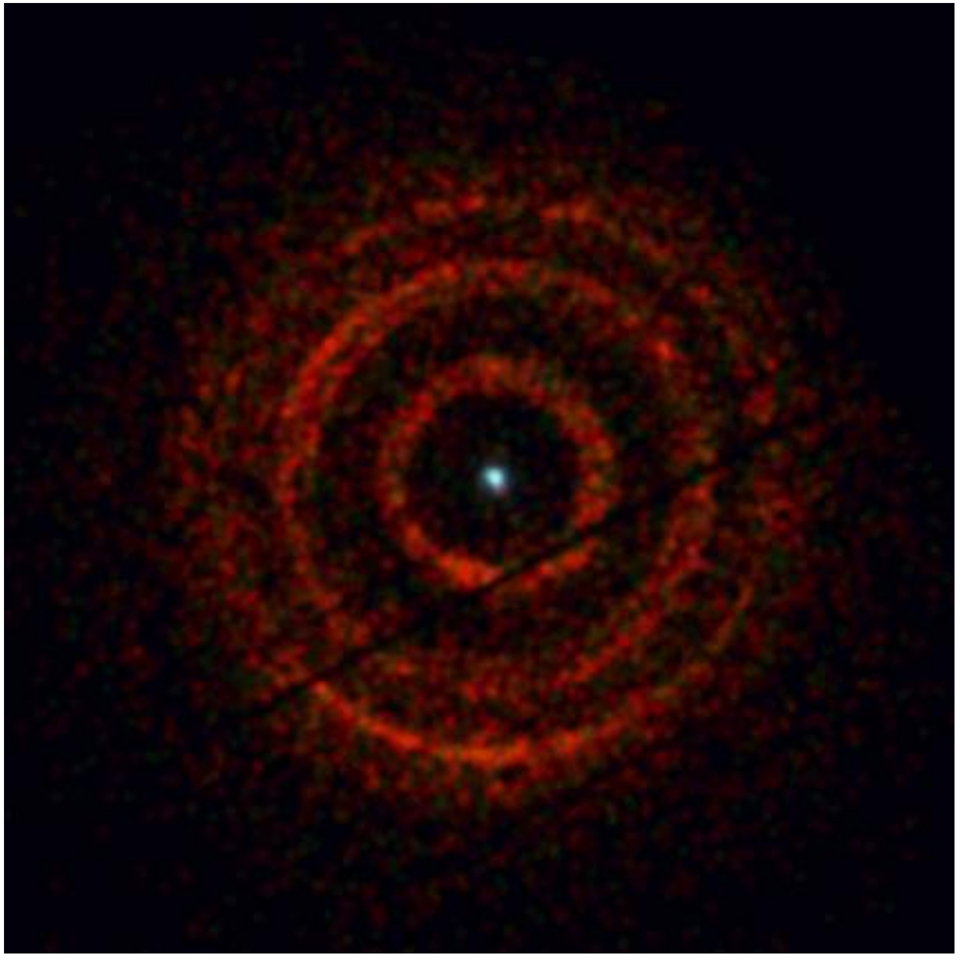


X-ray Diffraction

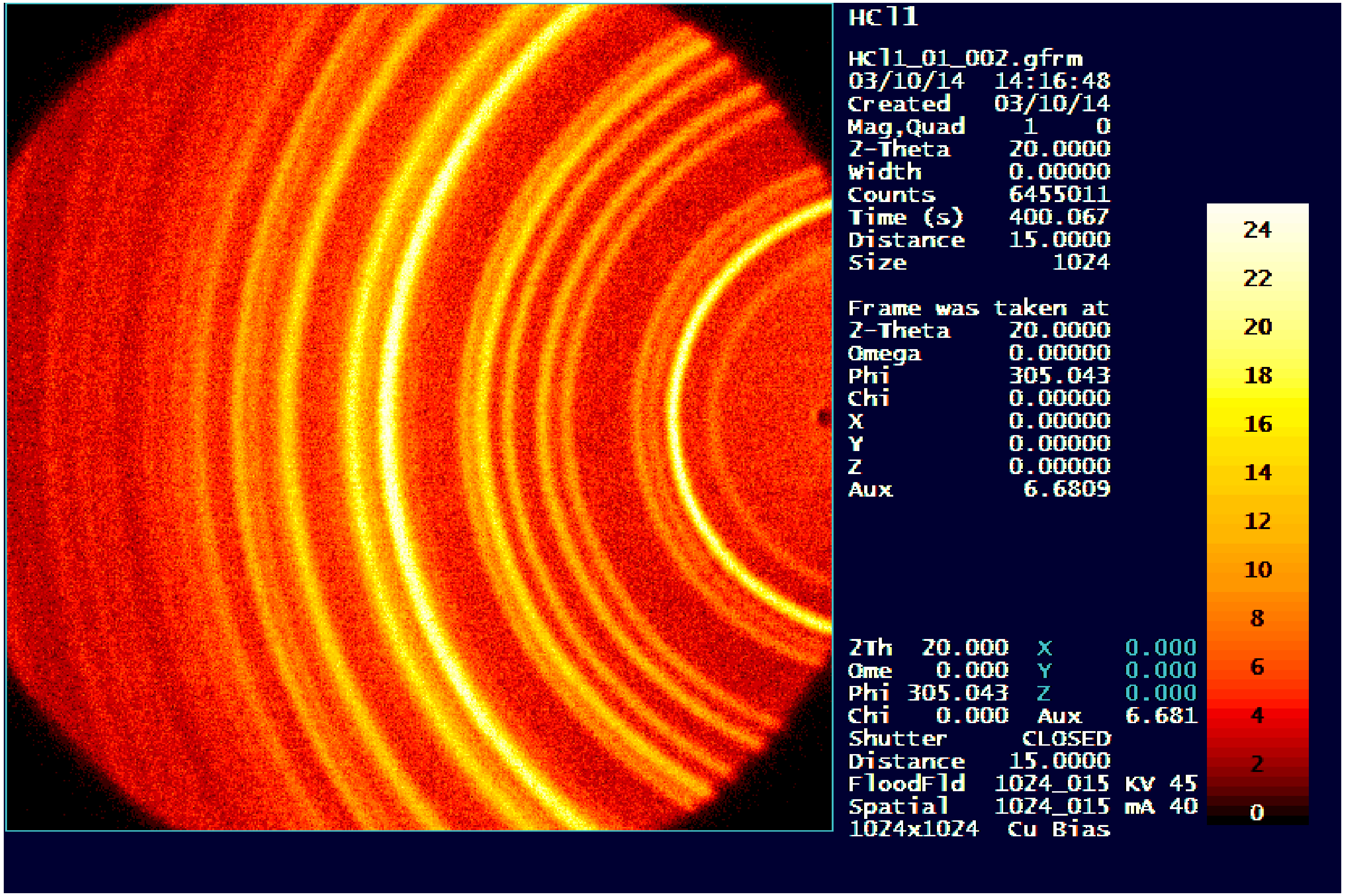


B He. 2009

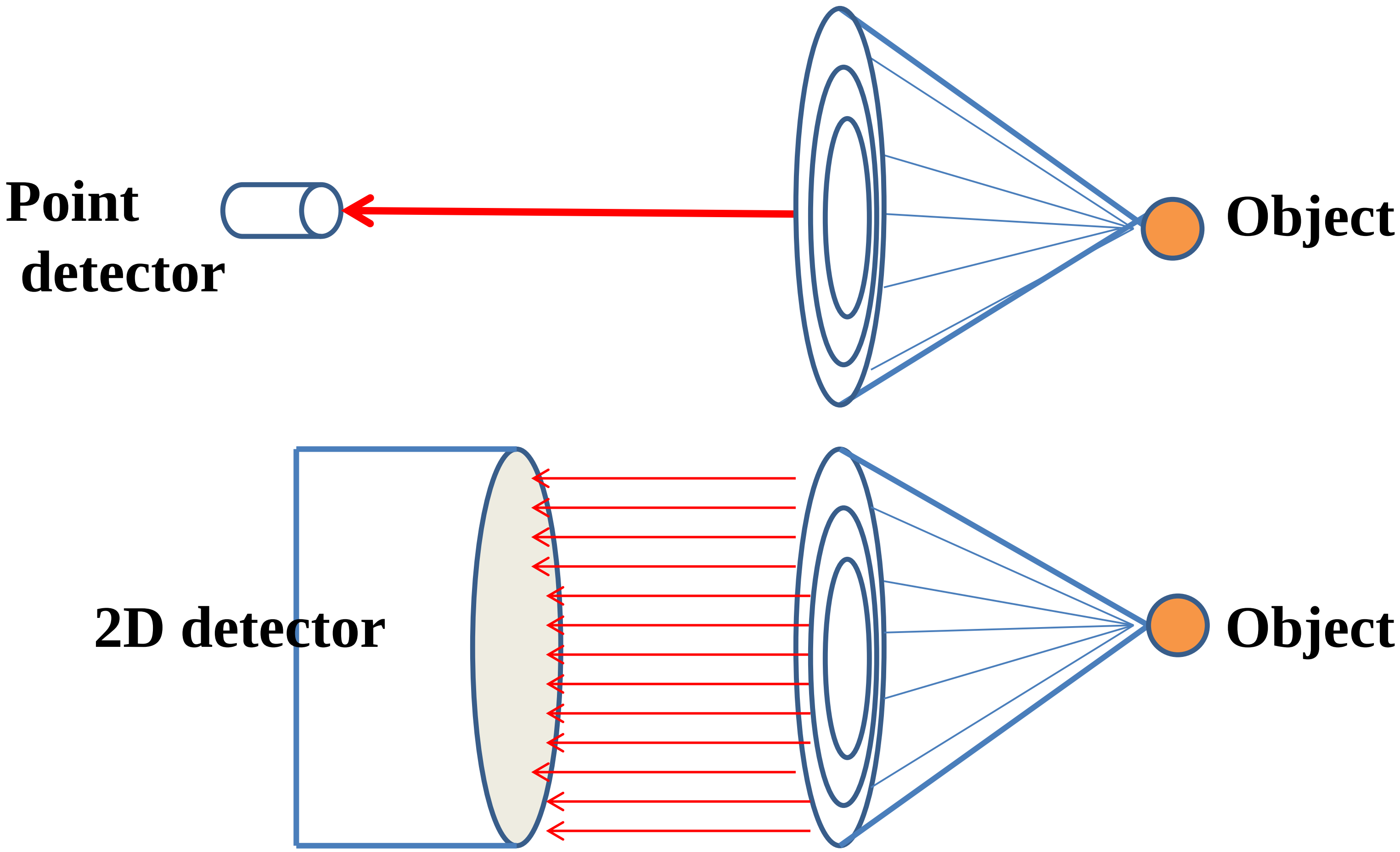
XRD in Space (NASA)



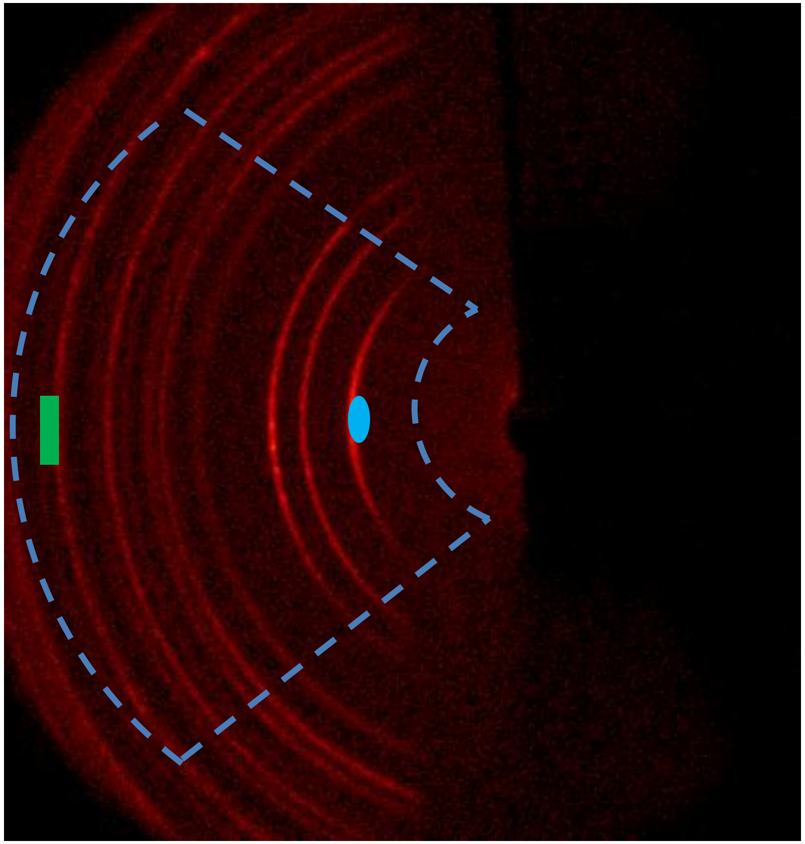
XRD in Lab.

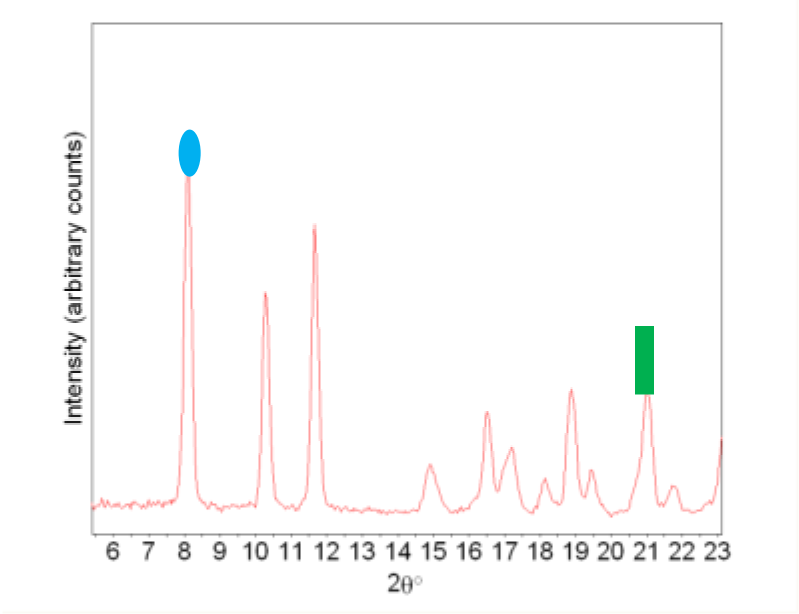

HCl1
HCl1_01_002.gfrm
03/10/14 14:16:48
Created 03/10/14
Mag,Quad 1 0
2-Theta 20.0000
Width 0.00000
Counts 6455011
Time (s) 400.067
Distance 15.0000
Size 1024
Frame was taken at
2-Theta 20.0000
Omega 0.00000
Phi 305.043
Chi 0.00000
X 0.00000
Y 0.00000
Z 0.00000
Aux 6.6809
2Th 20.000 X 0.000
Ome 0.000 Y 0.000
Phi 305.043 Z 0.000
Chi 0.000 Aux 6.681
Shutter CLOSED
Distance 15.0000
FloodFld 1024_015 KV 45
Spatial 1024_015 mA 40
1024x1024 Cu Bias
24
22
20
18
16
14
12
10
8
6
4
2
0

Conventional Vs 2-Dimensional XRD

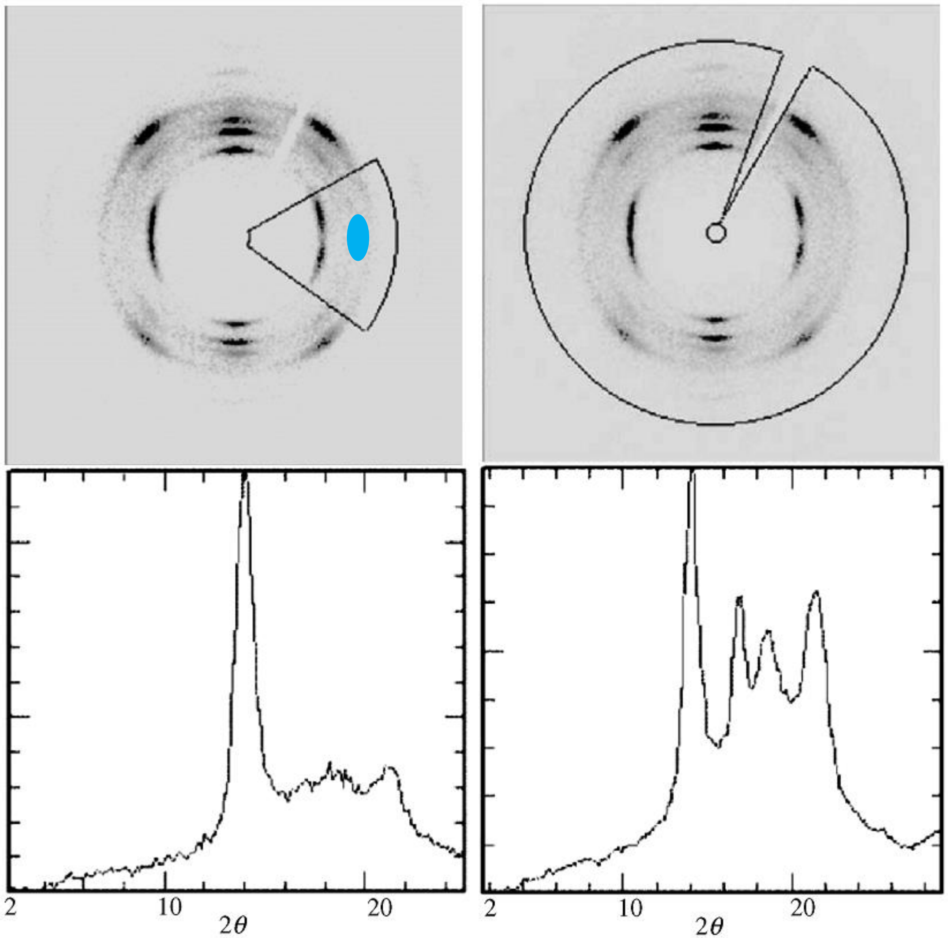


Averaging Integration Algorithm



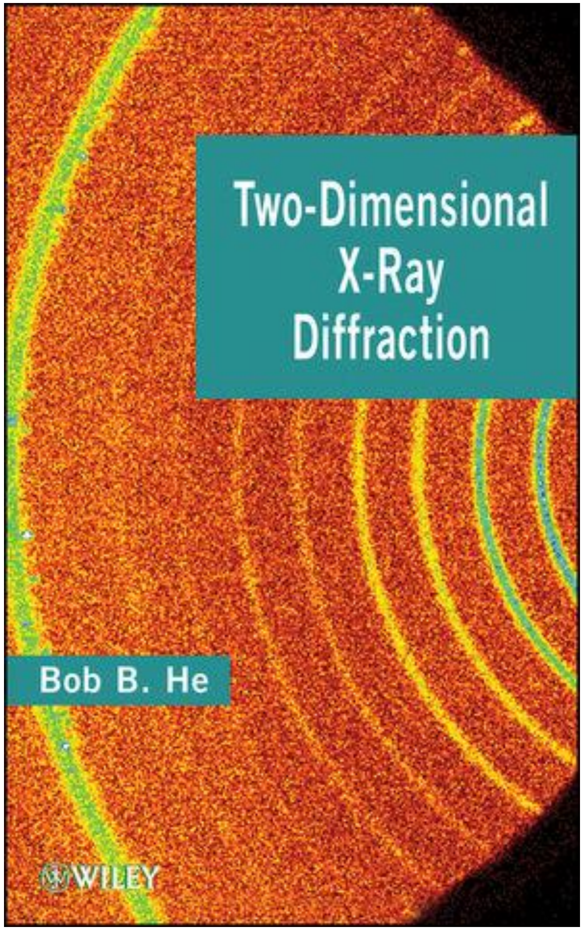


2-D and Texture (Preferred-Orientation)



Conventional XRD **2D XRD**

B He.2009


Two-Dimensional
X-Ray
Diffraction
Bob B. He
WILEY

- Introduction
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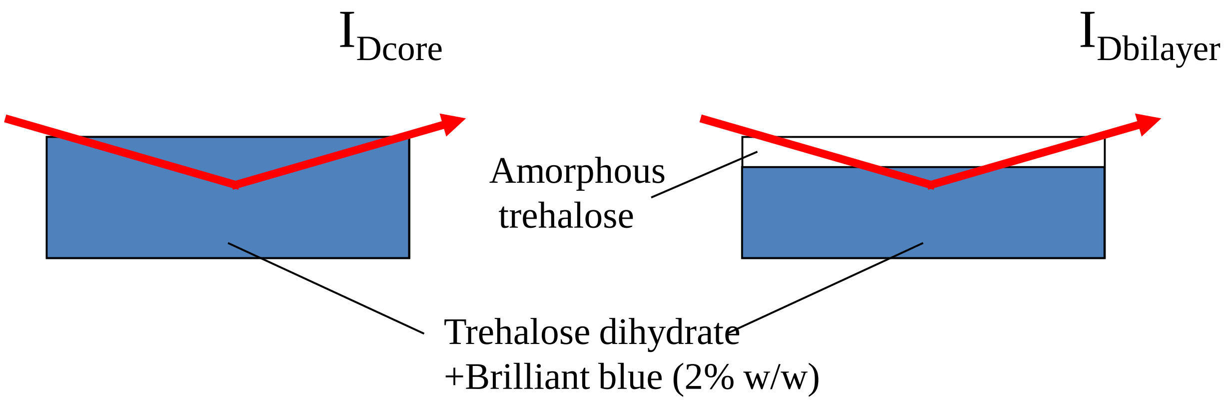
Glancing angle XRD
vs
2D-XRD

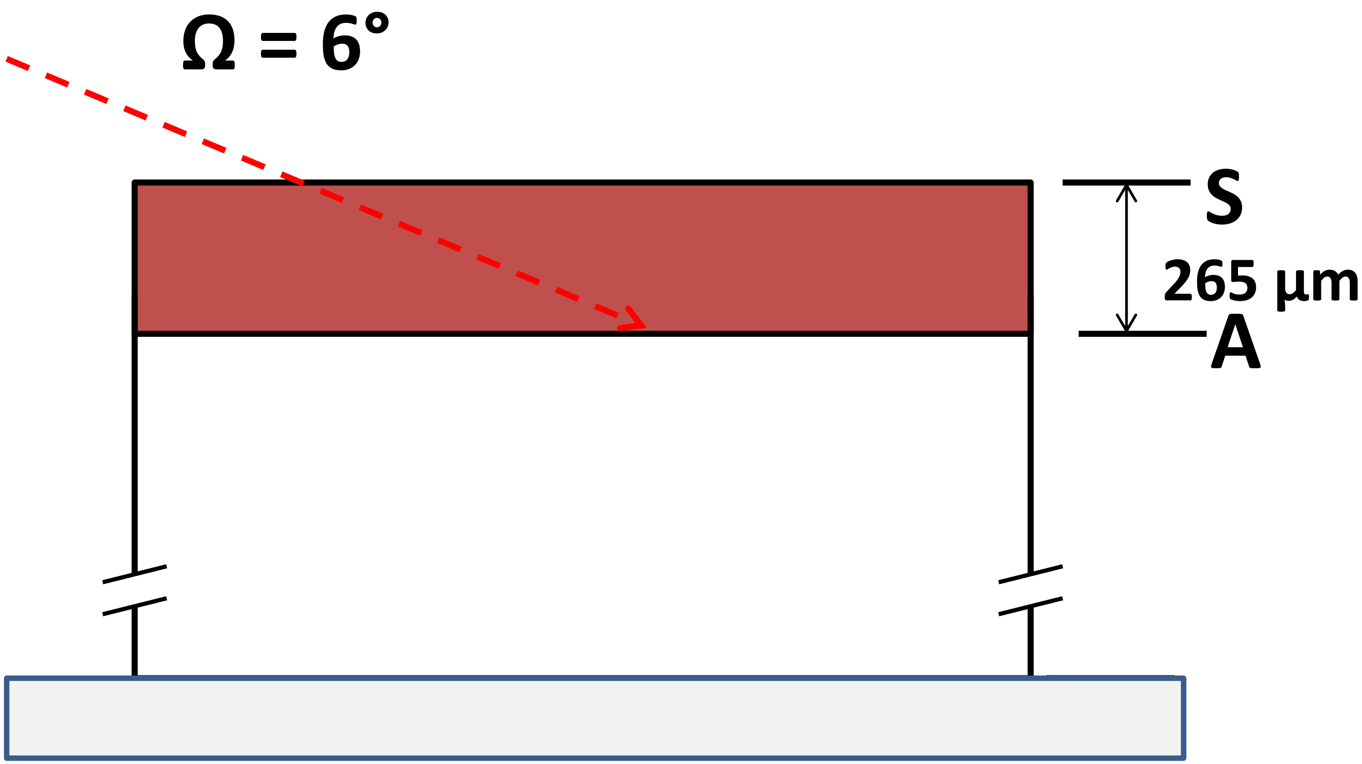
Glancing angle XRD – Depth of penetration: Amorphous trehalose



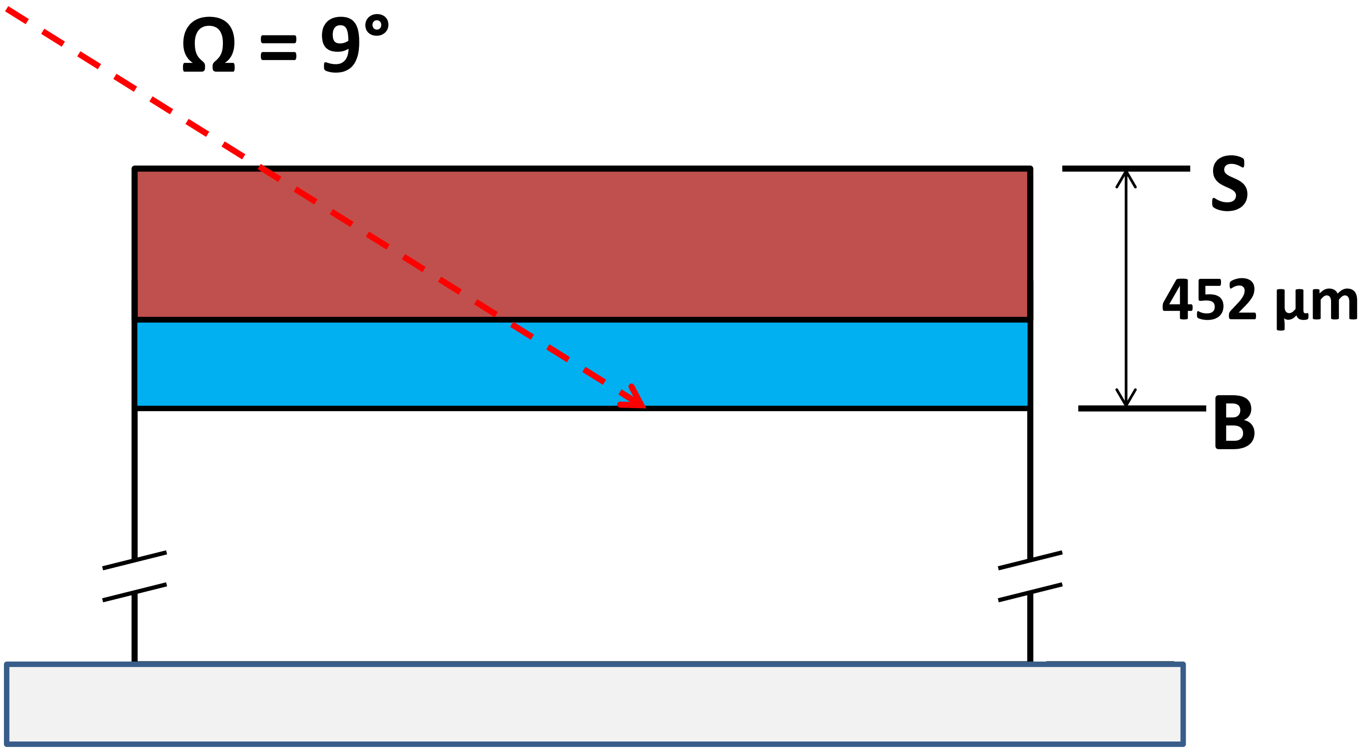
$$d = \ln\left[\frac{e^{-\mu_{upper} f\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)} - \frac{I_{Dbilayer}}{I_{Dcore}}}{e^{-\mu_{upper} f\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)}\left(1-\frac{I_{Dbilayer}}{I_{Dcore}}\right)}\right] \Big/ \left[-\mu_{lower}\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)\right]$$

Thakral et al 2015

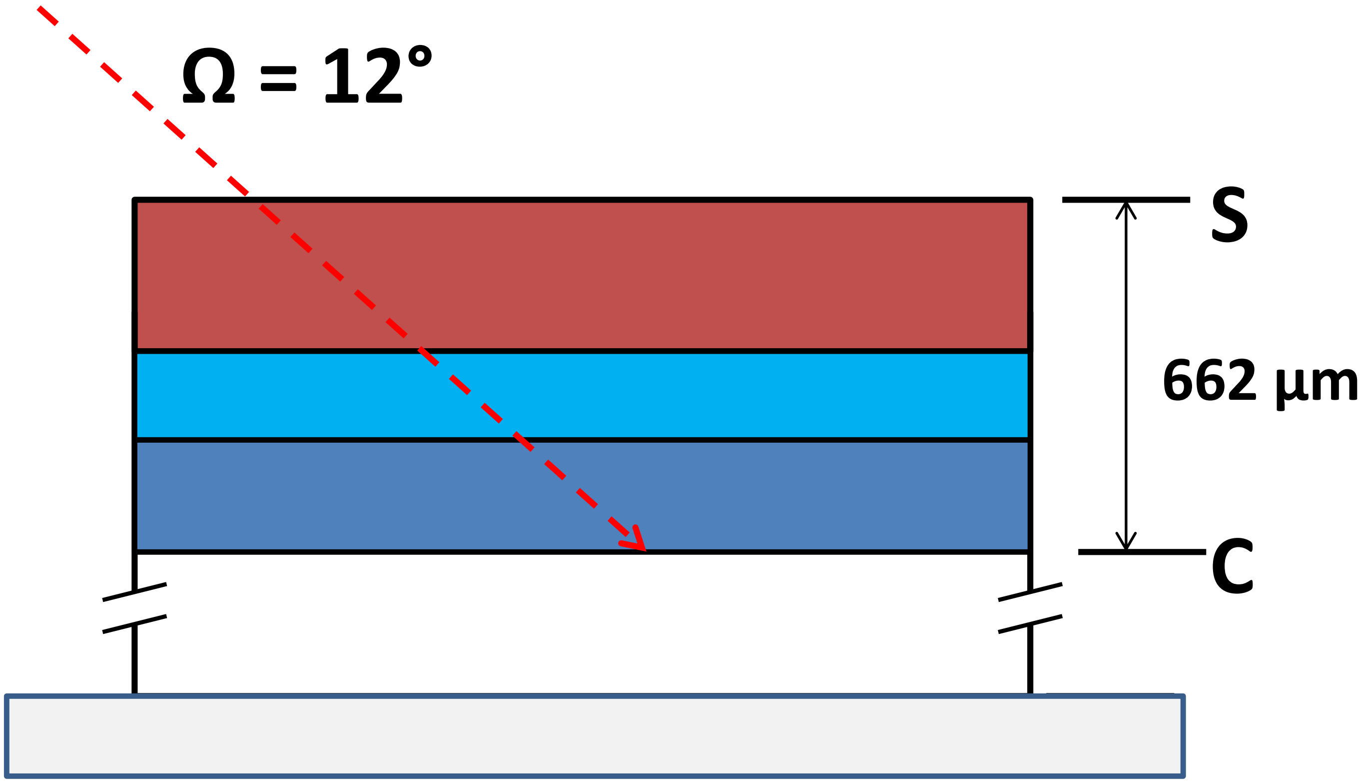
Depth of penetration as a function of incident angle



Depth of penetration as a function of incident angle



Depth of penetration as a function of incident angle



Integration of different layers

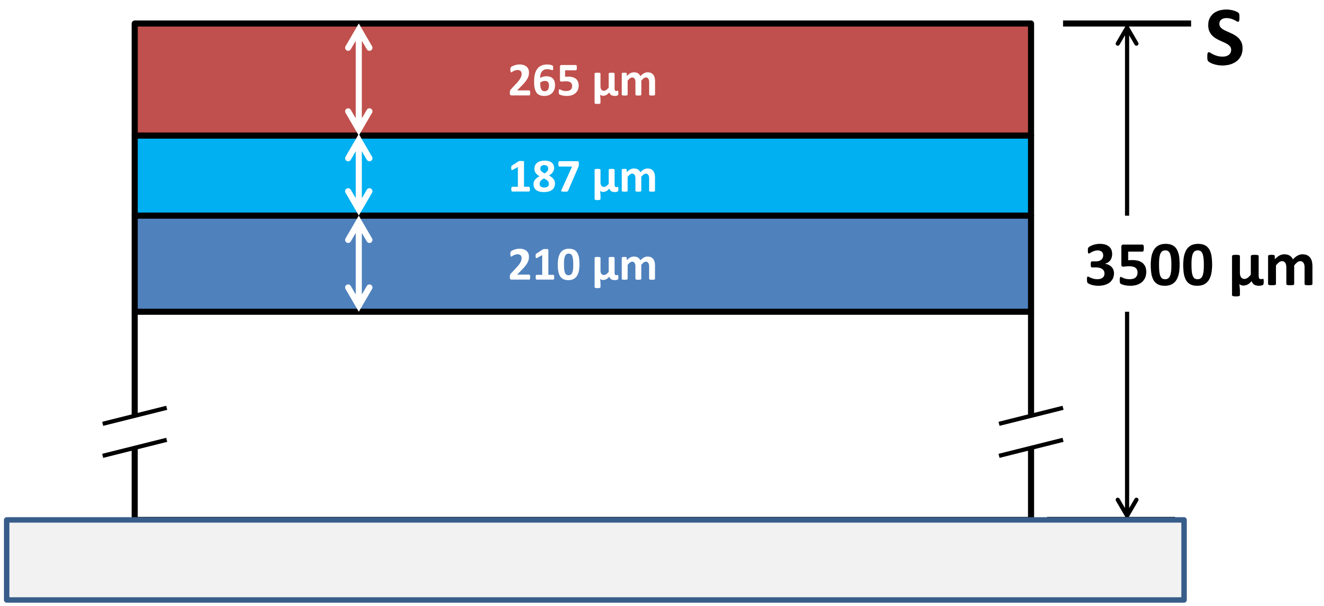
$$I_{SB} = I_0 K \int_S^B e^{-\mu x\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)} dx = I_0 K\left\{\frac{-\left[e^{-\mu B\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)}-1\right]}{\mu\left[\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right]}\right\}$$

$$I_{SA} = I_0 K \int_S^A e^{-\mu x\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)} dx = I_0 K\left\{\frac{-\left[e^{-\mu A\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)}-1\right]}{\mu\left[\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right]}\right\}$$

$$I_{AB} = I_0 K \int_A^B e^{-\mu x\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)} dx = I_0 K\left\{\frac{-\left[e^{-\mu B\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)}-e^{-\mu A\left(\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right)}\right]}{\mu\left[\frac{1}{\sin\Omega}+\frac{1}{\sin(2\theta-\Omega)}\right]}\right\}$$

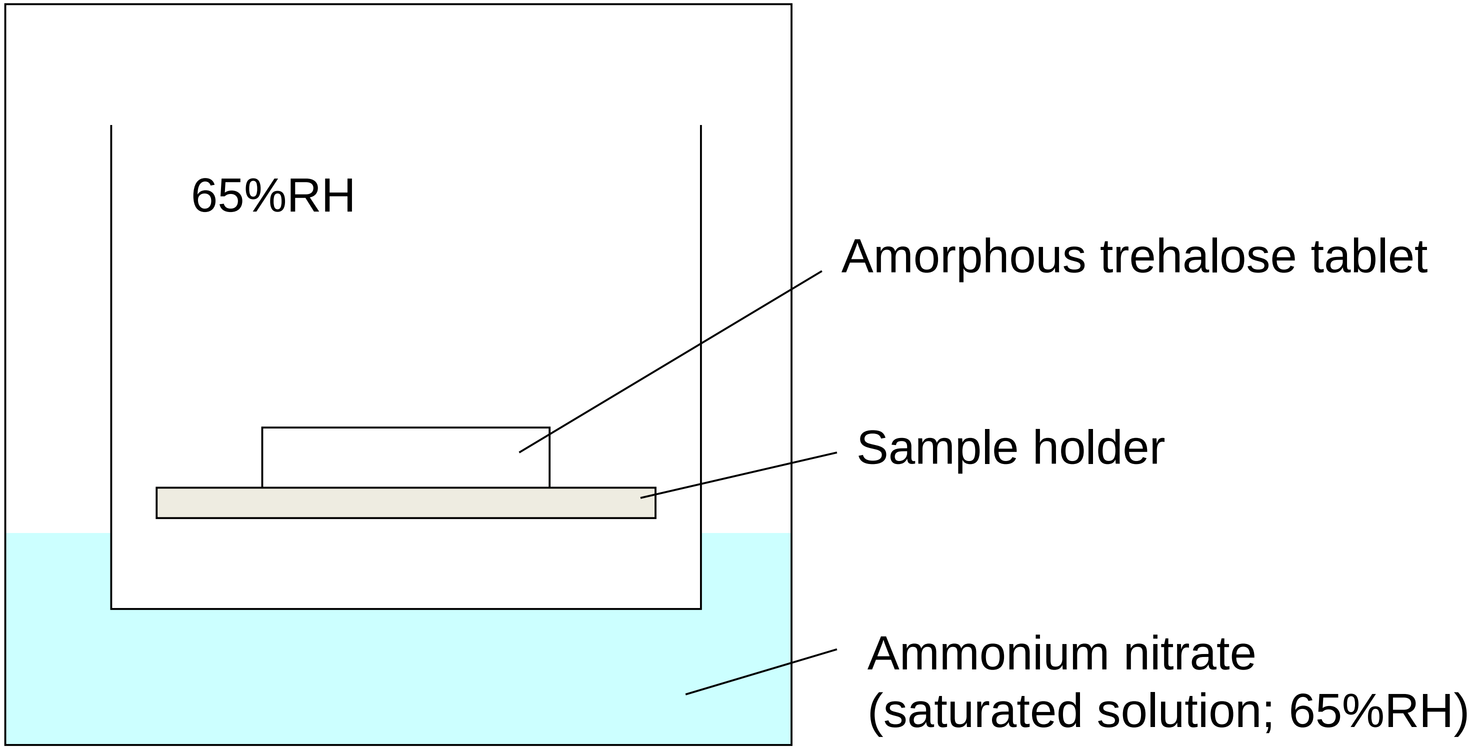
Thakral et al 2015

Integration of different layers

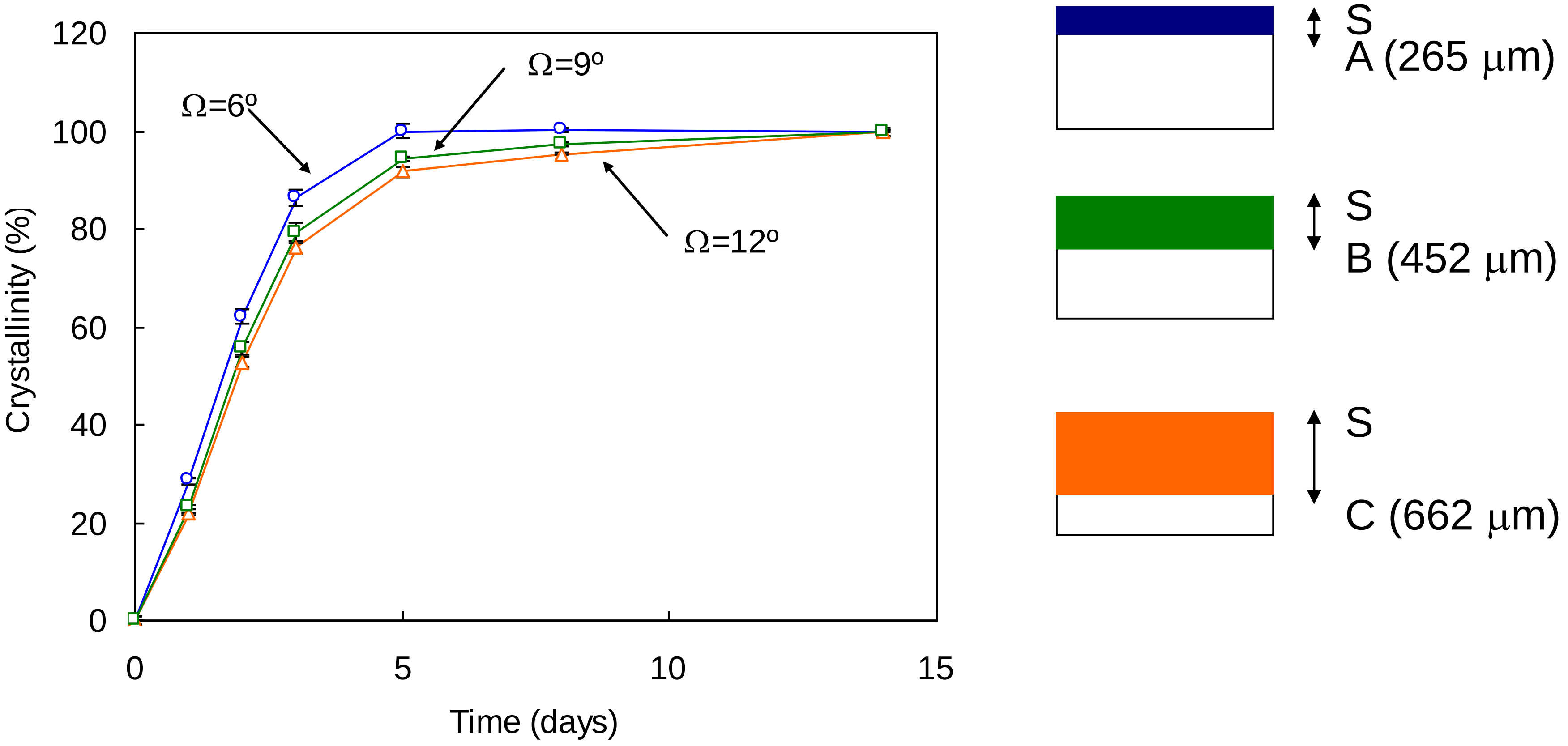


Thakral et al 2015

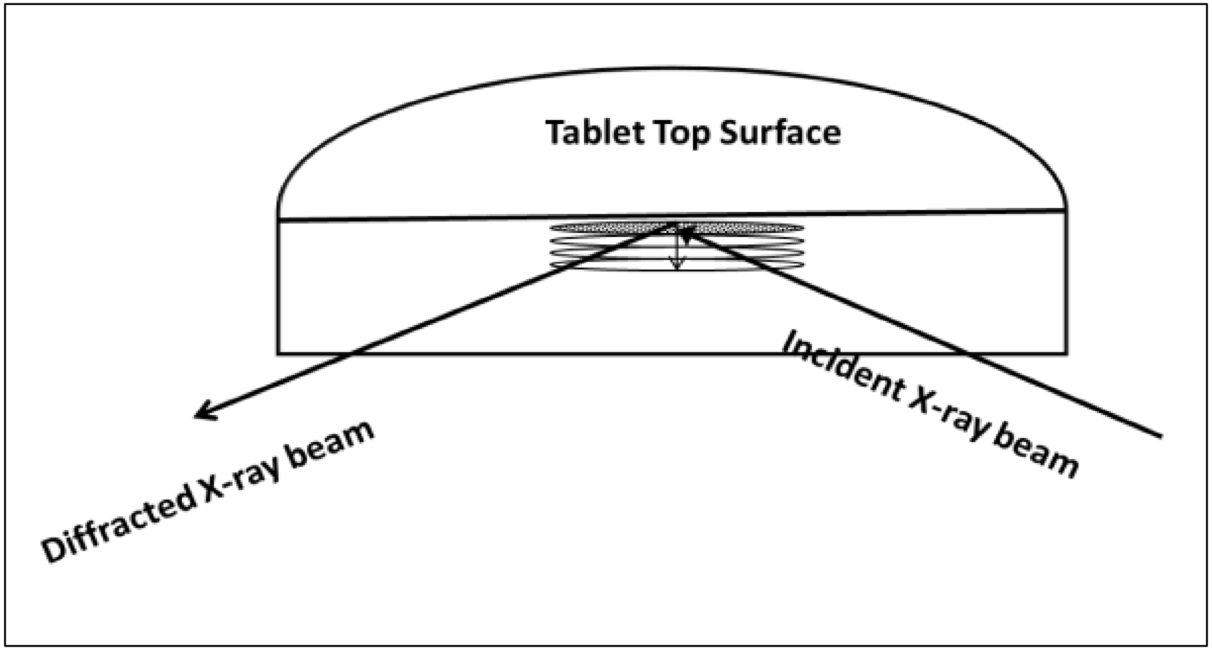
Crystallization– Amorphous trehalose tablets



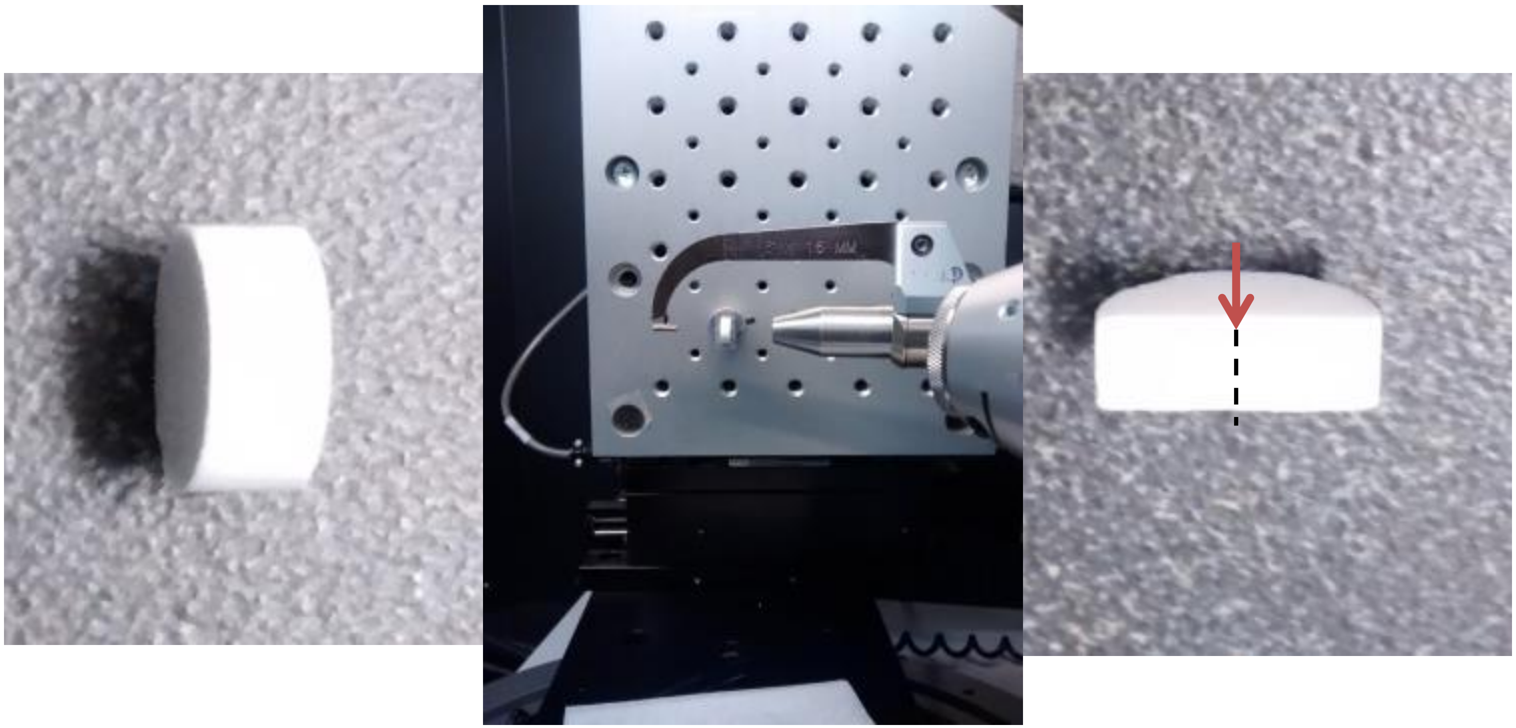
Glancing angle XRD



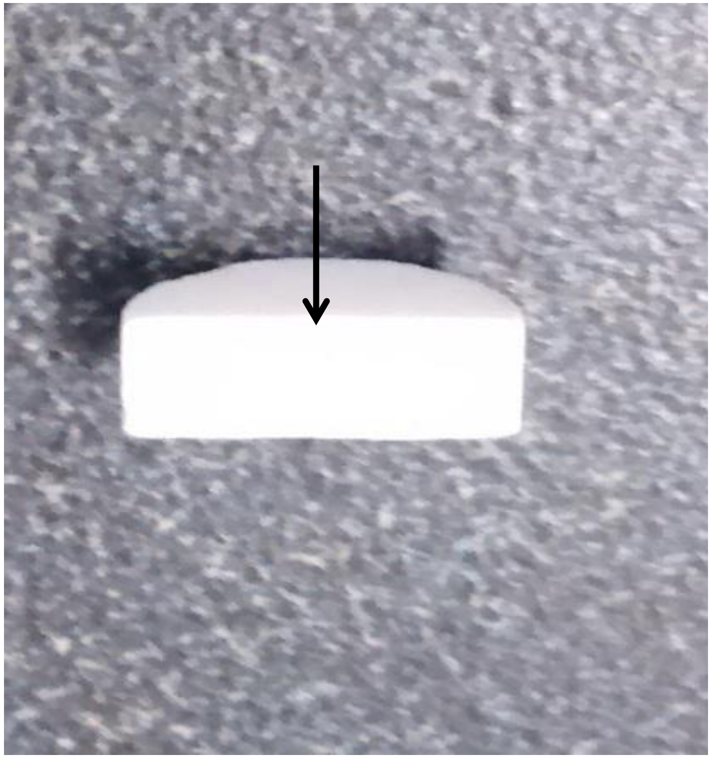
2DXRD of split tablets

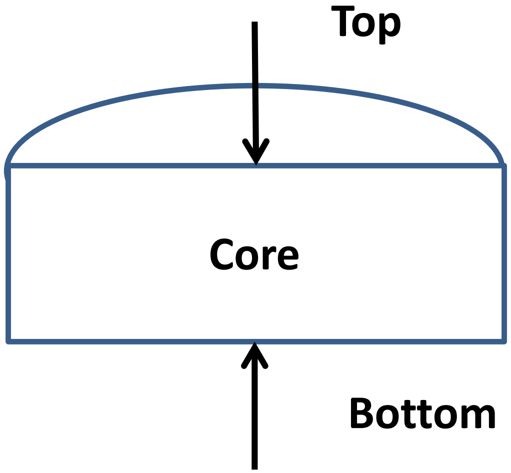


Specimen setup

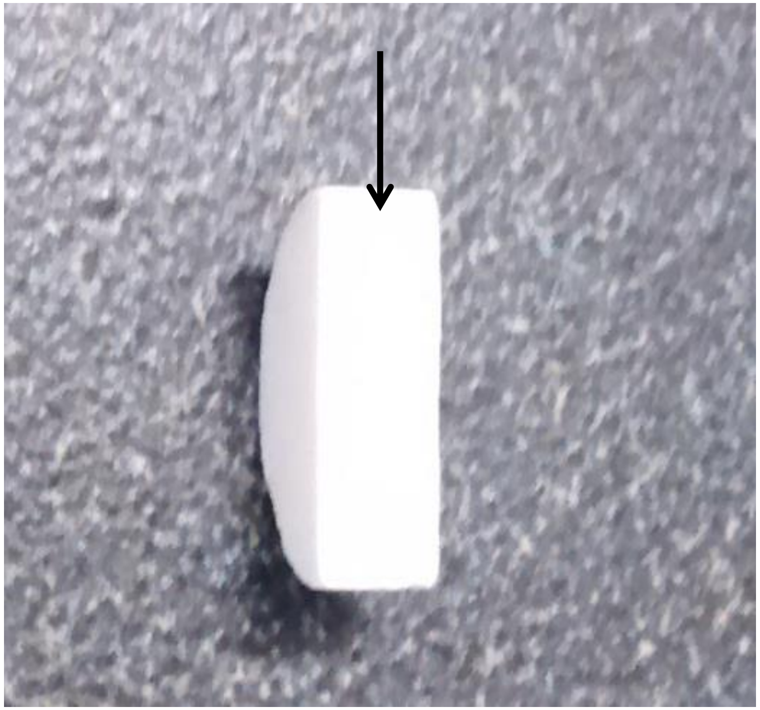


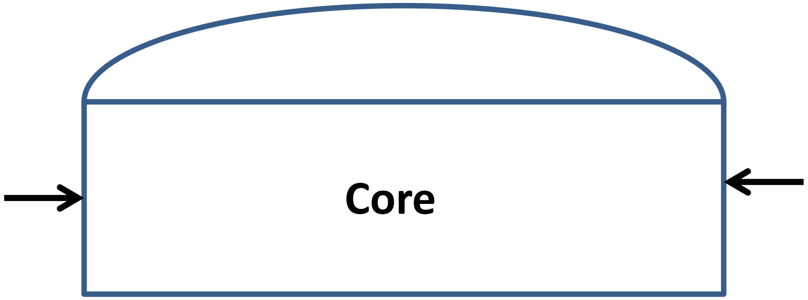
Mapping



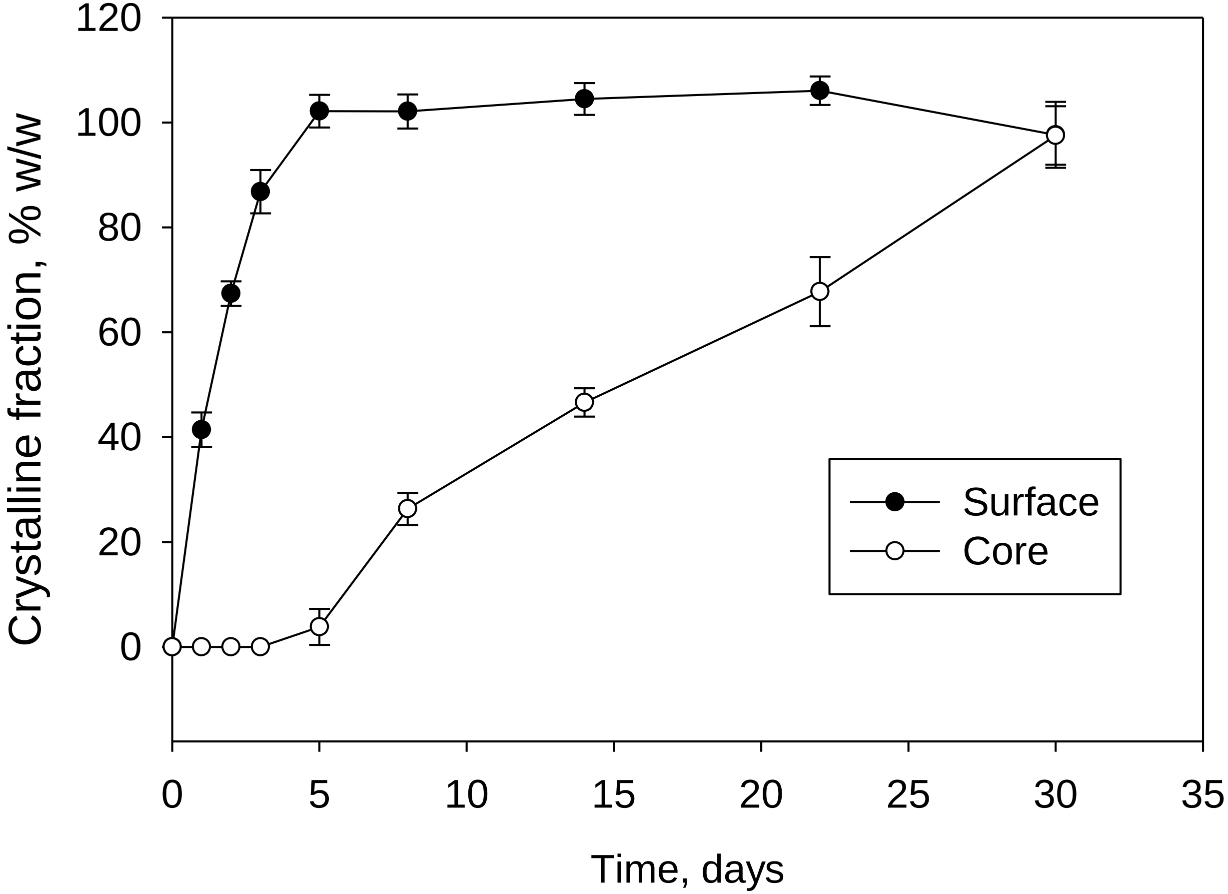


Mapping





Surface vs Core: Split tablets



Conclusion

XRD-2D

↓

Critical Spatial Information
(Not possible by
conventional XRD
or Glancing angle XRD)

↓

Mechanistic insight of phase transformatio

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Effect of Compression on Amorphous Indomethacin

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Description	: Round flat tablet.
Size	: Diameter 8 mm.
Identity	: Positive for active ingredient.
Assay	: ± 5% weight.
Physical form	: Amorphous.
In vivo availability	: Immediate release determined by *in vitro* dissolution test.
Dose Uniformity	: Meet pharmacopoeial standard.
Packaging	: Unit dose, moisture protection.

Product and Process Outline

Indomethacin (amorphous): particle size180 μm (# 80).

-Tablets (8 mm diameter); 200mg

-Compressed on Universal Material Testing Machine (Zwick GmbH & Co.)

- Compression pressure: 10, 25, 50, 100 MPa

-Compressed tablets stored in sealed Mylar pouch at 35 °C.

Prior Knowledge

Thermodynamically → Pressure is "intensive variable"

Amorphous compounds → lower density than their crystalline counterparts.

Compression → densify amorphous materials →promote intermolecular interactions and increase the probability of nucleation.

"Amorphous material has an upper density limit, beyond which the external pressure induces strain and causes the materials to crystallize."

Wu C T 1975

Product CQA

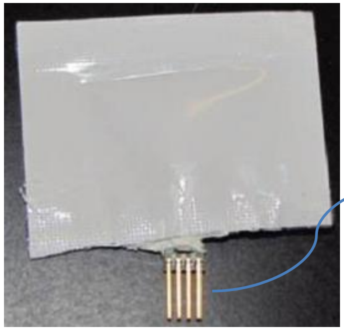
Risk:

Amorphous → crystalline (stable;low energy state) → dissolution failure → affect bioavailability

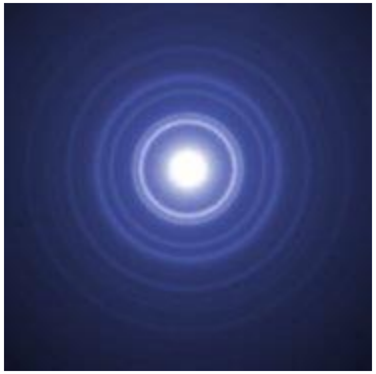
CQA → "Stable" amorphous state throughout the shelf life of the product.

Experiment

Sealed



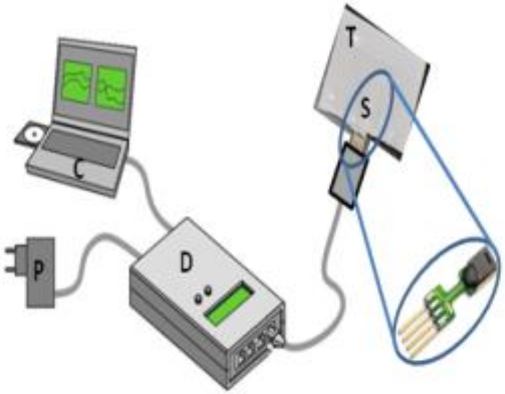
Mylar Pouch fitted with temperature and humidity sensor



2D XRD

Different Time Intervals

Stored at ~35°C in Oven



Analytical techniques

- Synchrotron XRD

(First evidence of crystallization)

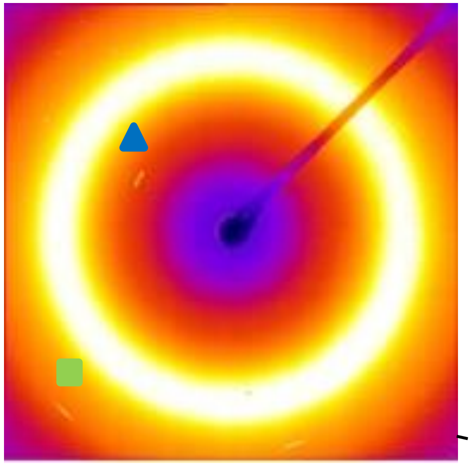
- 2D-XRD

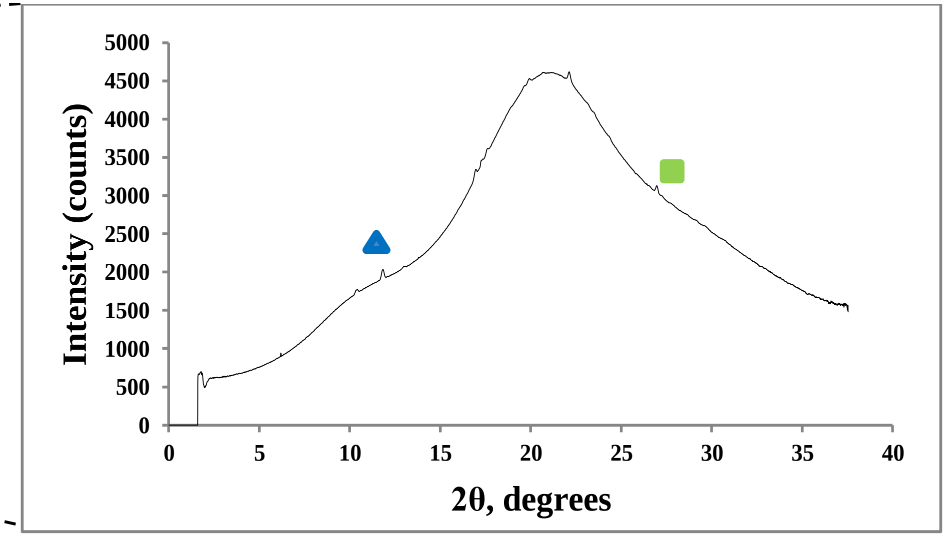
(Depth profiling)

Synchrotron XRD (Argonne National Laboratory) Beam-line 17 BM-B

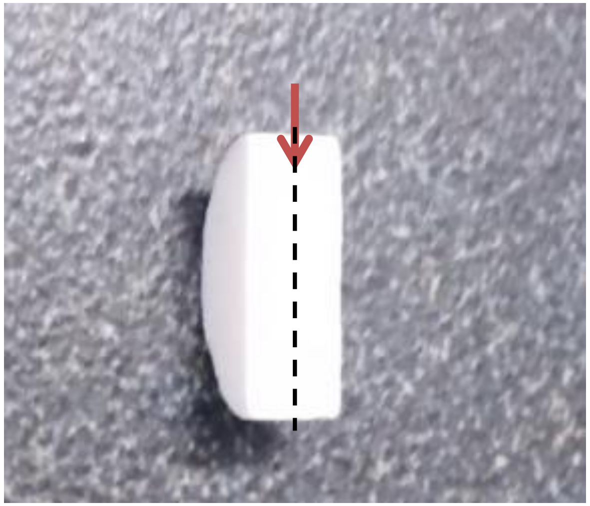
Source	Bending Magnet
Monochromator Type	Si(111)
Energy Range	15-18 keV
Resolution (ΔE/E)	1.5 x 10^{-4}
Flux (photons/sec)	8 x 10^{11} @15 keV
Beam Size (HxV)	
Focused	250µm x 160µm
Wavelength	0.72808 Å

Compressed Tablets (100 MPa) Time '0' (SXRD)

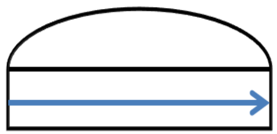


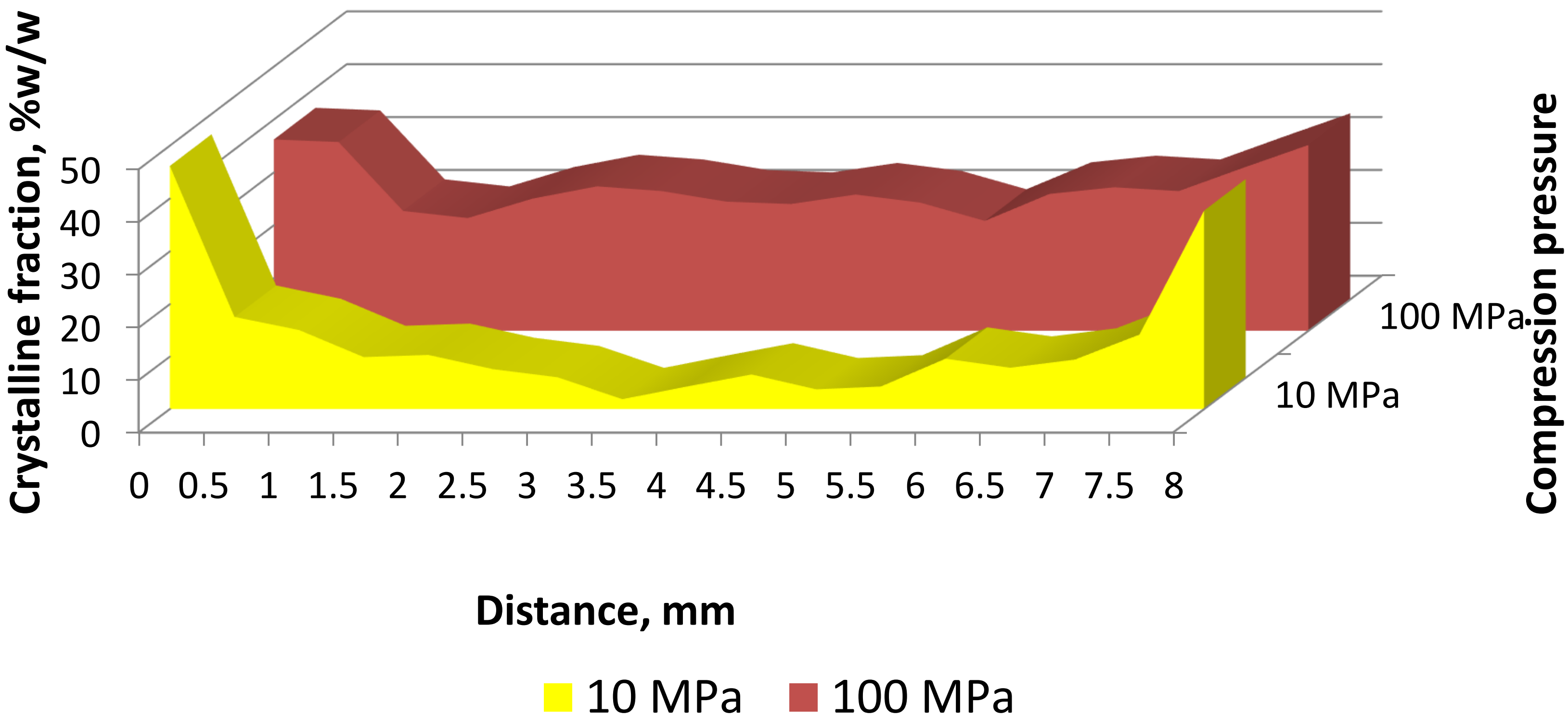


2D-XRD Depth Profiling Directions of Mapping

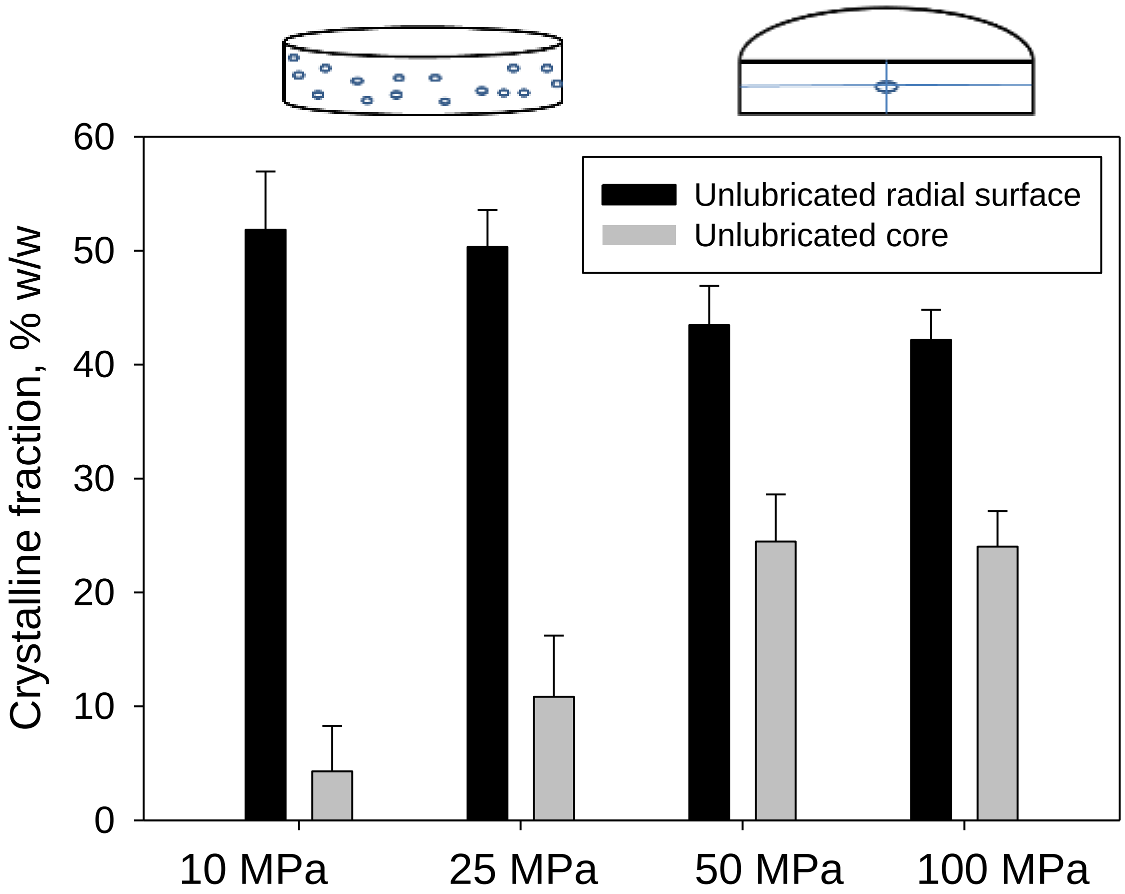


Depth Profiling (Radial) – 24 hours

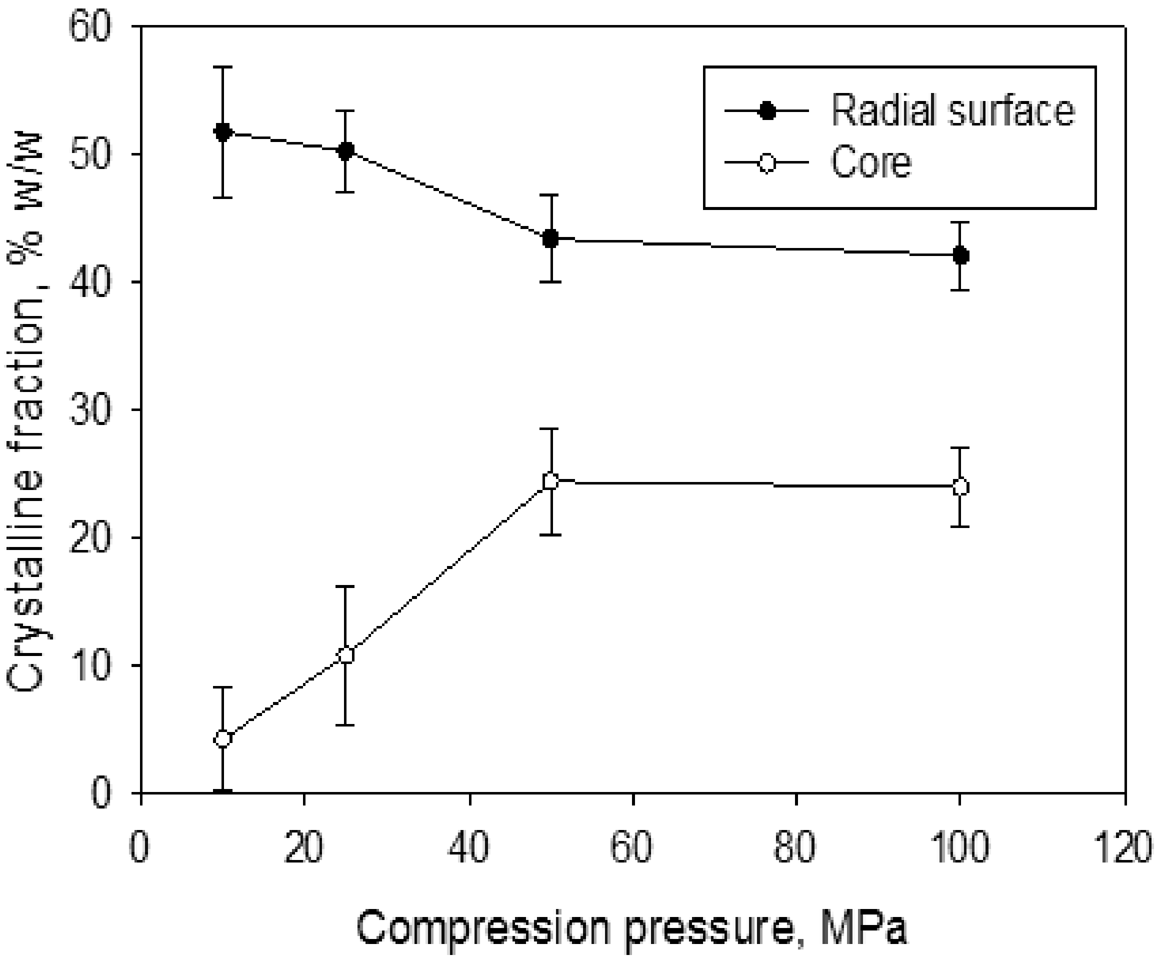




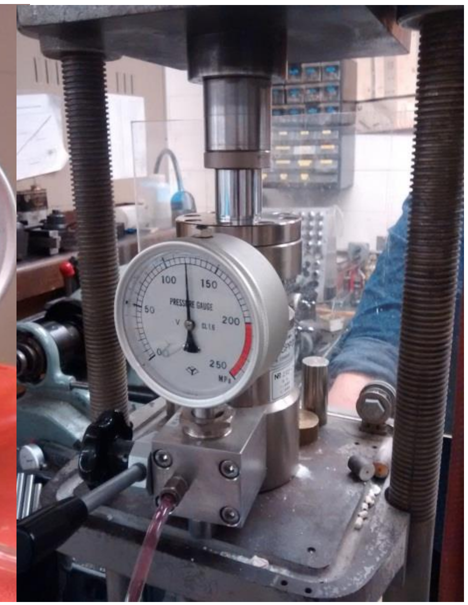
Unlubricated radial surface vs Core



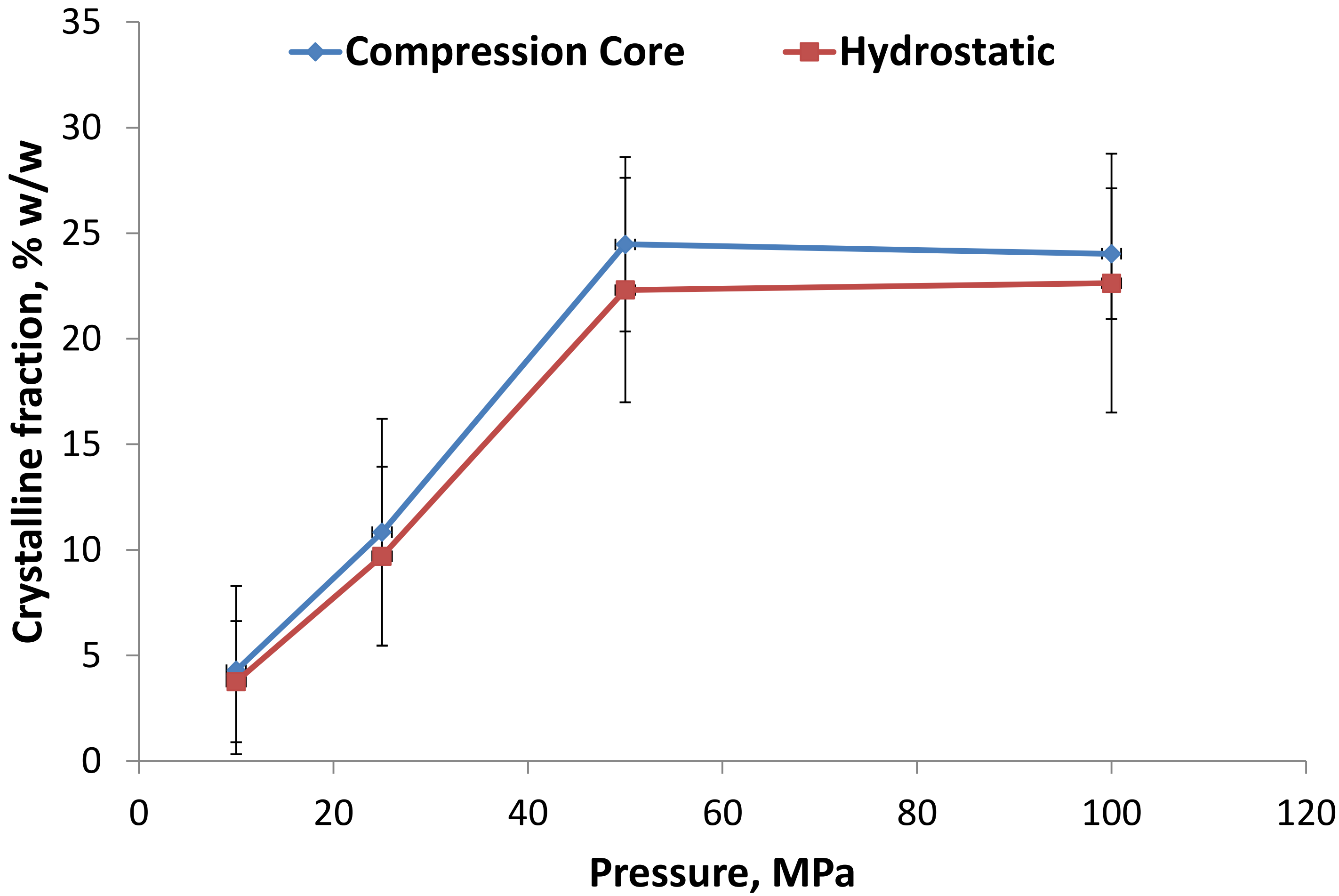
Unlubricated radial surface vs Core



Compression with no wall friction



Compression vs hydrostatic

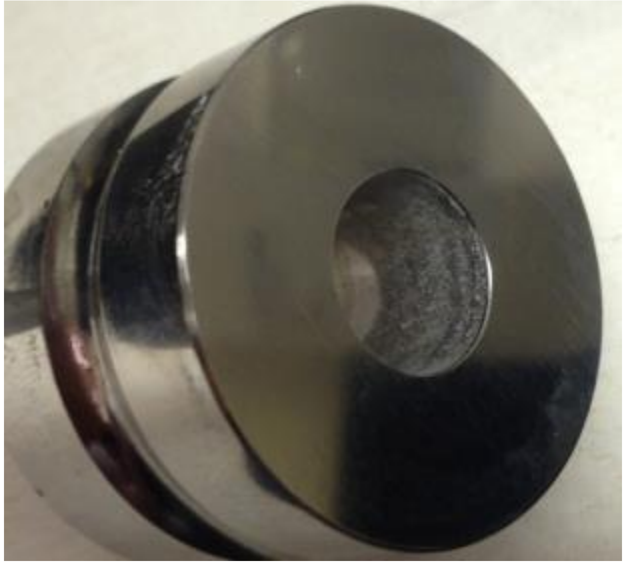


Lubrication (Magnesium stearate)

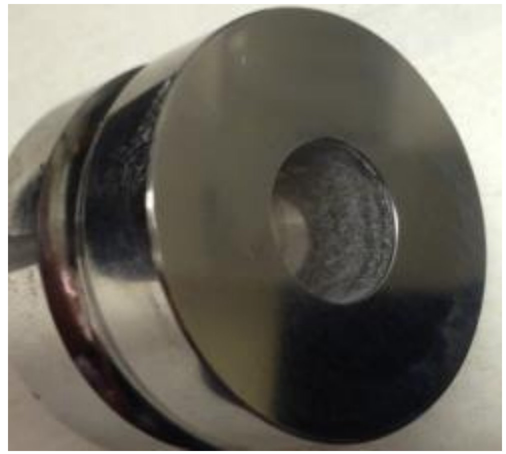
Internal lubrication

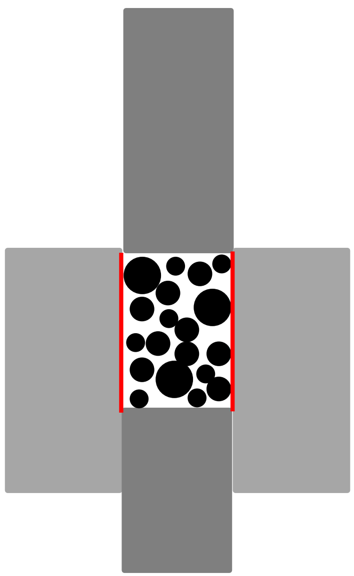
Magnesium stearate (1% w/w) was added to amorphous indomethacin, before compression

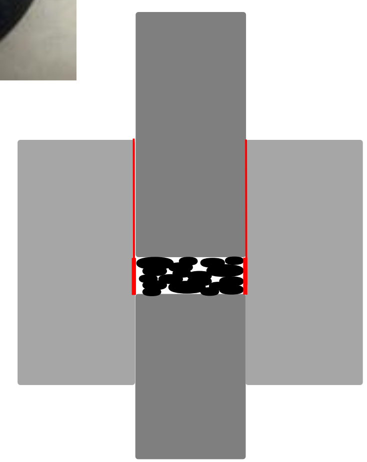
External lubrication



External lubrication

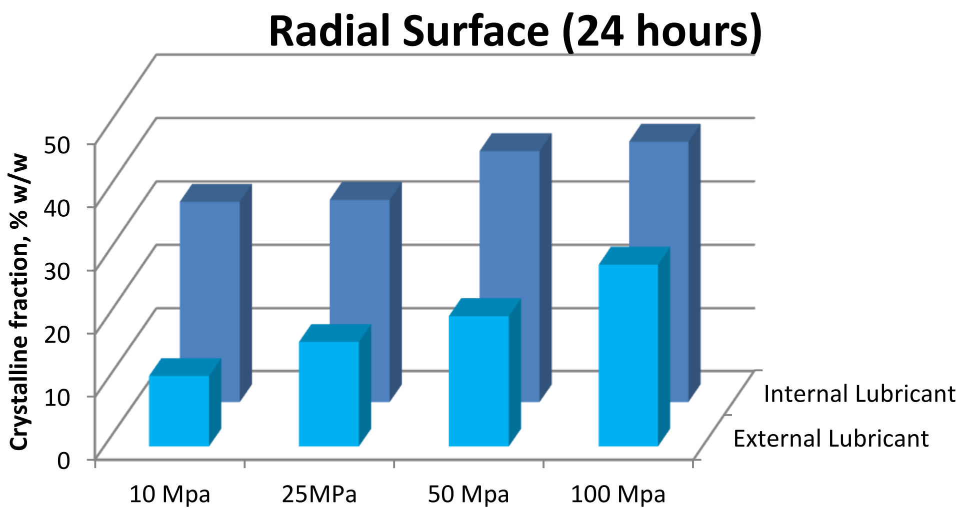


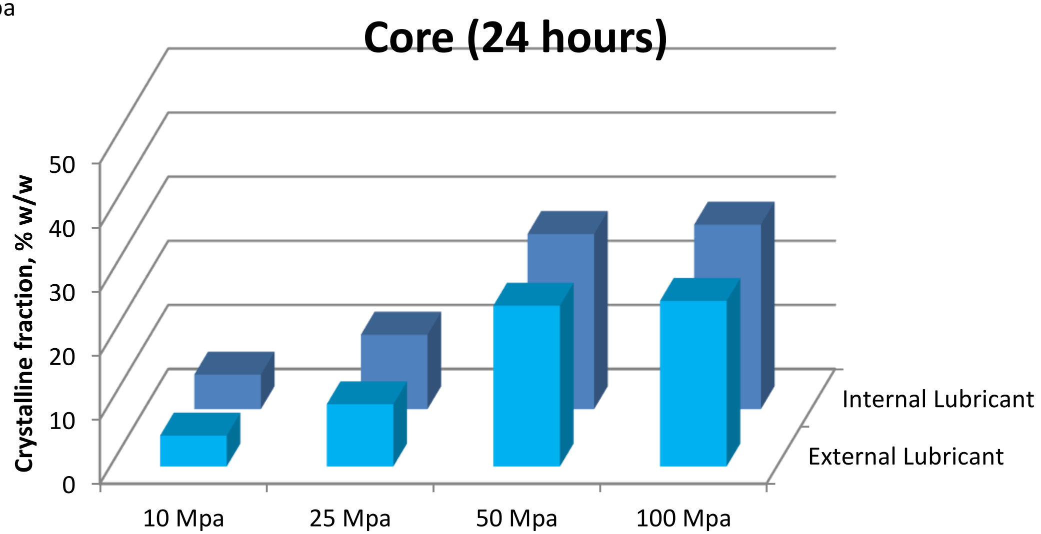




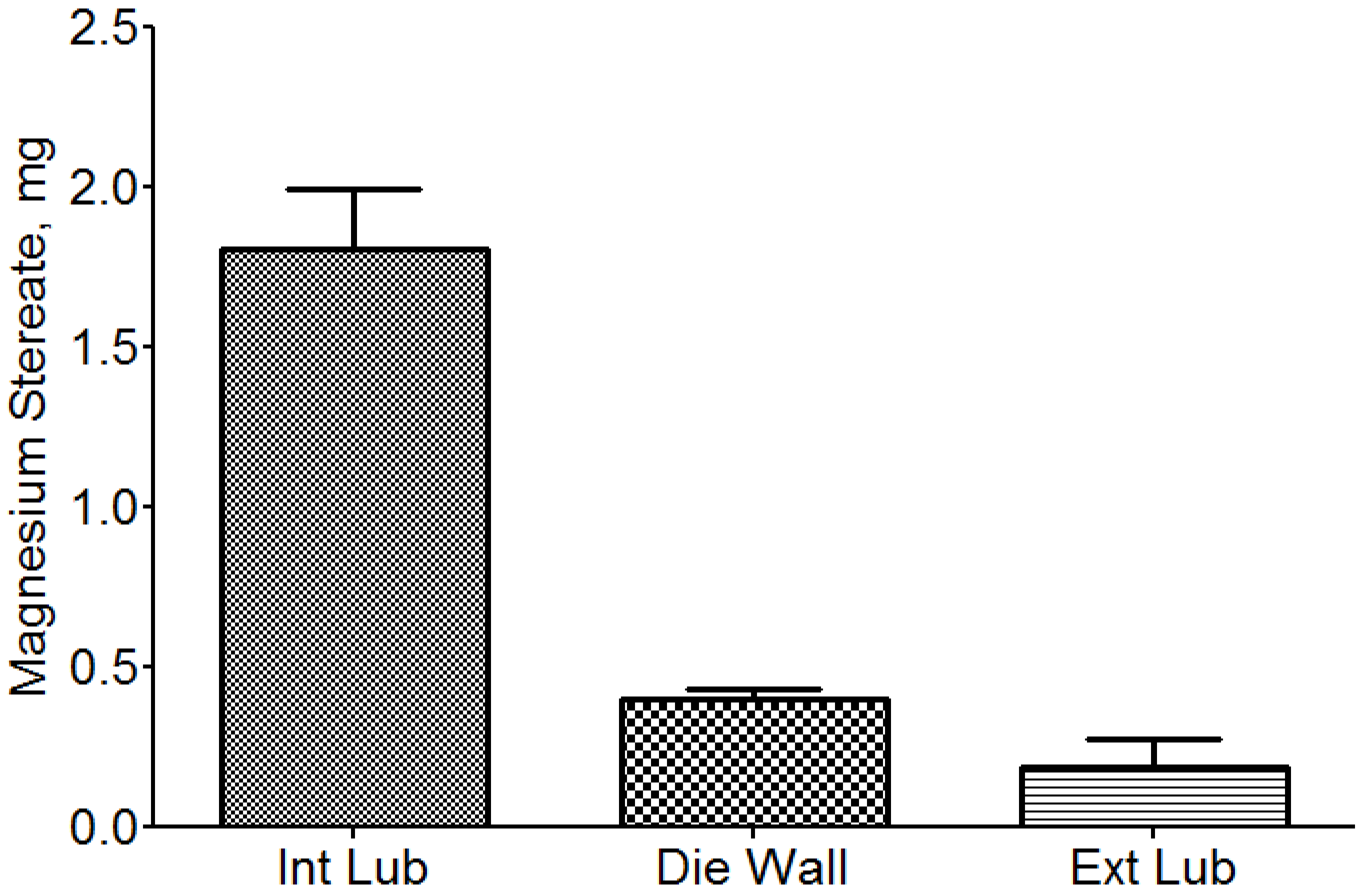
Magnesium stearate applied to die wall

Internal vs External lubrication





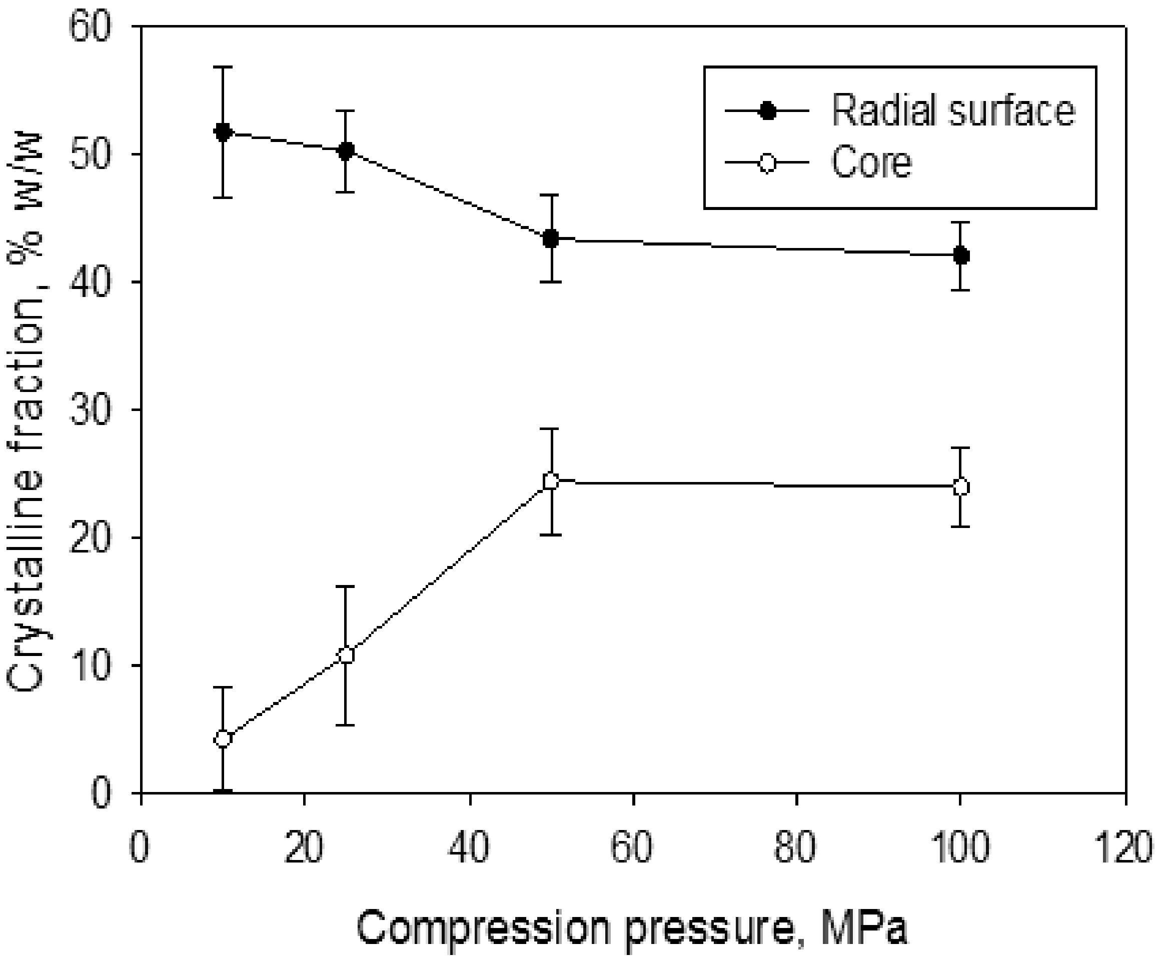
Inductively Coupled Plasma Mass Spectrometry (ICP-MS)



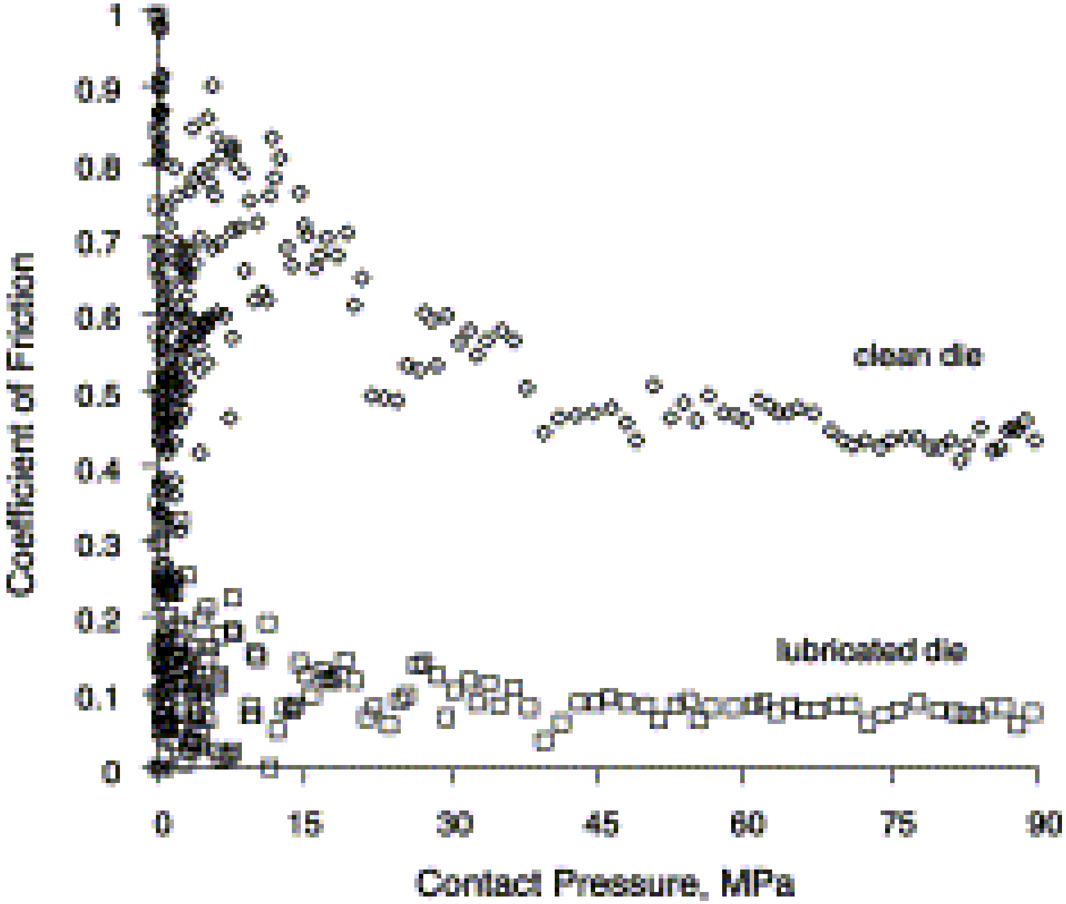
Conclusion

- Compression → induces crystallization.
- Shear stress due to die wall → additional crystallization.
- External lubrication → arrest additional crystallization.
- As pressure is inherent to compression, crystallization could not be stopped.

Unlubricated radial surface vs Core



Wall friction

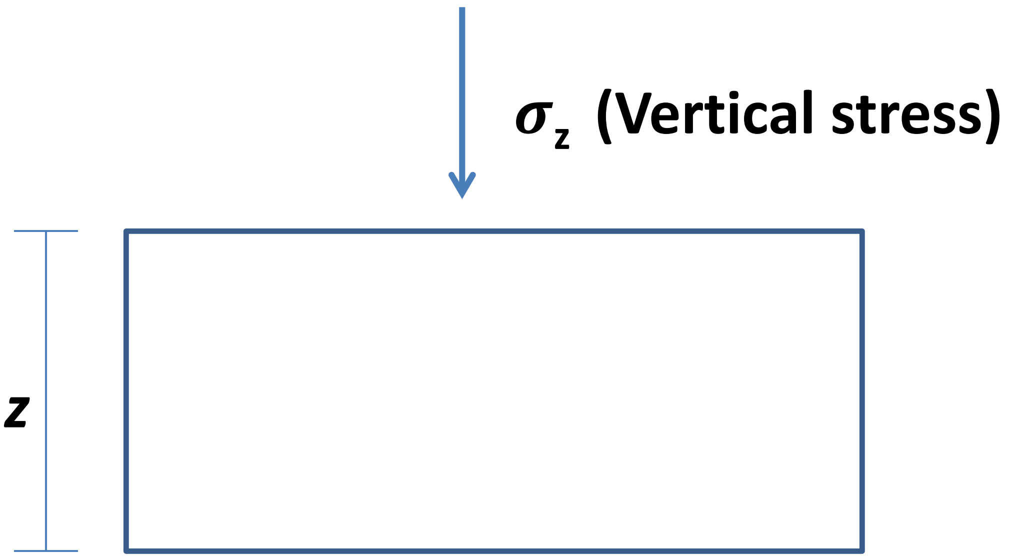


I.C Sinka 2003


INFLAMABLE
3
UN 1267

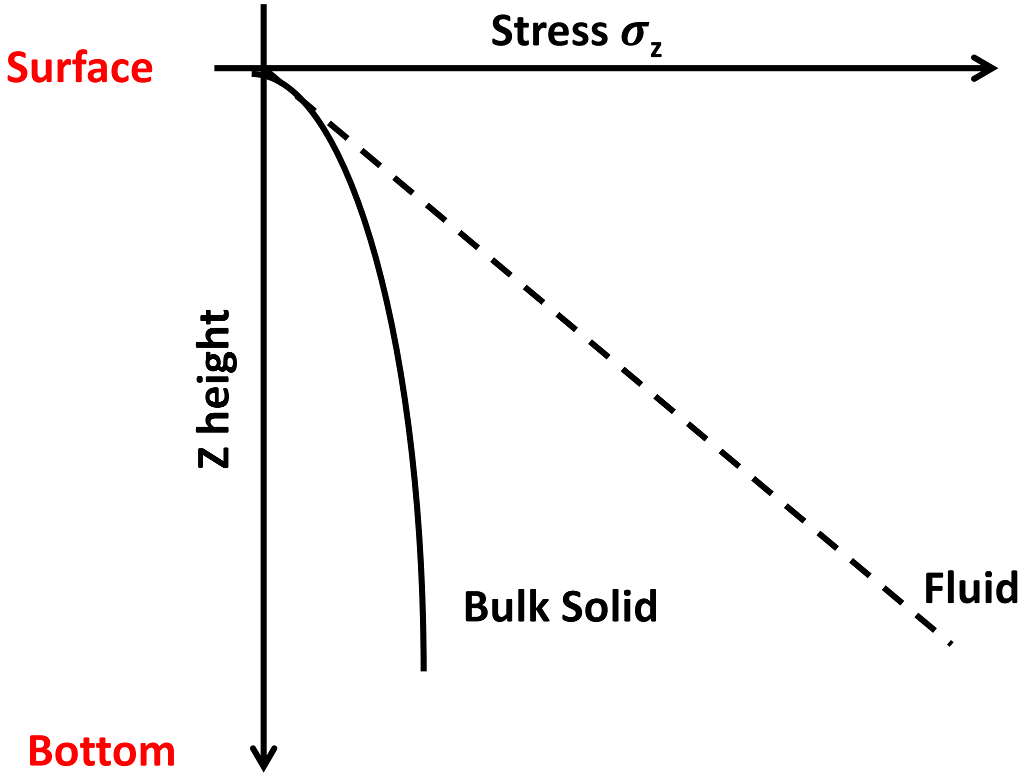
For liquids in a tank

$$\sigma_z = \rho g z$$



Z → height from top surface

Fluid vs Bulk solids



Janssen H A 1895

For bulk solids

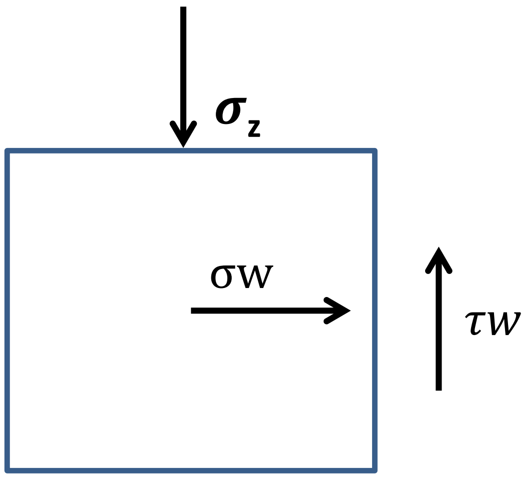
Janssen's analysis (stresses in a cylindrical silo)

$$\sigma_z = \frac{\rho g D}{4 \mu K}\left[1 - e^{\left(4\mu\frac{K}{D}\right)z}\right]$$

D → Diameter

μ → wall friction ($\mu = \frac{\tau w}{\sigma w}$)

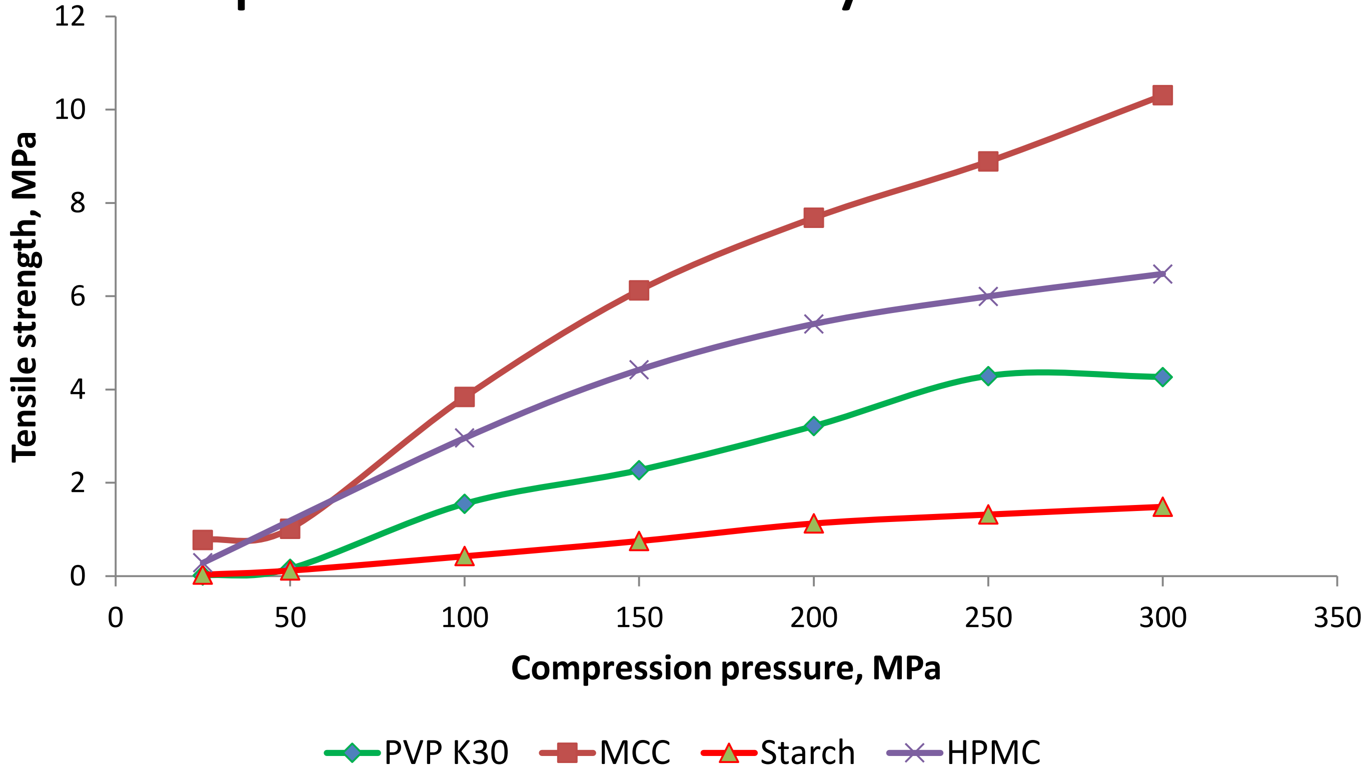
K → Stress ration ($\frac{\sigma w}{\sigma z}$)



Janssen H A 1895

Ongoing research

Reducing the compression pressure without compromising the tensile strength, by using plastic excipient like microcrystalline cellulose.



THANK YOU

QUESTIONS?