THE ANALYSIS OF NON-CRYSTALLINE MATERIALS IN PHARMACEUTICAL FORMULATIONS

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CONTRIBUTION BY GLOBAL ICDD MEMBERS

- 63 Members of the Organic and Pharmaceutical Subcommittee
- 31 Members of the Polymer Materials subcommittee

Subfile editing
Classifications
Focus on excipients
Support on non-crystalline references
Both data and specimens of commercial polymers

- Expert member task team on Nanomaterials
- Expert member task team on Cellulosic materials

(1,911 entries, 17% of pharmaceutical subfile)

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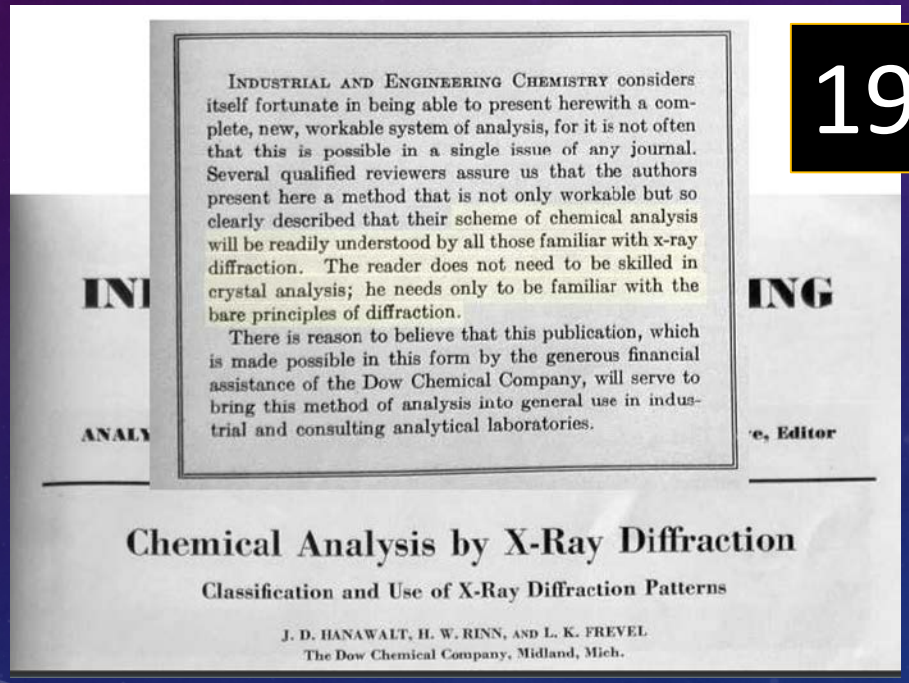
France.

THE ANALYSIS OF NON-CRYSTALLINE MATERIALS IN PHARMACEUTICAL FORMULATIONS

"A complete new workable system of analysis"



INDUSTRIAL AND ENGINEERING CHEMISTRY considers itself fortunate in being able to present herewith a complete, new, workable system of analysis, for it is not often that this is possible in a single issue of any journal. Several qualified reviewers assure us that the authors present here a method that is not only workable but so clearly described that their scheme of chemical analysis will be readily understood by all those familiar with x-ray diffraction. The reader does not need to be skilled in crystal analysis; he needs only to be familiar with the bare principles of diffraction.

There is reason to believe that this publication, which is made possible in this form by the generous financial assistance of the Dow Chemical Company, will serve to bring this method of analysis into general use in industrial and consulting analytical laboratories.

IN ING

ANALY e, Editor

Chemical Analysis by X-Ray Diffraction

Classification and Use of X-Ray Diffraction Patterns

J. D. HANAWALT, H. W. RINN, AND L. K. FREVEL
The Dow Chemical Company, Midland, Mich.

1938

1938 – Chemical Analysis by X-ray Diffraction

Celebrating 75 years 1941–2016 ICDD® INTERNATIONAL CENTRE FOR DIFFRACTION DATA

2016

Workable System of Analysis

- A relational database
- 516,054 reference data sets
- Organized for identification and quantitation
- 64 Searches
- 94 Display Fields
- JAVA point and click interfaces
- Extensive embedded applications for analyses

NON CRYSTALLINE MATERIALS IN PHARMACEUTICALS

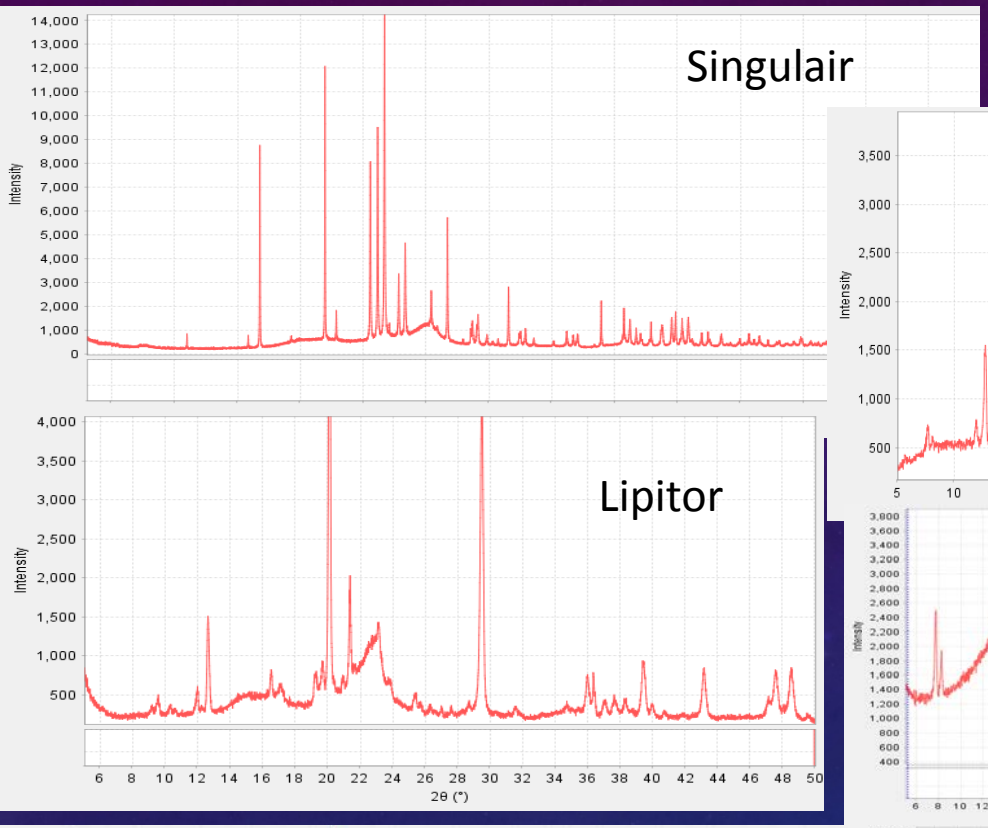
Definition

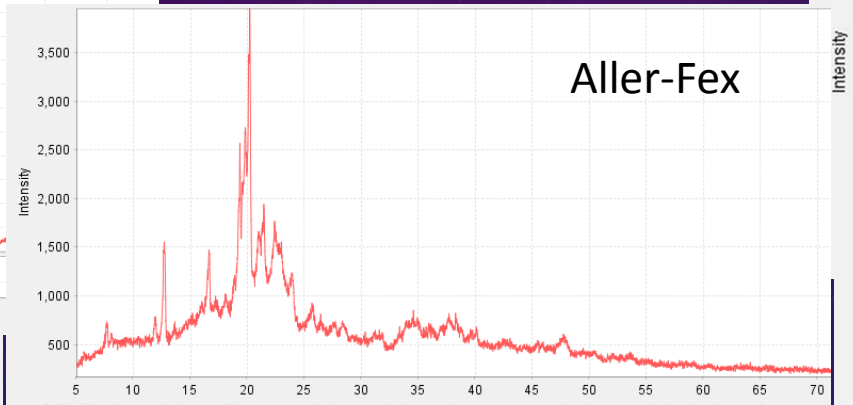
- Nanomaterials, amorphous materials, dimensional materials (i.e. clays)

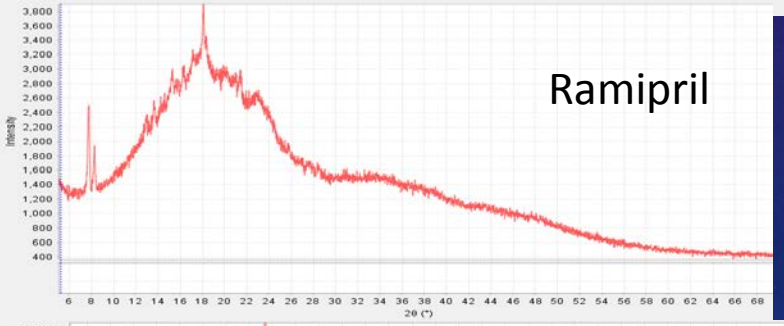
Application

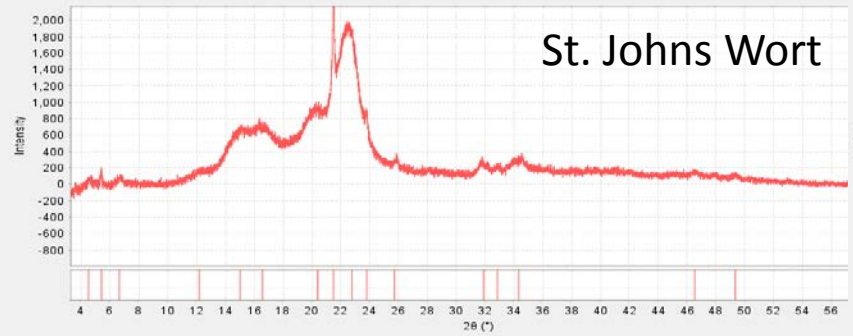
- High surface area materials – change dissolution rate
- Excipients with low density, high porosity can be chemically functionalized for features such as chemical binding and time release
- Functionalized polymers are used as binders or gelling agent

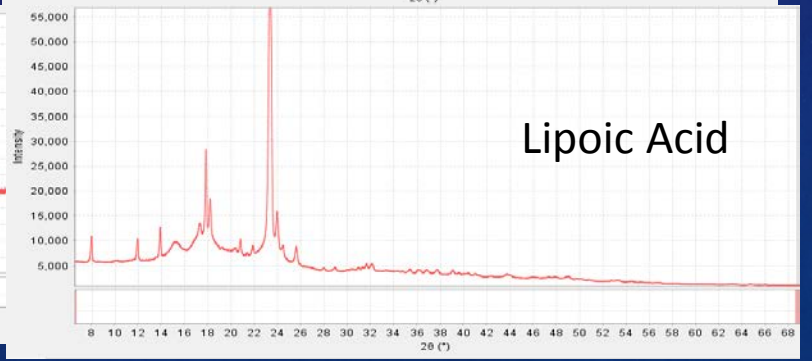
PRACTICAL CONSIDERATION – THE FREQUENT USE OF NON CRYSTALLINE INGREDIENTS IN PHARMACEUTICAL FORMULATIONS

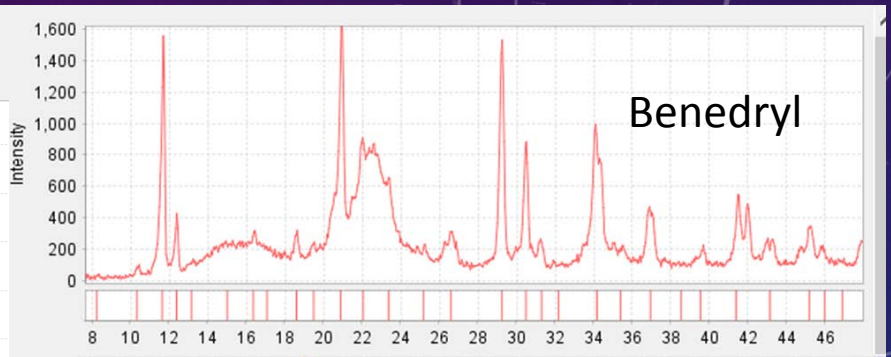


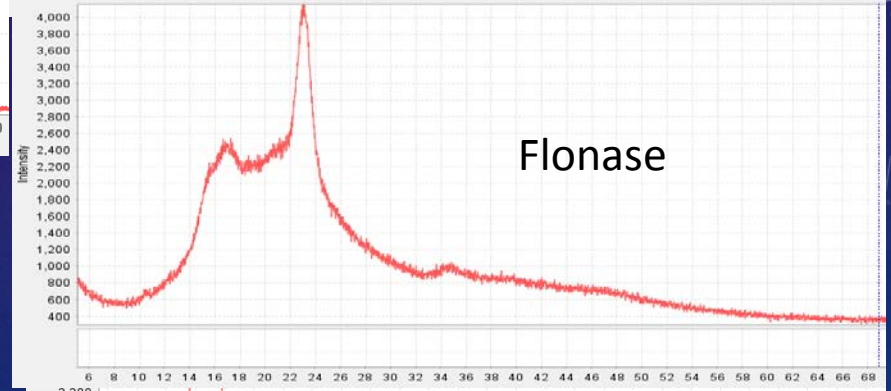


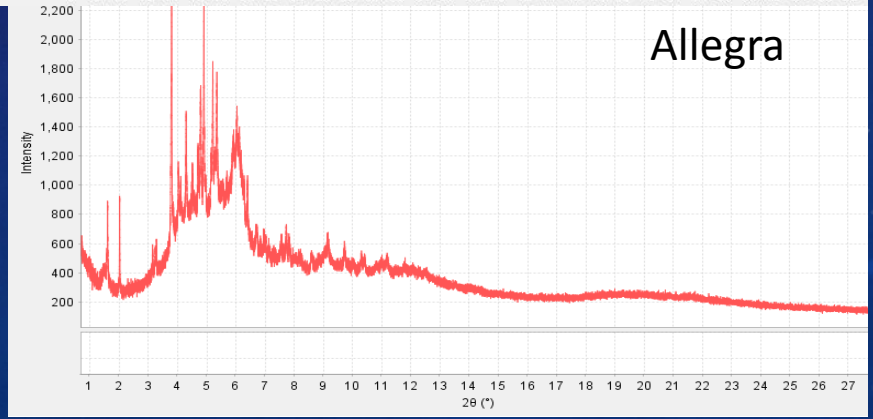












TOTAL PATTERN ANALYSIS METHOD

STEP 1

Experimental Data

Phase Identification via reference patterns

Analyze Components

Identification

STEP 2

Series of Reference Patterns

Add and Scale

Match to Experimental Data

- Crystallinity
- Crystallite Size
- Molecular Orientation

Reference Libraries

- *Polymers*
- *Clays*
- *Amorphous API's*
- *Nanomaterials*

Plotting and Scaling Programs

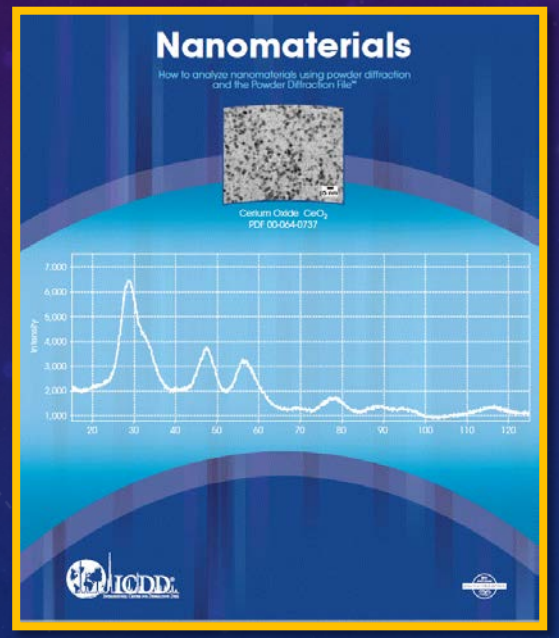
Crystallite Size Algorithms

Common corrections

- *Displacement*
- *Molecular Orientation*

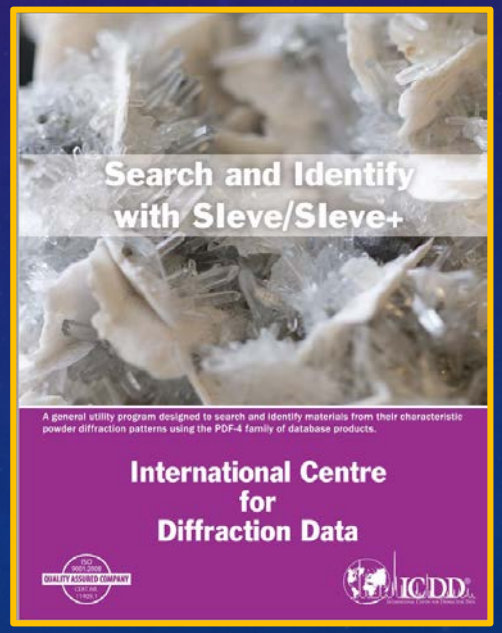
TOTAL PATTERN ANALYSIS METHOD

- Direct Method – Uses non crystalline reference patterns (pattern libraries)
- Uses nanocrystalline references – experimental and calculated
- Based on the use of additive patterns of both crystalline and non crystalline references
- Not a refinement method, the RIR method quantitation does use an intensity optimization
- A simulation, that does have corrections for crystallite size and molecular orientation
- Method does integrate ICDD quality reviews for both crystalline and noncrystalline materials



Crystallite Size Determinations

Tools for analyzing nanomaterials



Phase Identification

Quantitation by Reference Intensity Ratio

TOTAL PATTERN ANALYSIS METHOD

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Plotting and Scaling Programs

Crystallite Size Algorithms

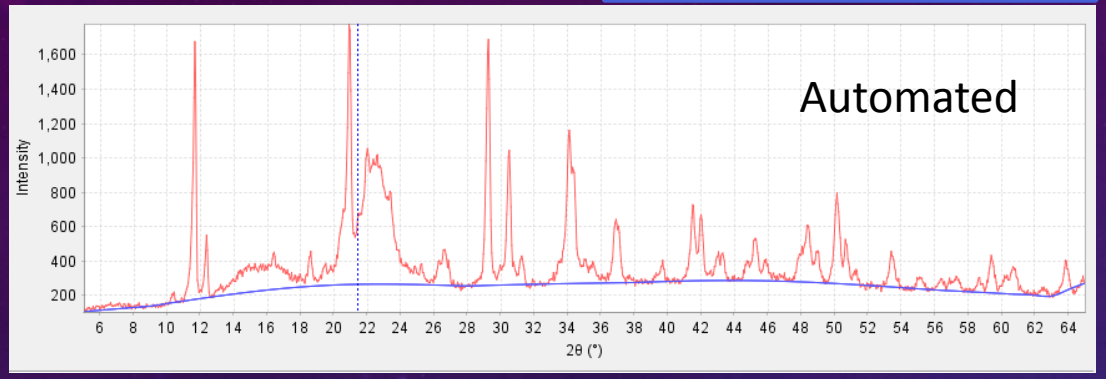
Common corrections

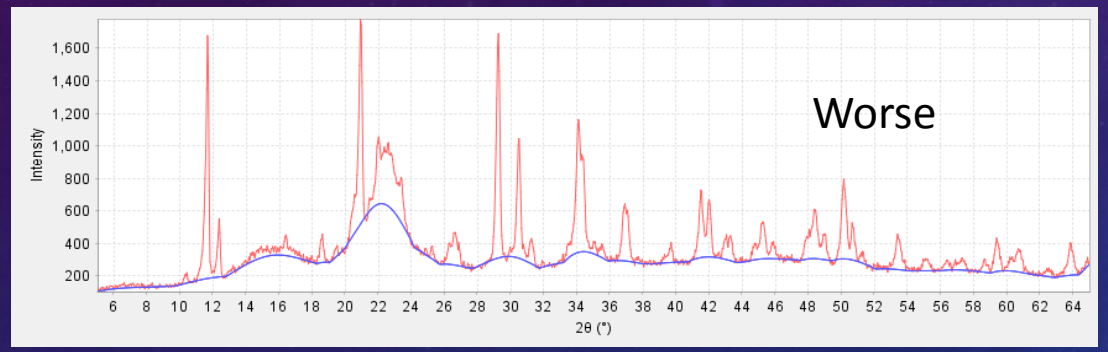
- *Displacement*
- *Molecular Orientation*

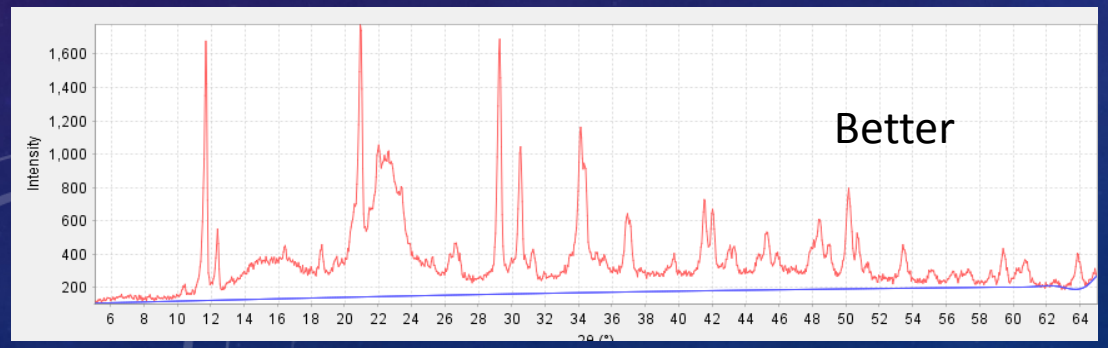
STEP 1 - SEARCH/MATCH

This

Background Correction







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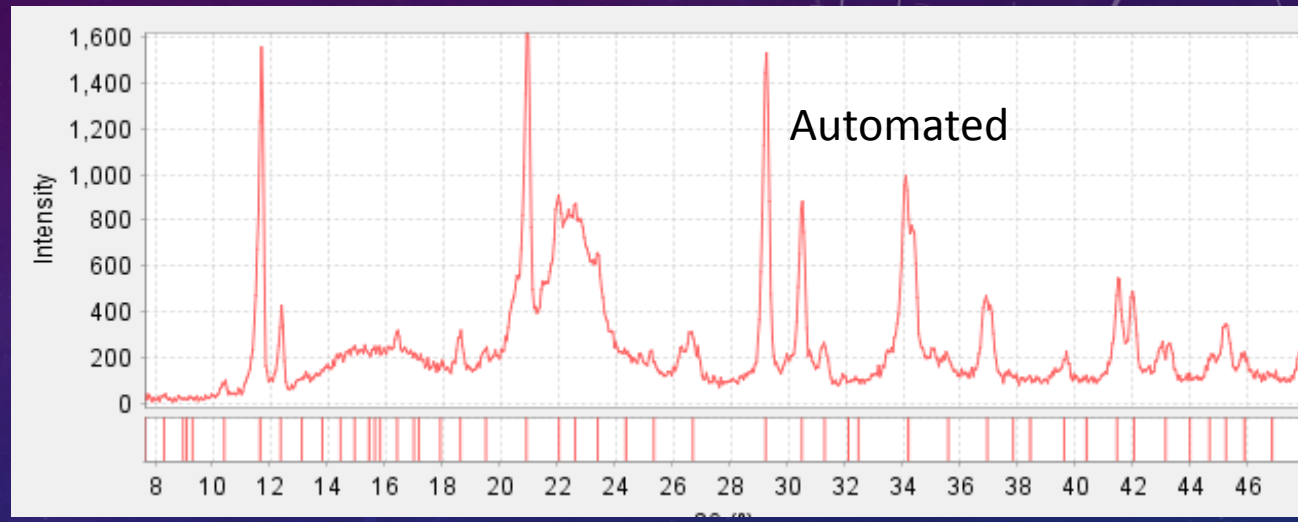
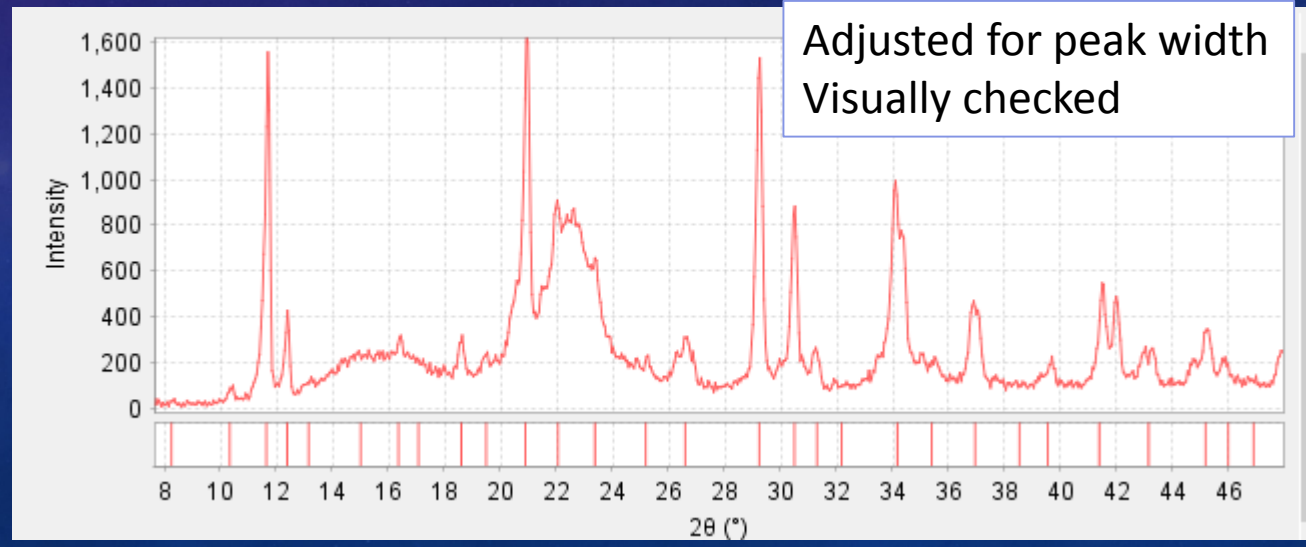
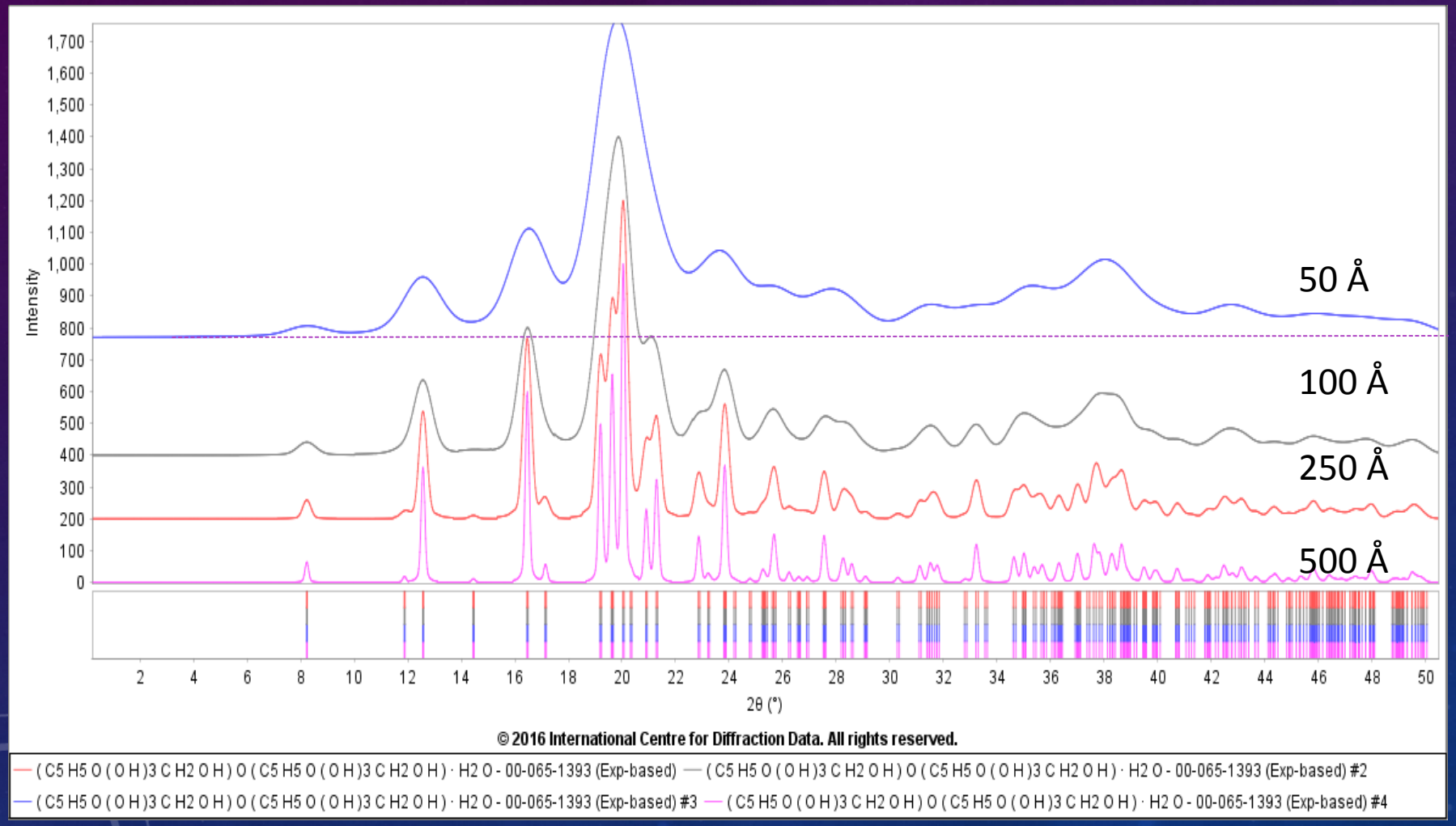
Peak Finding

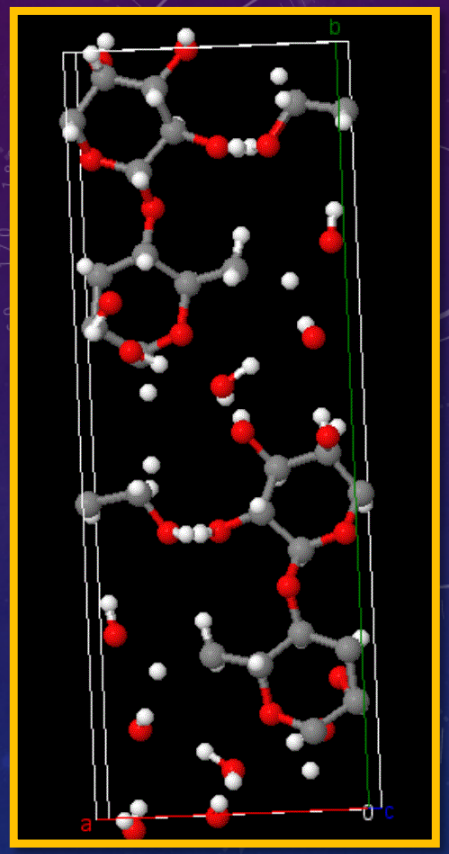


or This



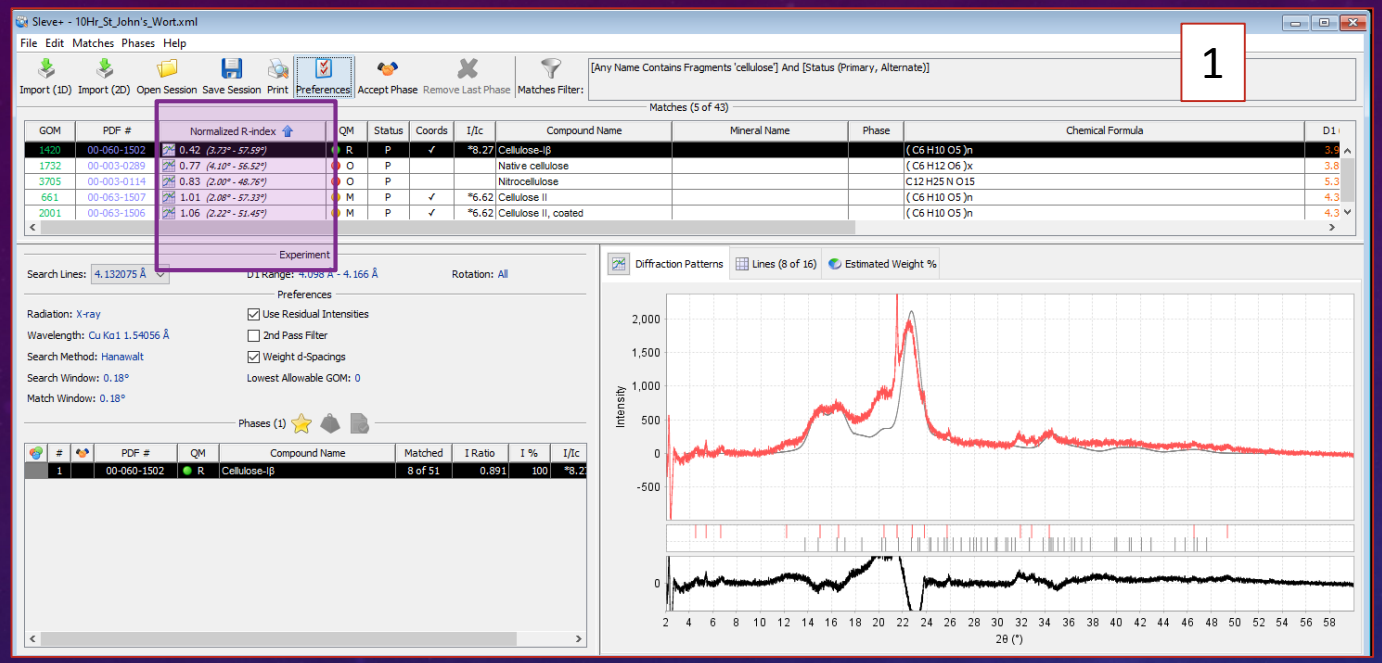
CRYSTALLITE SIZE - NANOMATERIALS

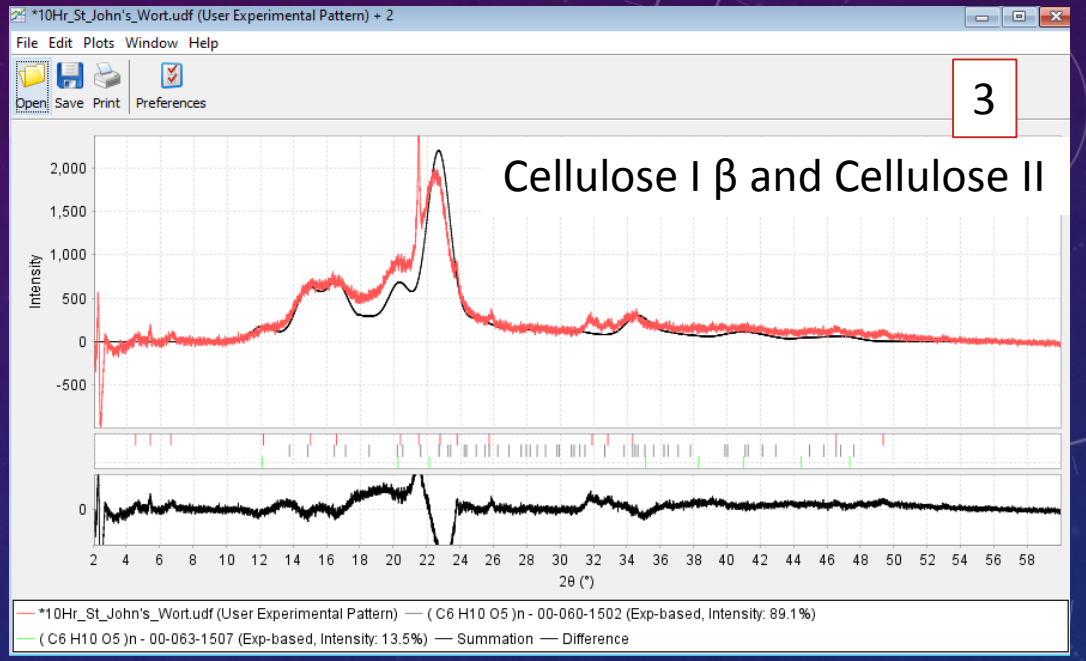




Lactose Monohydrate

INTEGRAL INDEX MATCH – NORMALIZED R INDEX





Created a reference file with 45 Å references

This is a full pattern profile match using all data points

STEP 1 – SEARCH MATCH

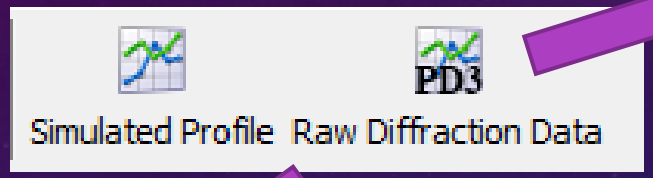
- All global major commercial software packages (6) will identify crystalline phases above 10 wt %
- To identify low concentration materials, nanomaterials, and amorphous materials - adjustments are required for background subtraction and peak finding

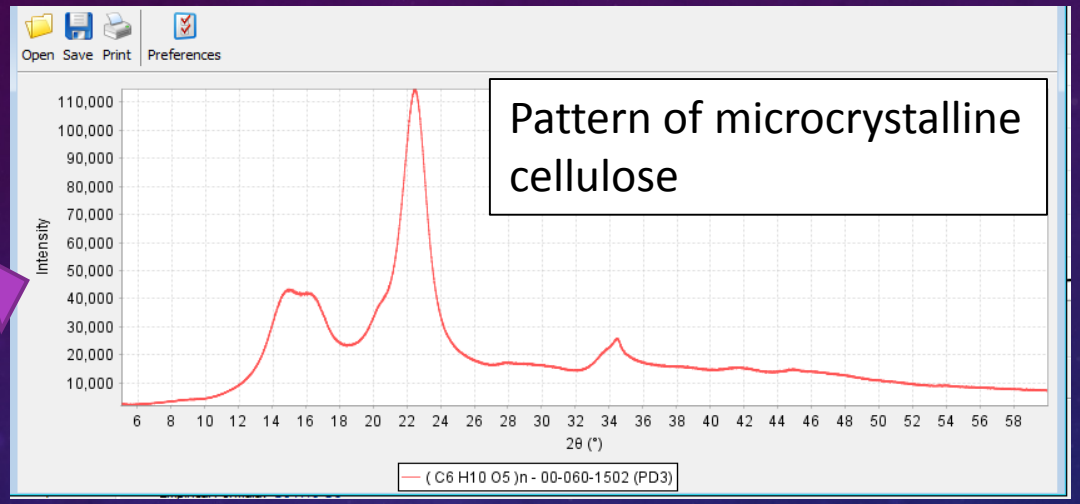
Find all peaks
Find all broad peaks
Obtain correct peak intensities

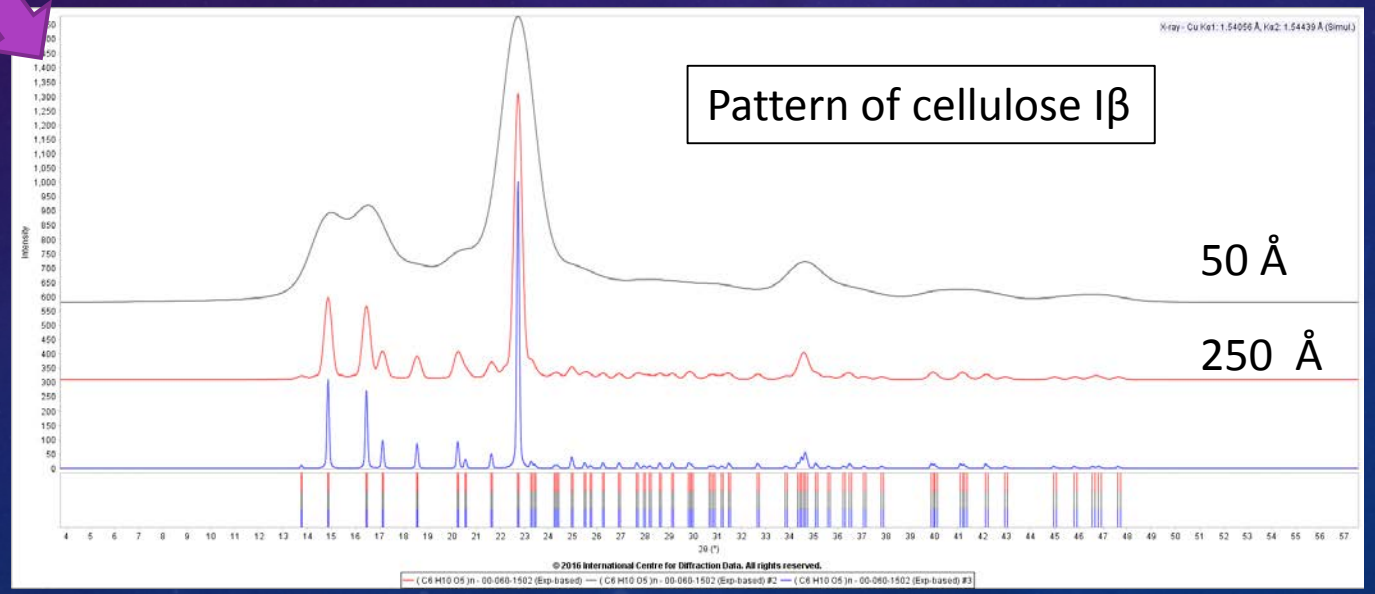
STEP 2 - PATTERN MATCHING

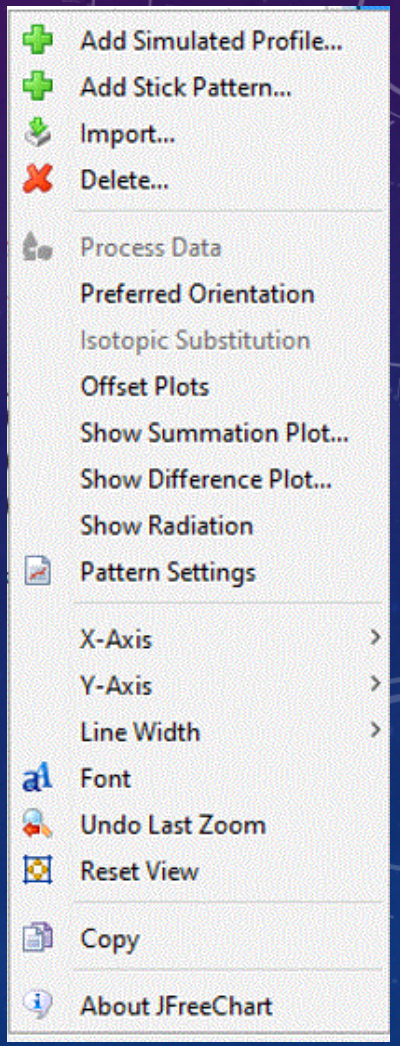
Via

Sieve+ Search Match or *Any* reference Pattern

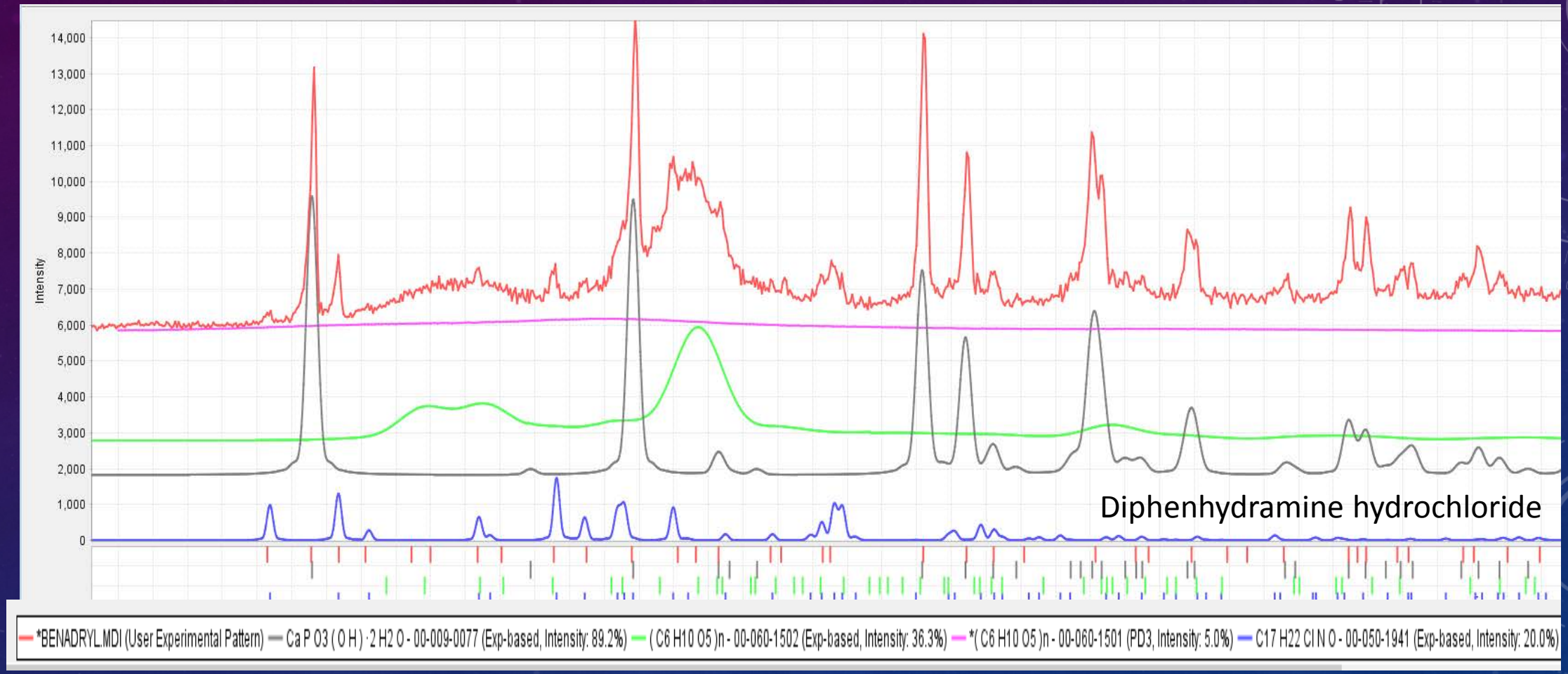








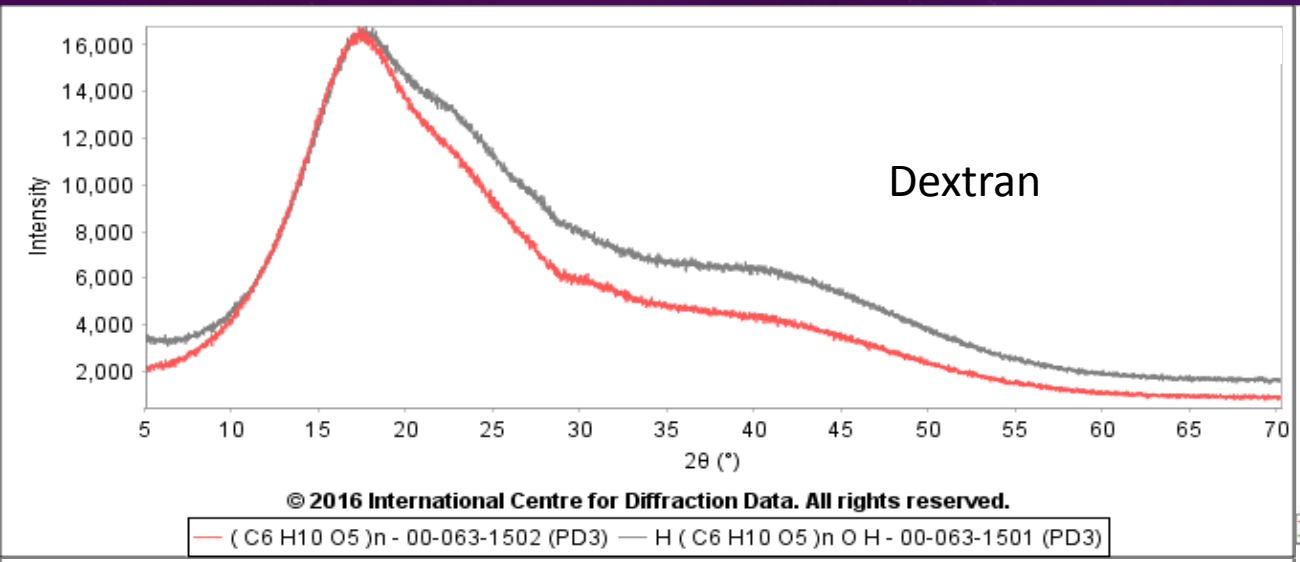
BENEDRYL

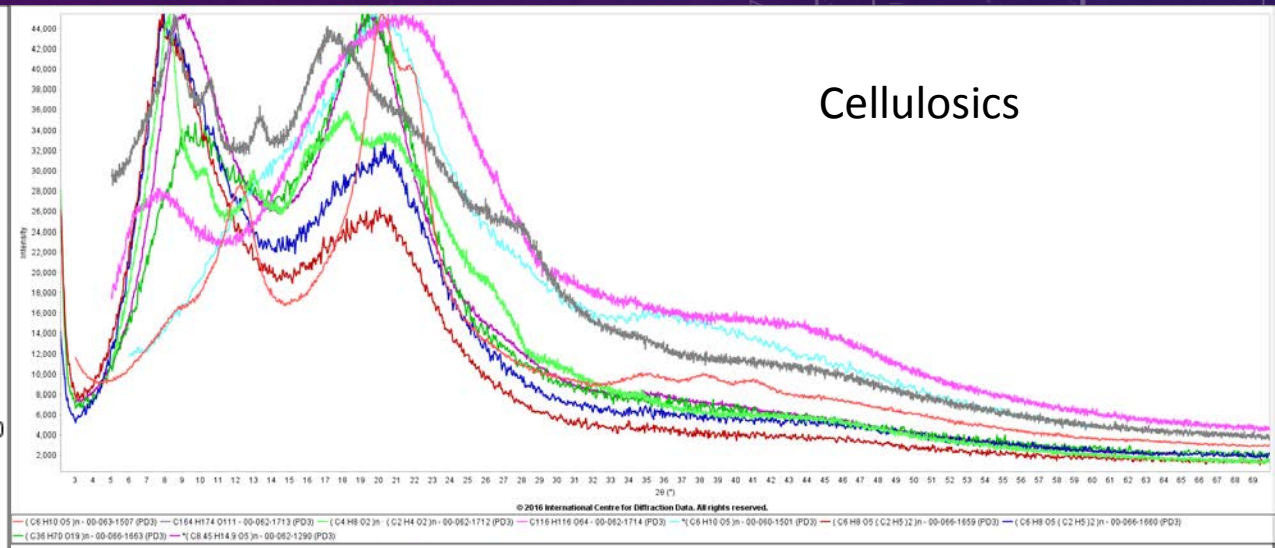

Intensity
14,000
13,000
12,000
11,000
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
Diphenhydramine hydrochloride
*BENADRYL.MDI (User Experimental Pattern)
Ca P O3 (O H) ·2 H2 O - 00-009-0077 (Exp-based, Intensity: 89.2%)
(C6 H10 O5)n - 00-060-1502 (Exp-based, Intensity: 36.3%)
*(C6 H10 O5)n - 00-060-1501 (PD3, Intensity: 5.0%)
C17 H22 Cl N O - 00-050-1941 (Exp-based, Intensity: 20.0%)

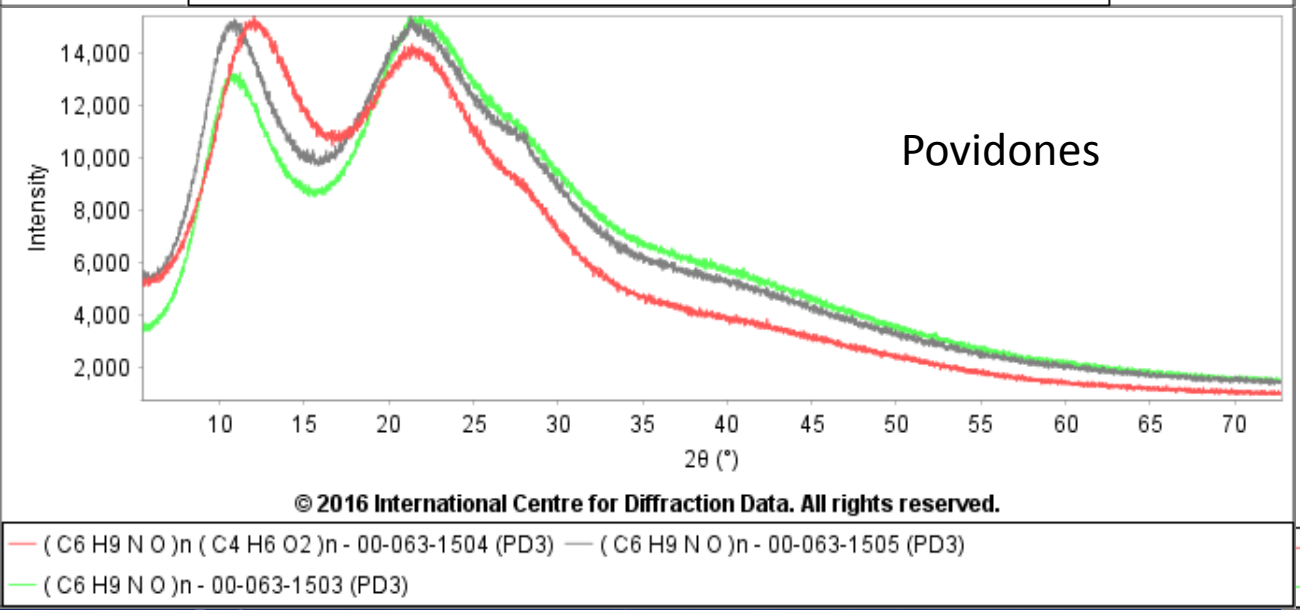
WHY FULL PATTERN ANALYSIS

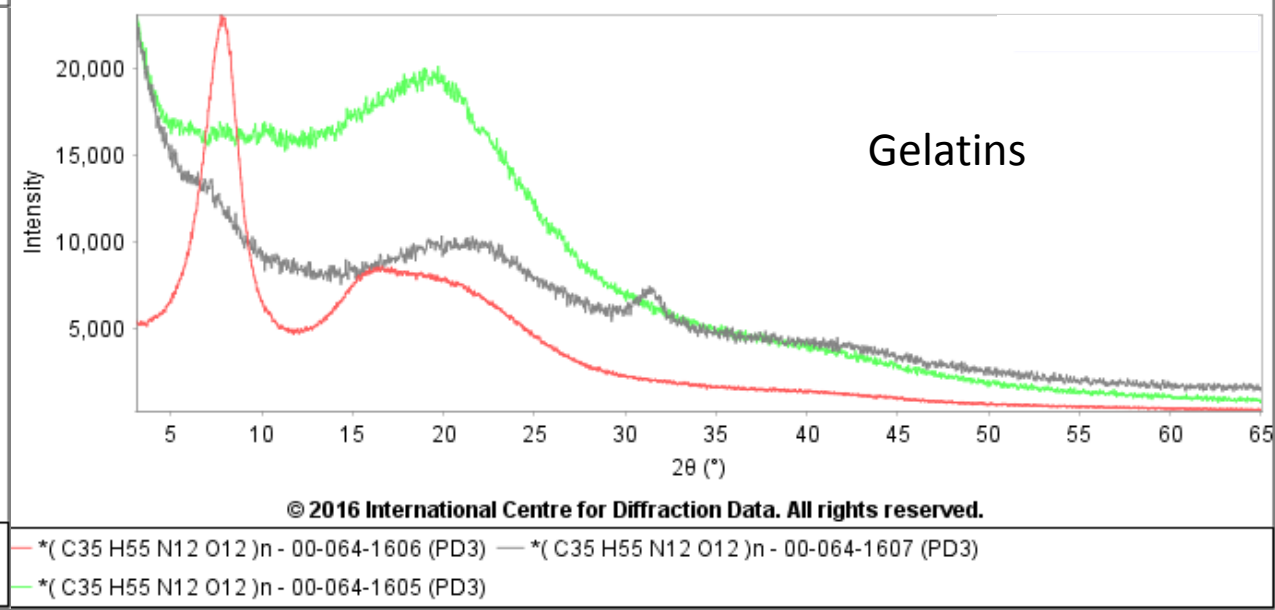
- Patterns are additive
- Visual
- Fast and convenient (to the user)

LIBRARY OF AMORPHOUS EXCIPIENTS







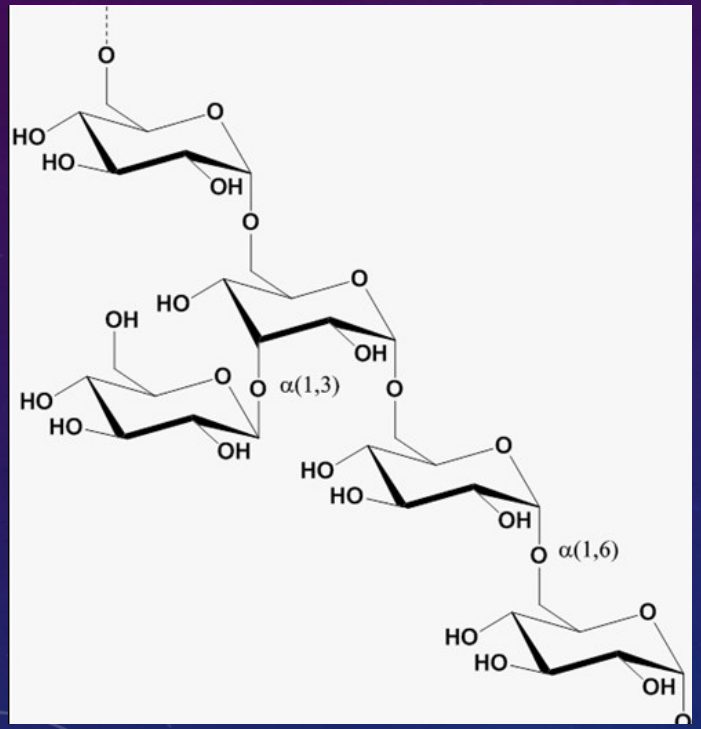


CHEMISTRY

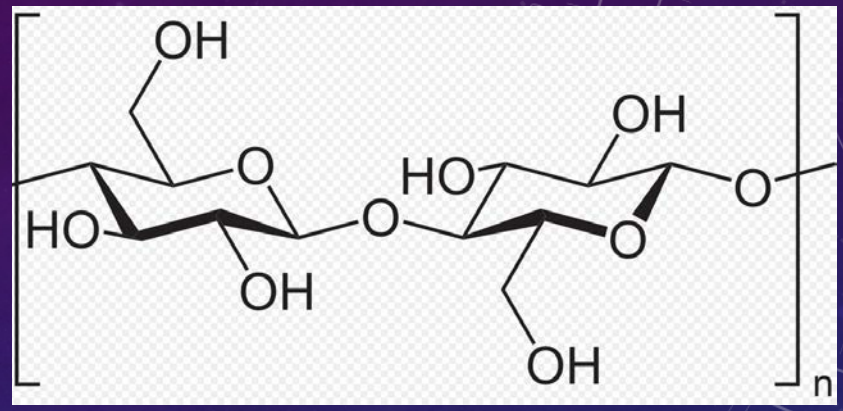
Define chemistry
…….Degree of substitution

Characterize Molecular Weight
Cross linking
Water content (TGA,DSC)

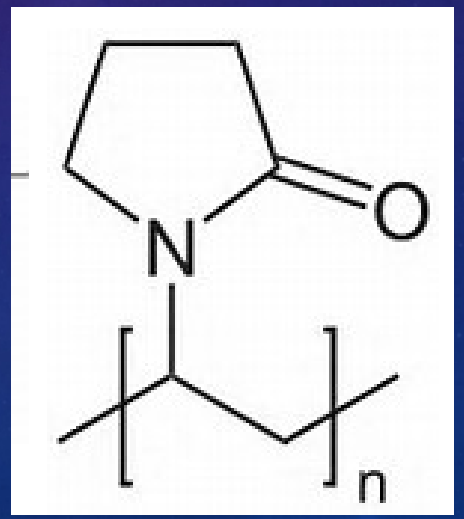
Dextran



Cellulose



3 – OH's / monomer



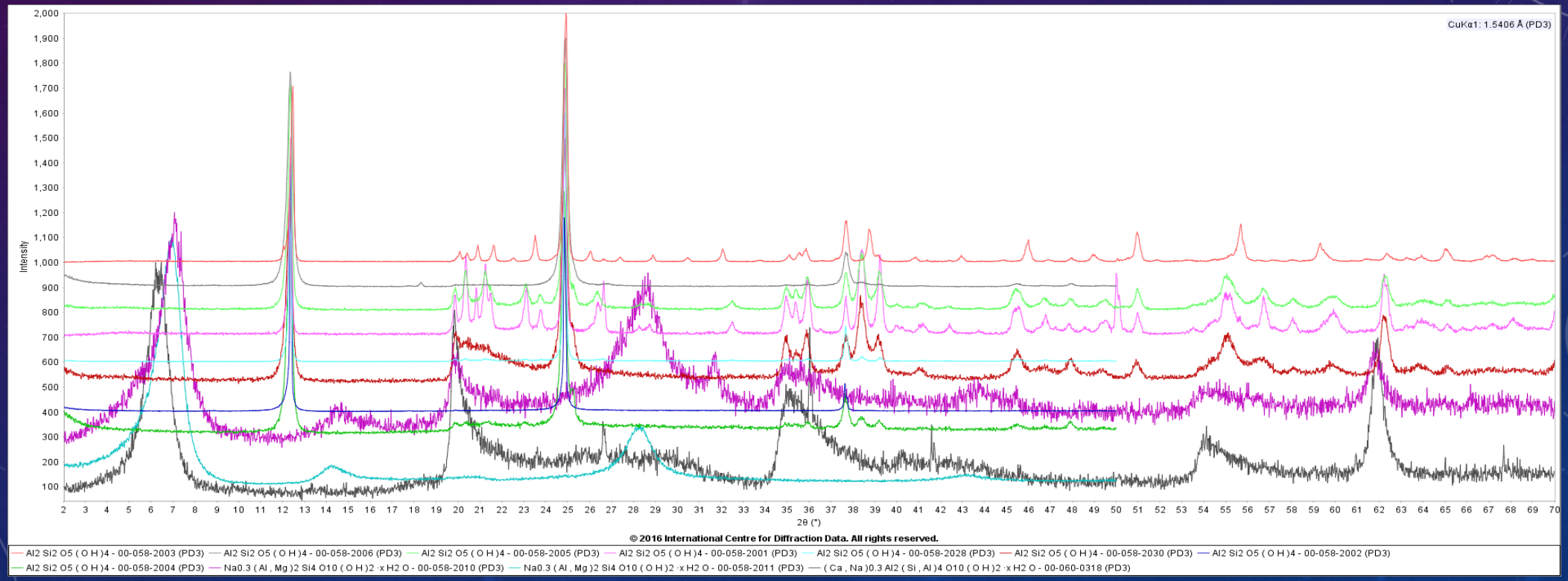
Povidone

Polyvinylpyrollidine

CLAY EXCIPIENTS

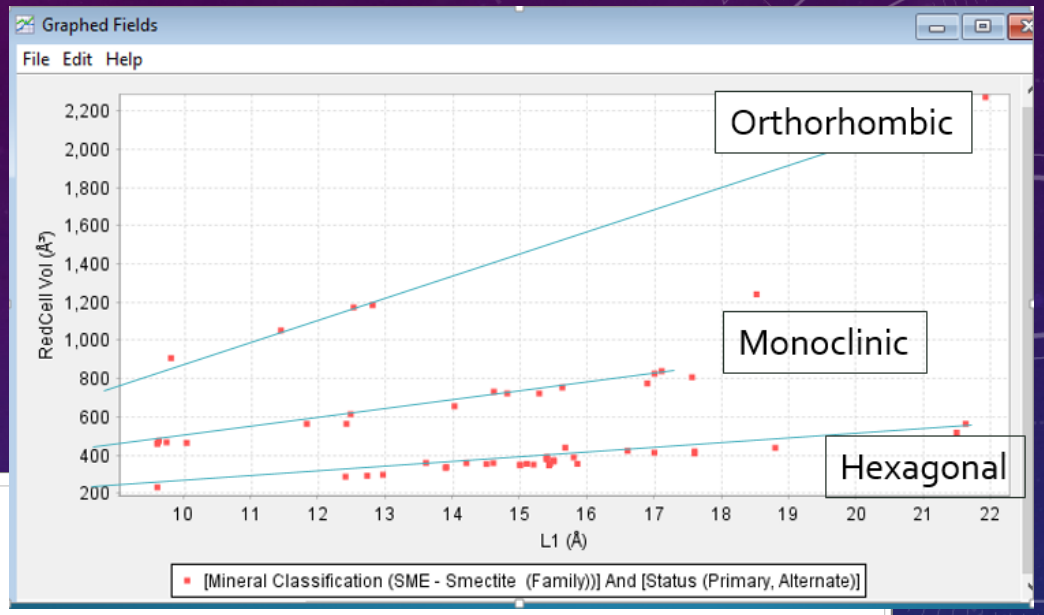
Drying agents
Absorb water

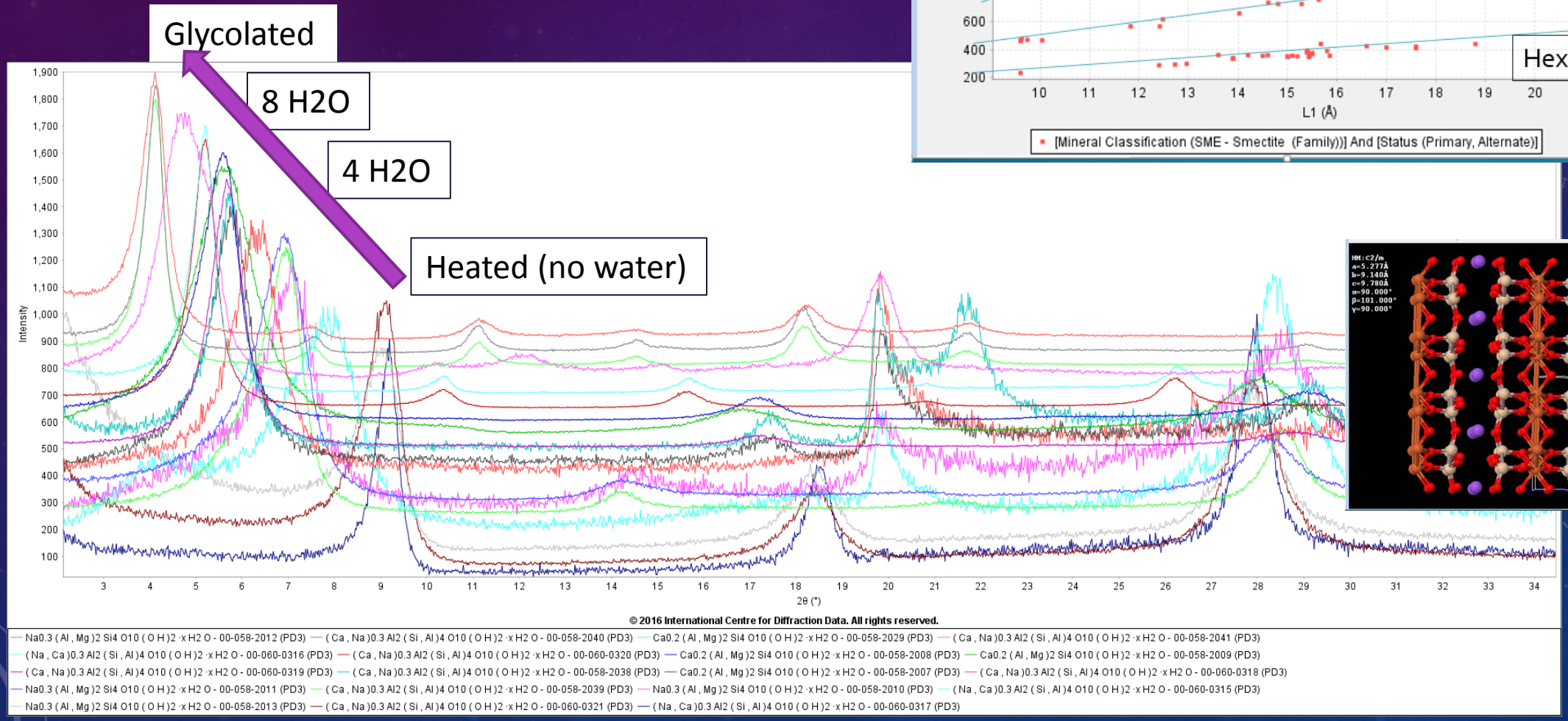
Montmorillonite, Dickite, Kaolinite



MONTMORILLONITE/SMECTITE

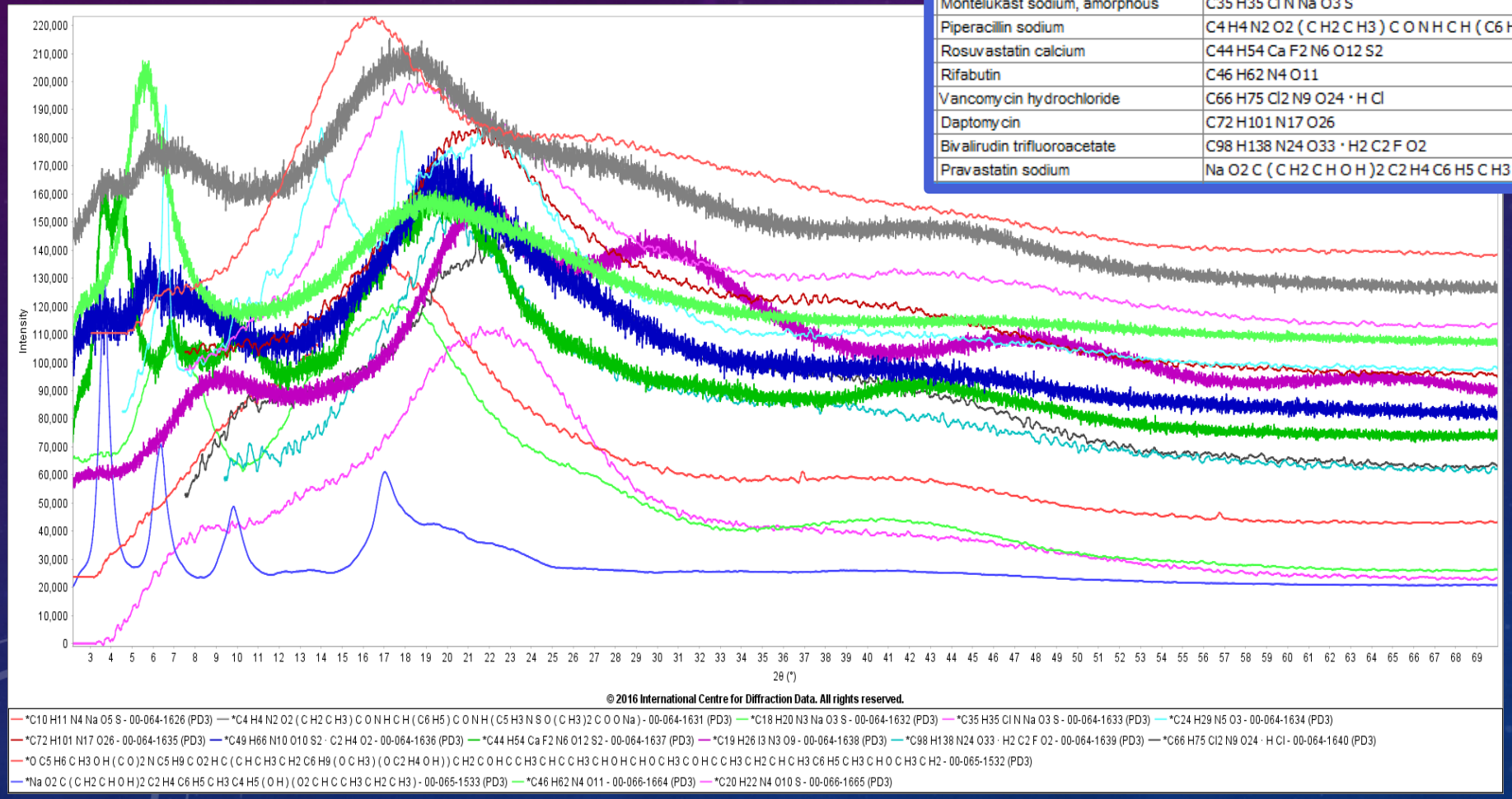
How much absorbed H_2O ?



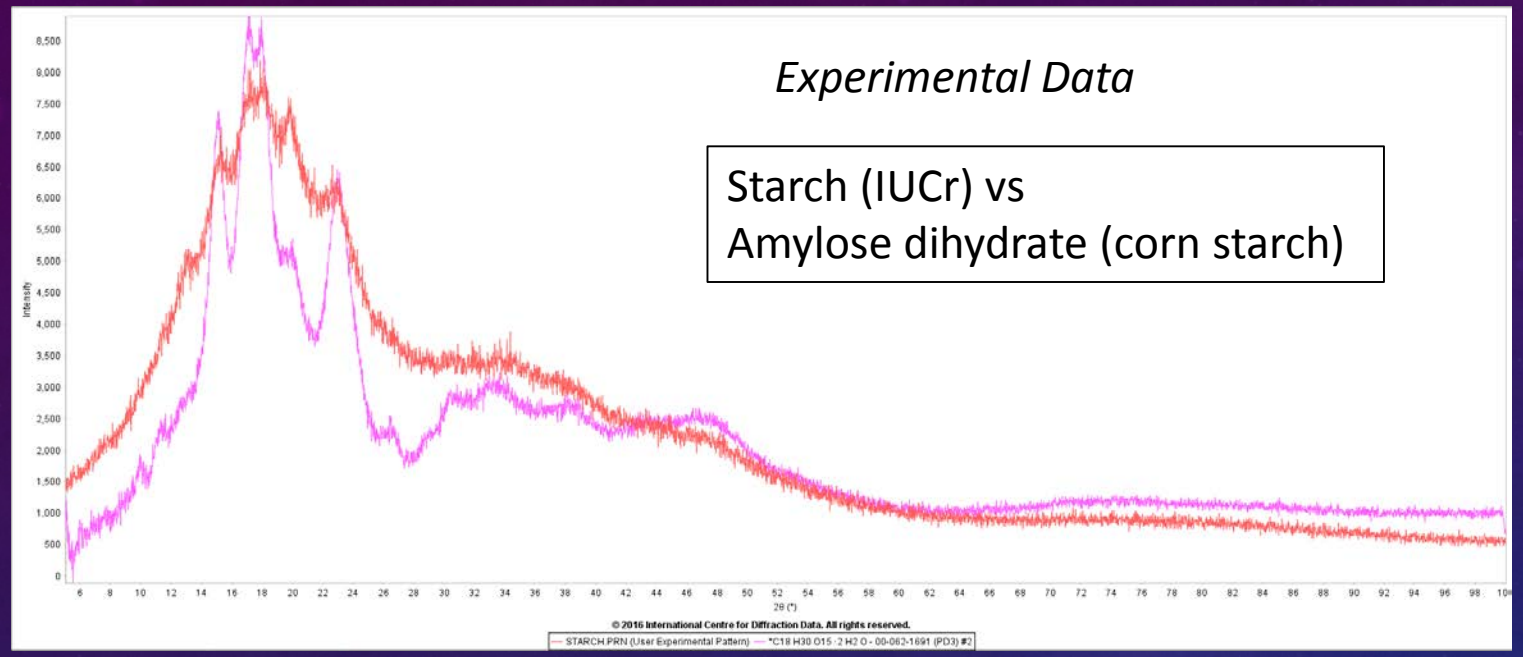


LIBRARY OF AMORPHOUS PHARMACEUTICALS

Compound Name	Chemical Formula
Valsartan	C24 H29 N5 O3
Iohexol	C19 H26 I3 N3 O9
Tazobactam sodium	C10 H11 N4 Na O5 S
Octreotide acetate	C49 H66 N10 O10 S2 · C2 H4 O2
Rabeprazole sodium	C18 H20 N3 Na O3 S
Cefuroxime axetil	C20 H22 N4 O10 S
Montelukast sodium, amorphous	C35 H35 Cl N Na O3 S
Piperacillin sodium	C4 H4 N2 O2 (C H2 C H3) C O N H C H (C6 H5) C O N H (C5 H3 N S O (C H3)2 C O O Na)
Rosuvastatin calcium	C44 H54 Ca F2 N6 O12 S2
Rifabutin	C46 H62 N4 O11
Vancomycin hydrochloride	C66 H75 Cl2 N9 O24 · H Cl
Daptomycin	C72 H101 N17 O26
Bivalirudin trifluoroacetate	C98 H138 N24 O33 · H2 C2 F O2
Pravastatin sodium	Na O2 C (C H2 C H O H)2 C2 H4 C6 H5 C H3 C4 H5 (O H) (O2 C H C C H3 C H2 C H3)

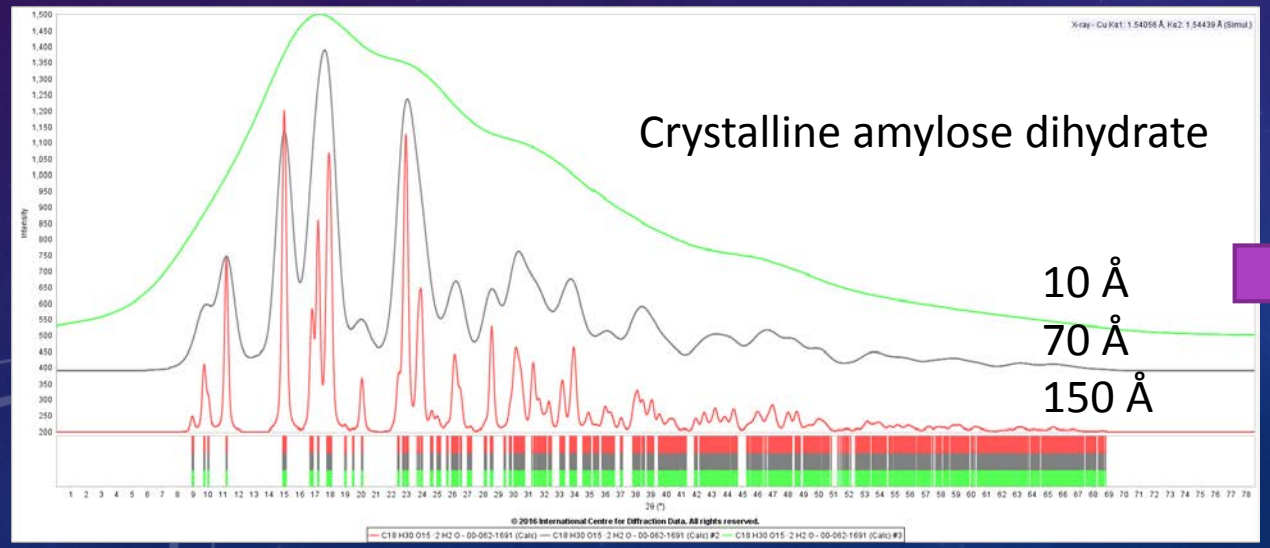


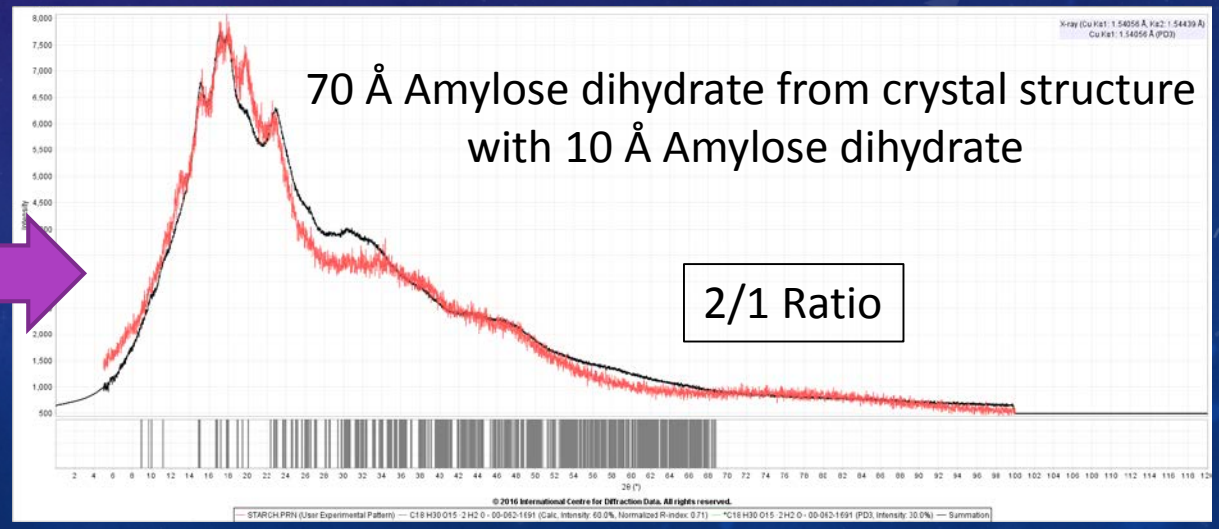
PARTIALLY CRYSTALLINE……CORN STARCH



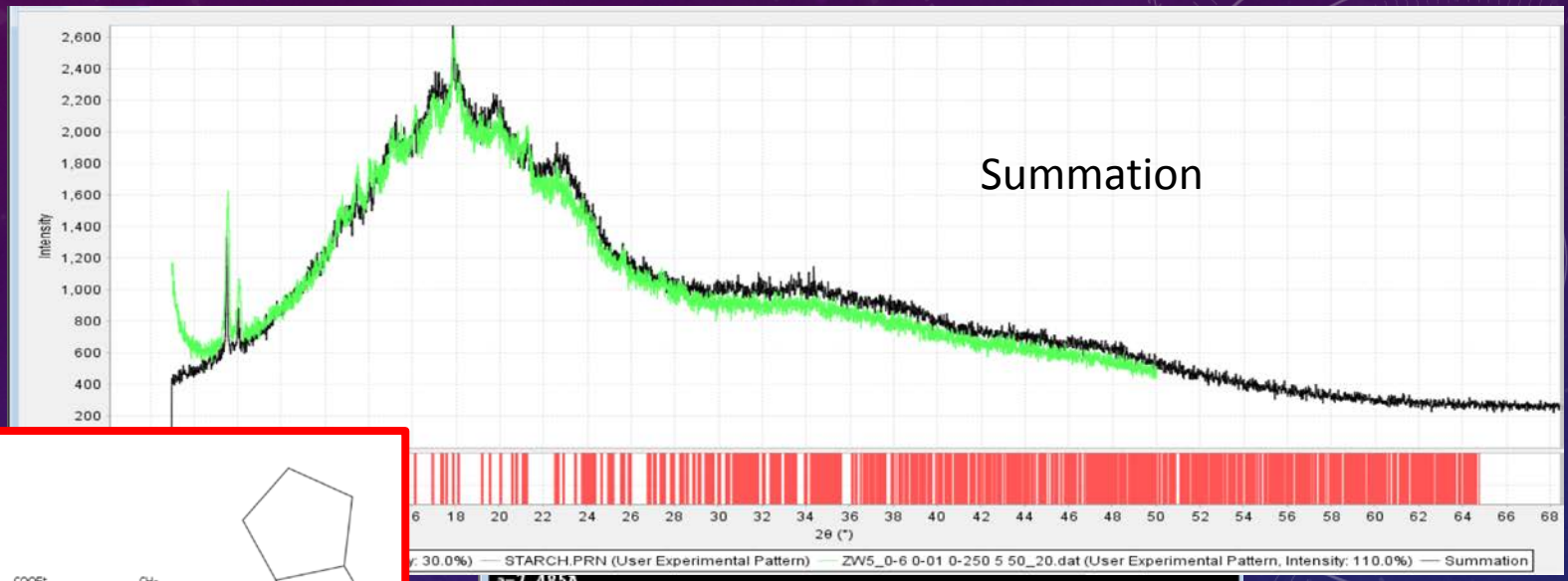
2 Approaches

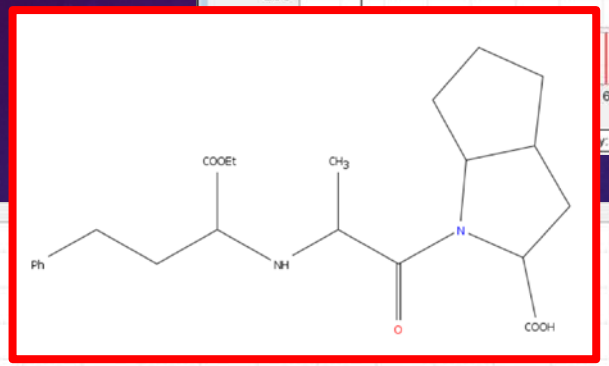
Experimental and simulation

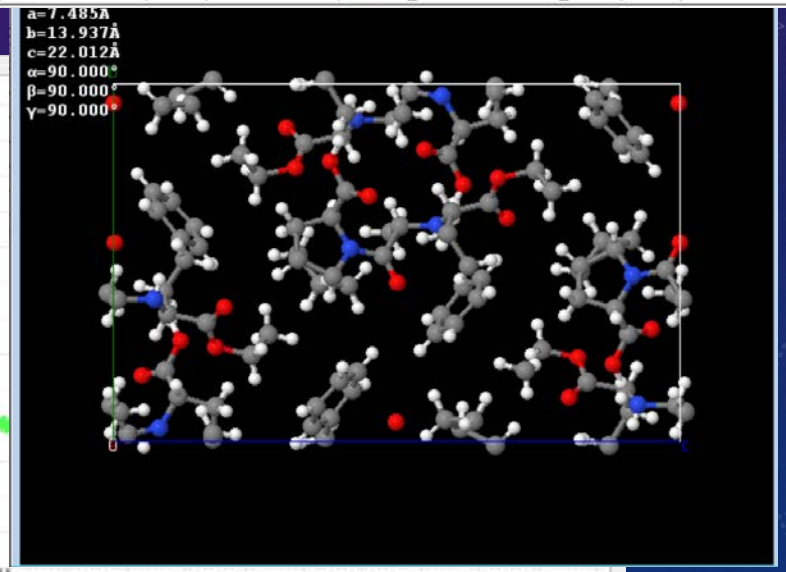




RAMIPRIL

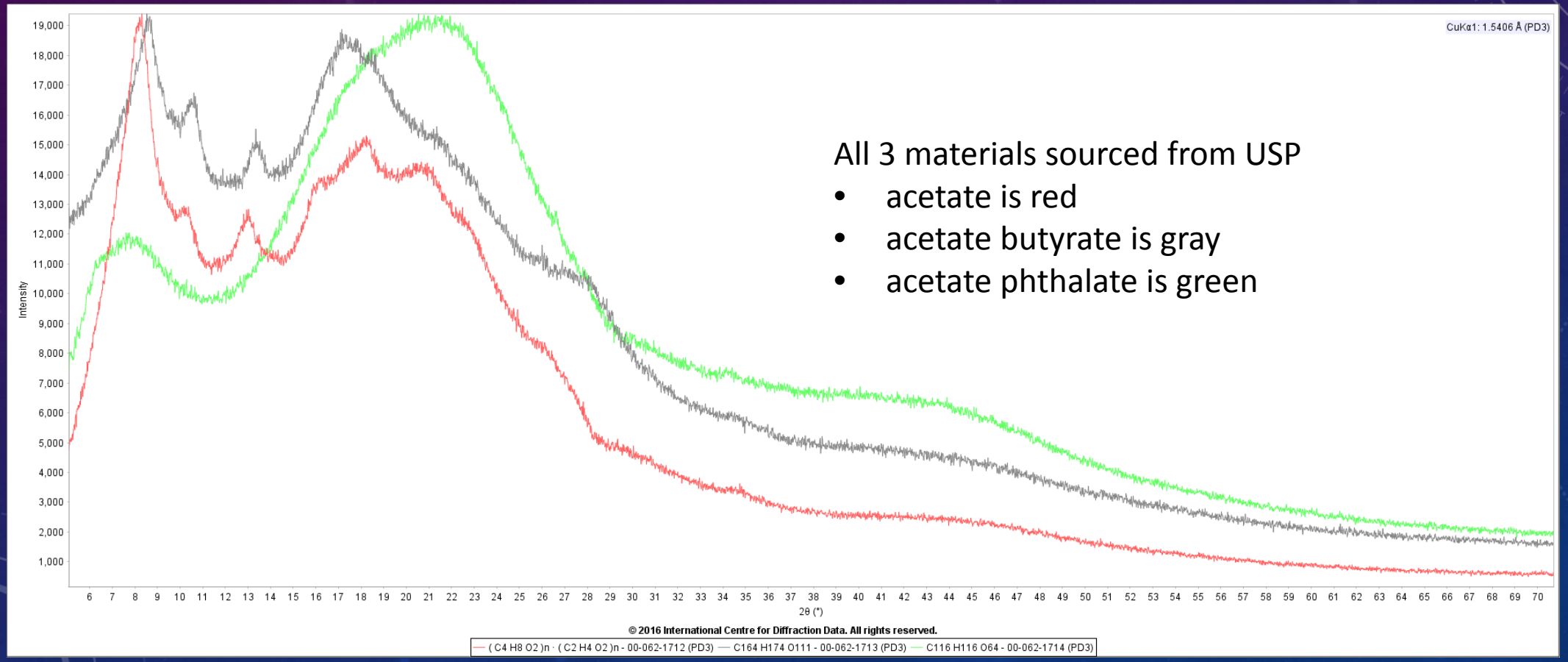

Summation
Intensity
2θ (°)
STARCH.PRN (User Experimental Pattern)
ZW5_0-6 0-01 0-250 5 50_20.dat (User Experimental Pattern, Intensity: 110.0%)
Summation


COOEt
CH3
Ph
NH
N
O
COOH


a=7.485Å
b=13.937Å
c=22.012Å
α=90.000°
β=90.000°
γ=90.000°

Intensity
2θ (°)
C23 H32 N2 O5 - 02-077-8941 (Calc, Intensity: 30.0%)
STARCH.PRN (User Experimental Pattern)
ZW5_0-6 0-01 0-250 5 50_20.dat (User Experimental Pattern)

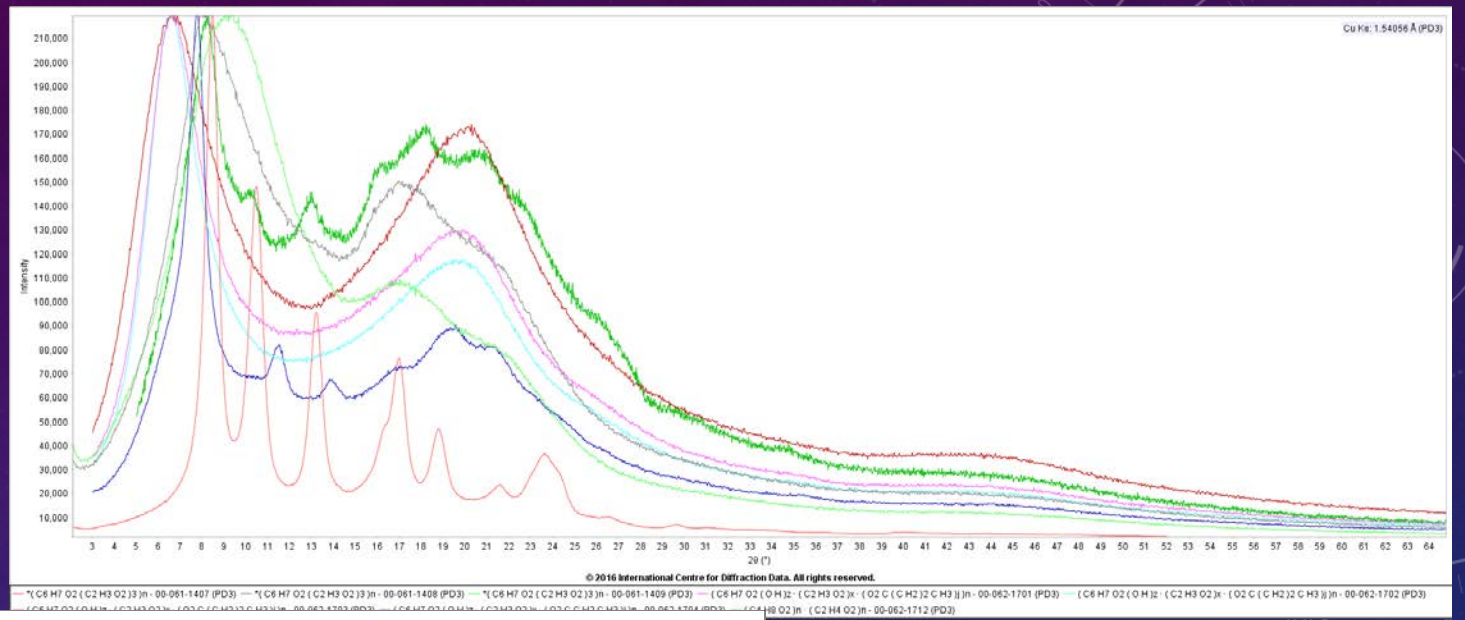
PARTIALLY CRYSTALLINE – CELLULOSE ACETATE AND CELLULOSE ACETATE BUTYRATE, CELLULOSE ACETATE PTHALATE

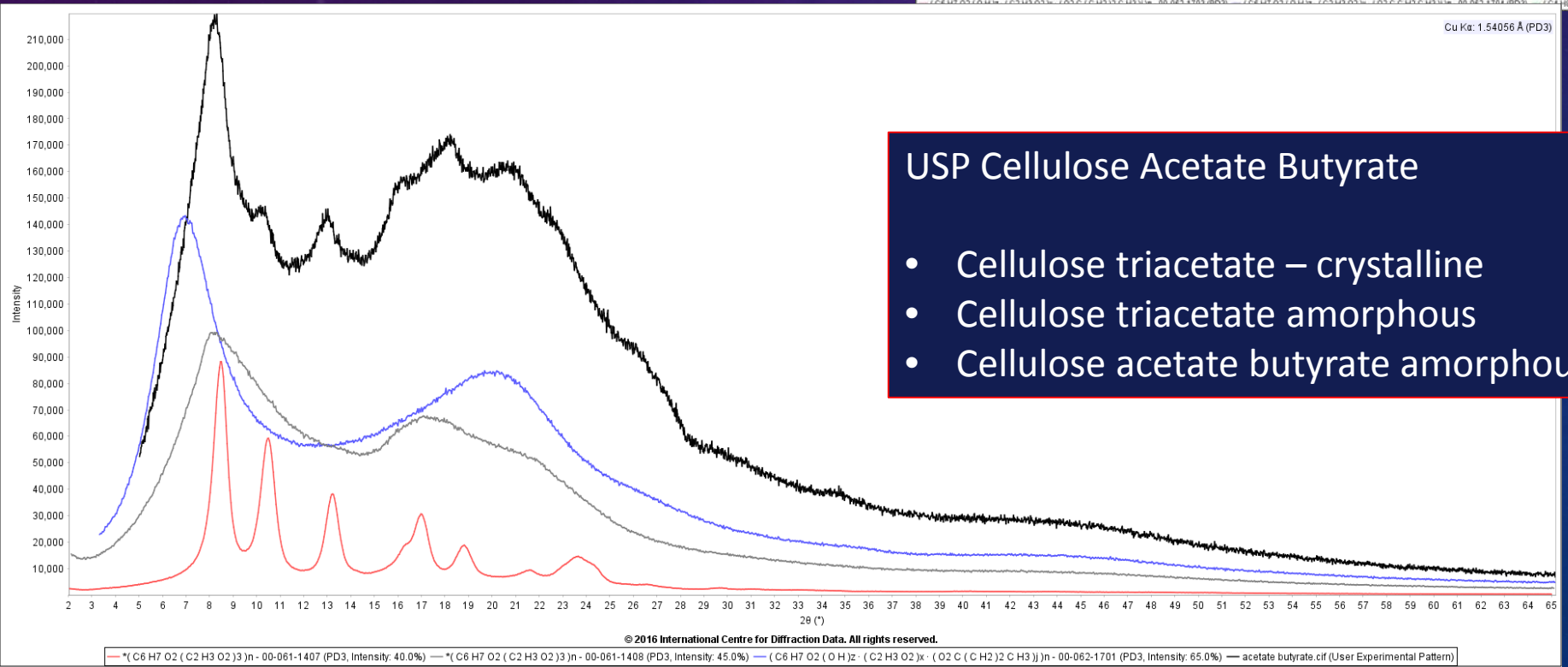


All 3 materials sourced from USP

- acetate is red
- acetate butyrate is gray
- acetate phthalate is green

CELLULOSE ACETATES

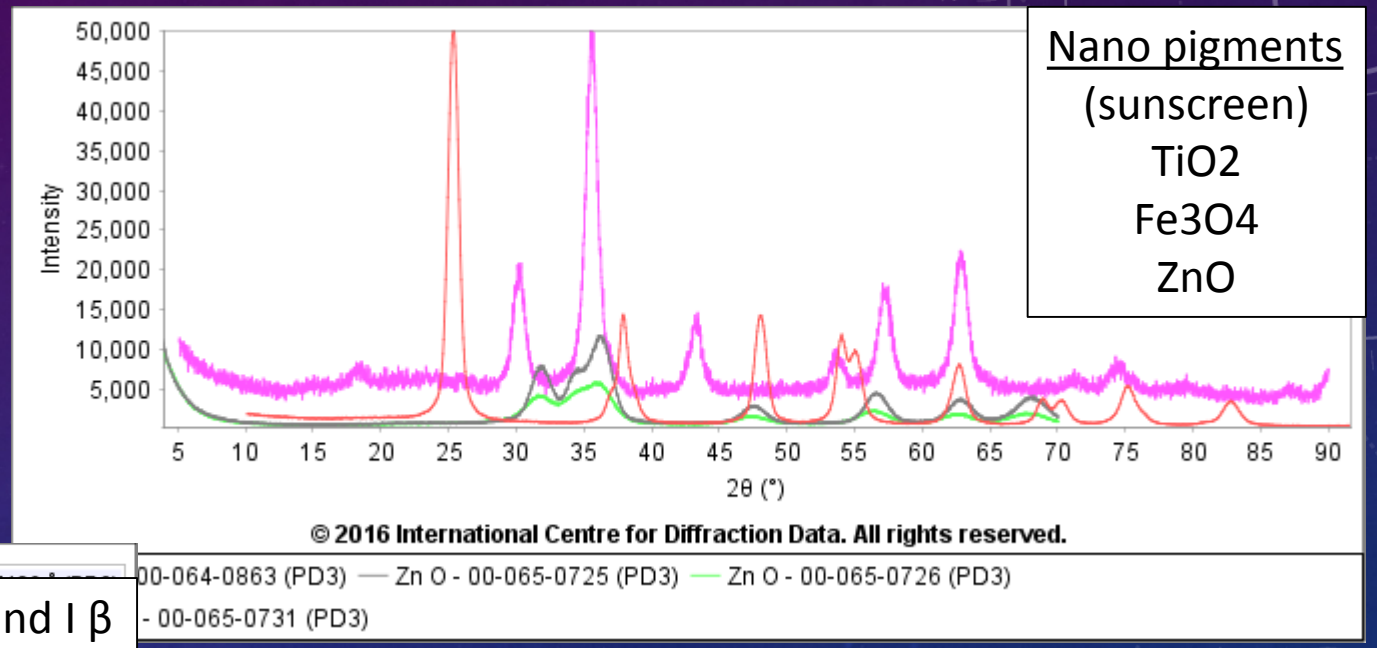




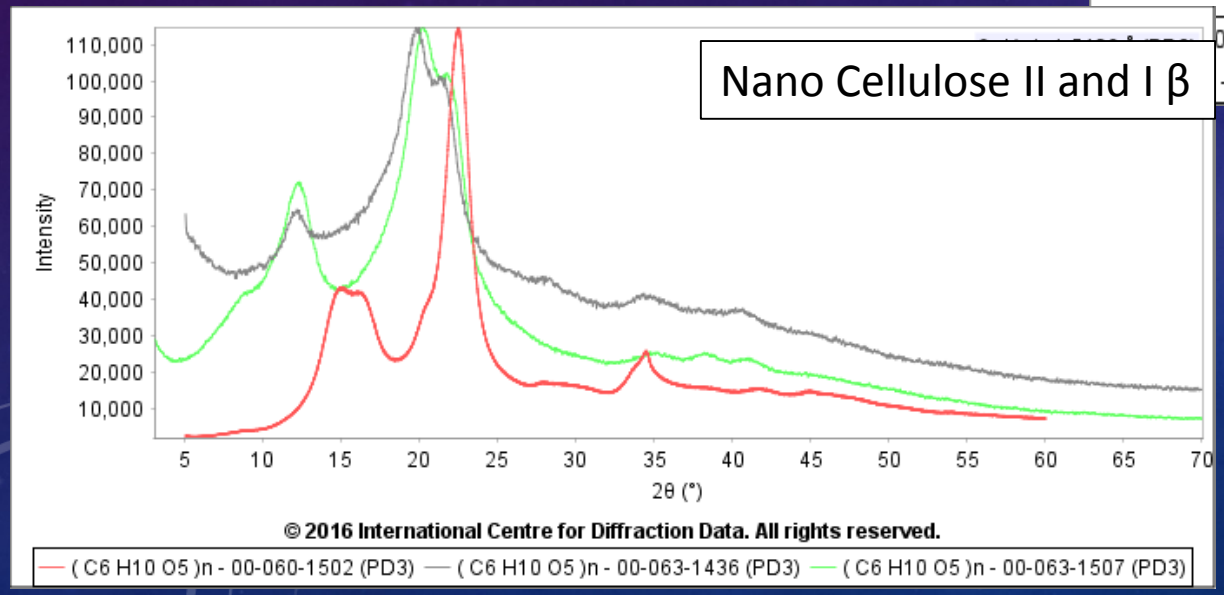
USP Cellulose Acetate Butyrate

- Cellulose triacetate – crystalline
- Cellulose triacetate amorphous
- Cellulose acetate butyrate amorphous

NANO CRYSTALLINE MATERIALS



Nano pigments
(sunscreen)
TiO2
Fe3O4
ZnO

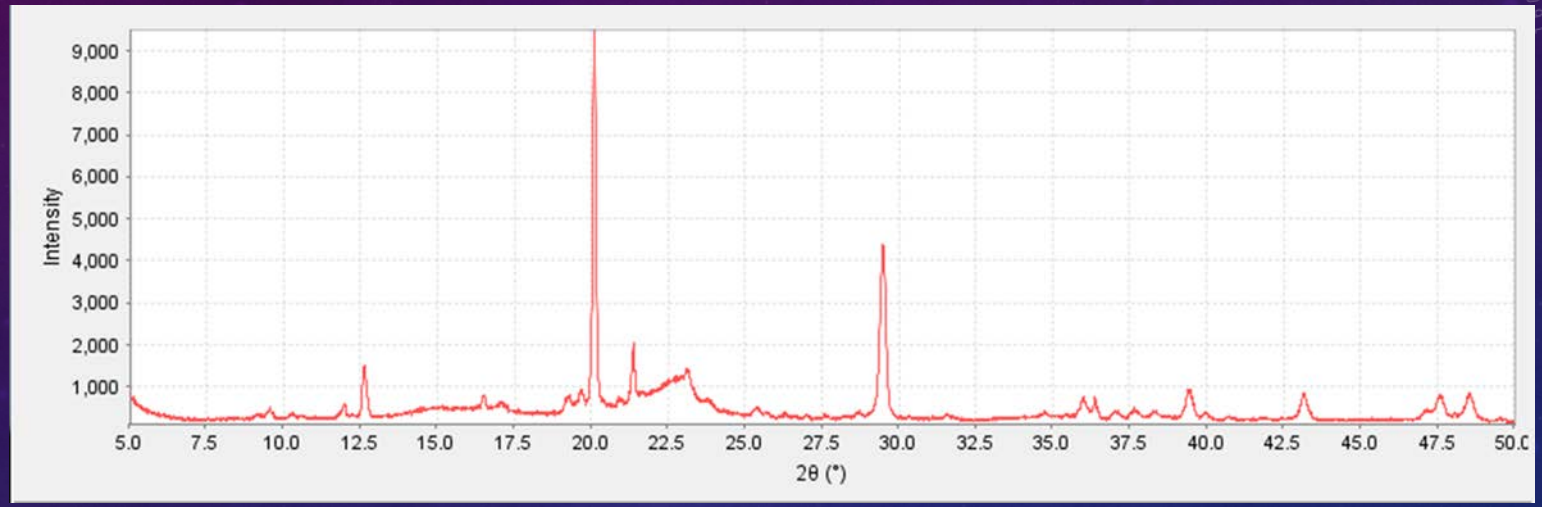


Nano Cellulose II and I β

APPLY

LIPITOR

1	✓	01-072-4582	Calcium Carbonate	0.610	36.87	3.23*	
2	✓	00-056-1718	Cellulose Iβ	0.078	4.715	8.27	
3	✓	00-030-1716	Lactose hydrate	0.682	41.222	1.55	
4	✓	00-063-0877	Atorvastatin	0.187	11.303		



			Int %
01-072-4582	Calcite		35
00-056-1718	Cellulose Iβ - 65Å	Alternative 00-062-1502 Microcrystalline Cellulose (contains amorphous content)	6
00-060-1501	Amorphous Cellulose		2
00-030-1716	Lactose Monohydrate (oriented 011)		54
00-063-0877	Ca Atorvastatin *USP 5,969,156* *Form I*		3

MOLECULAR ORIENTATION – LIPITOR AND SINGULAR

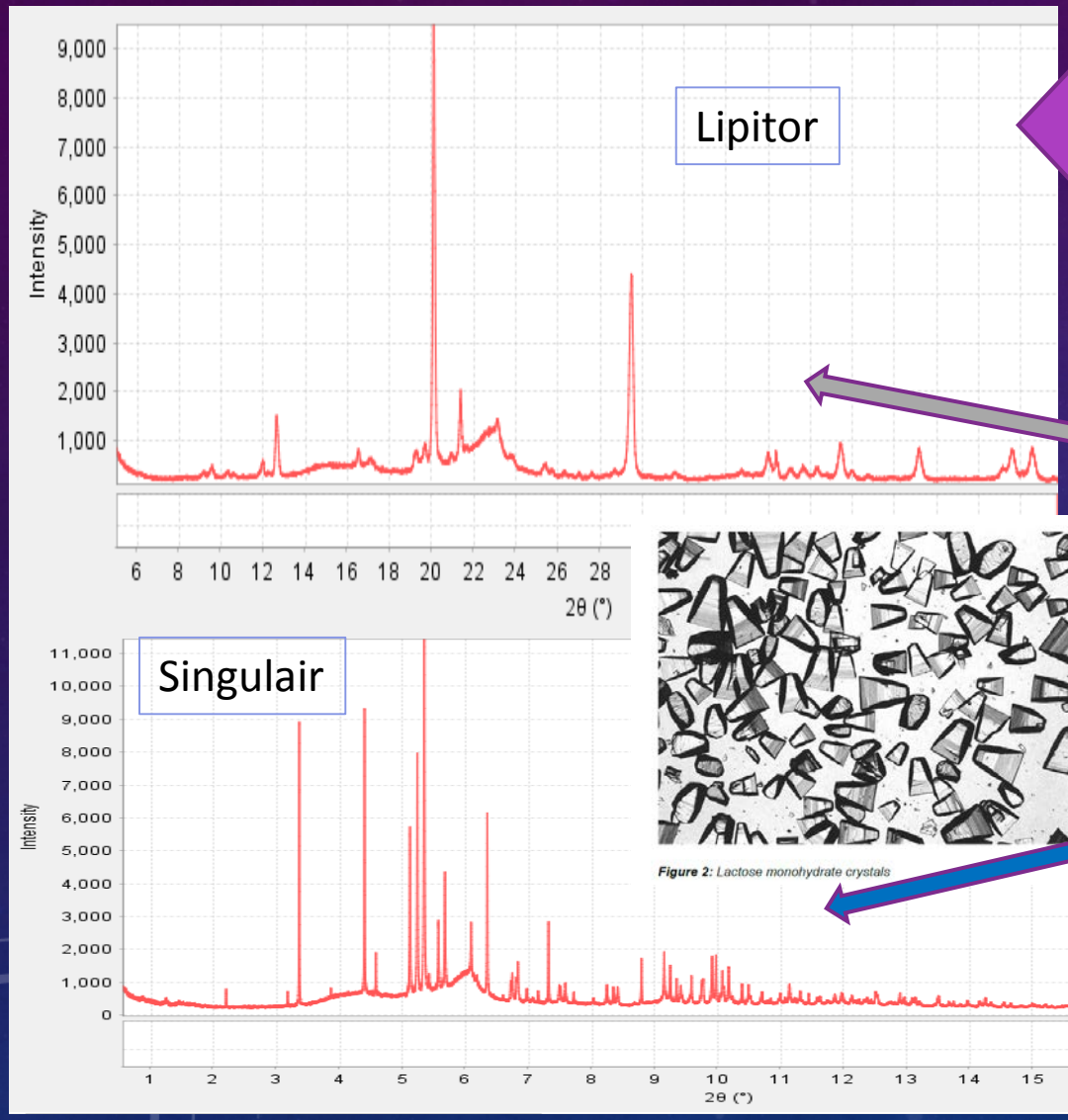
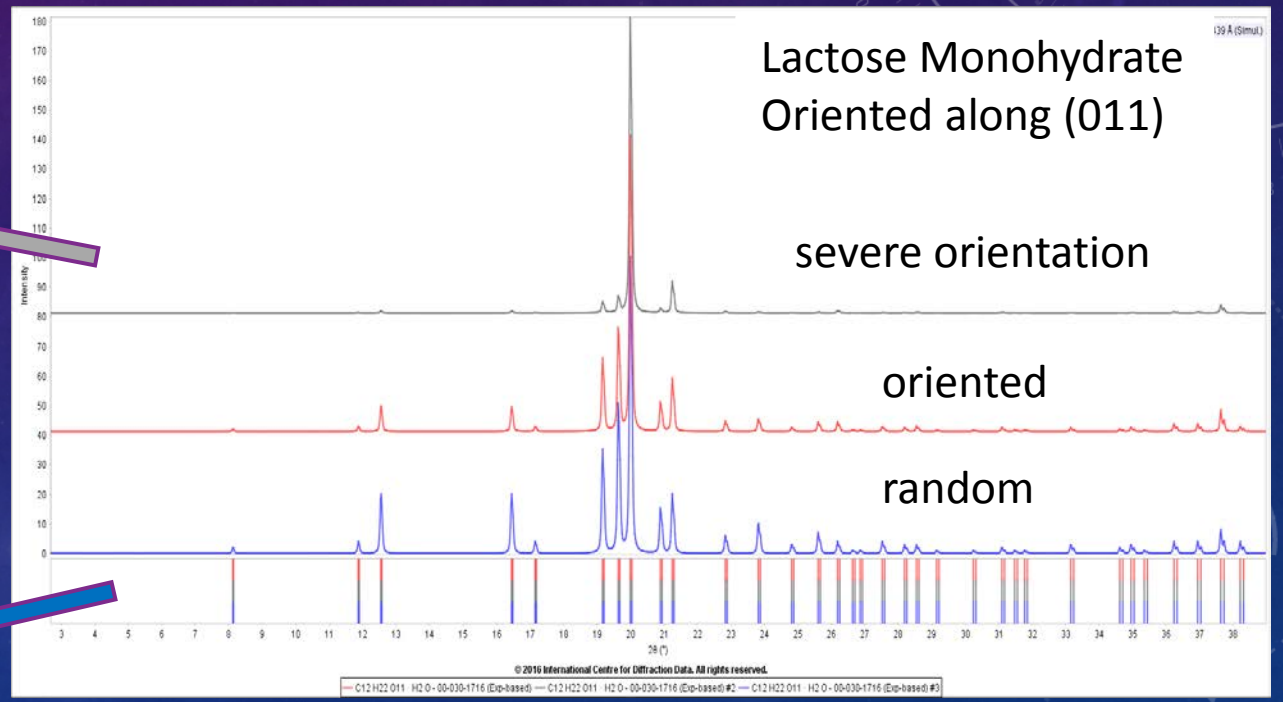


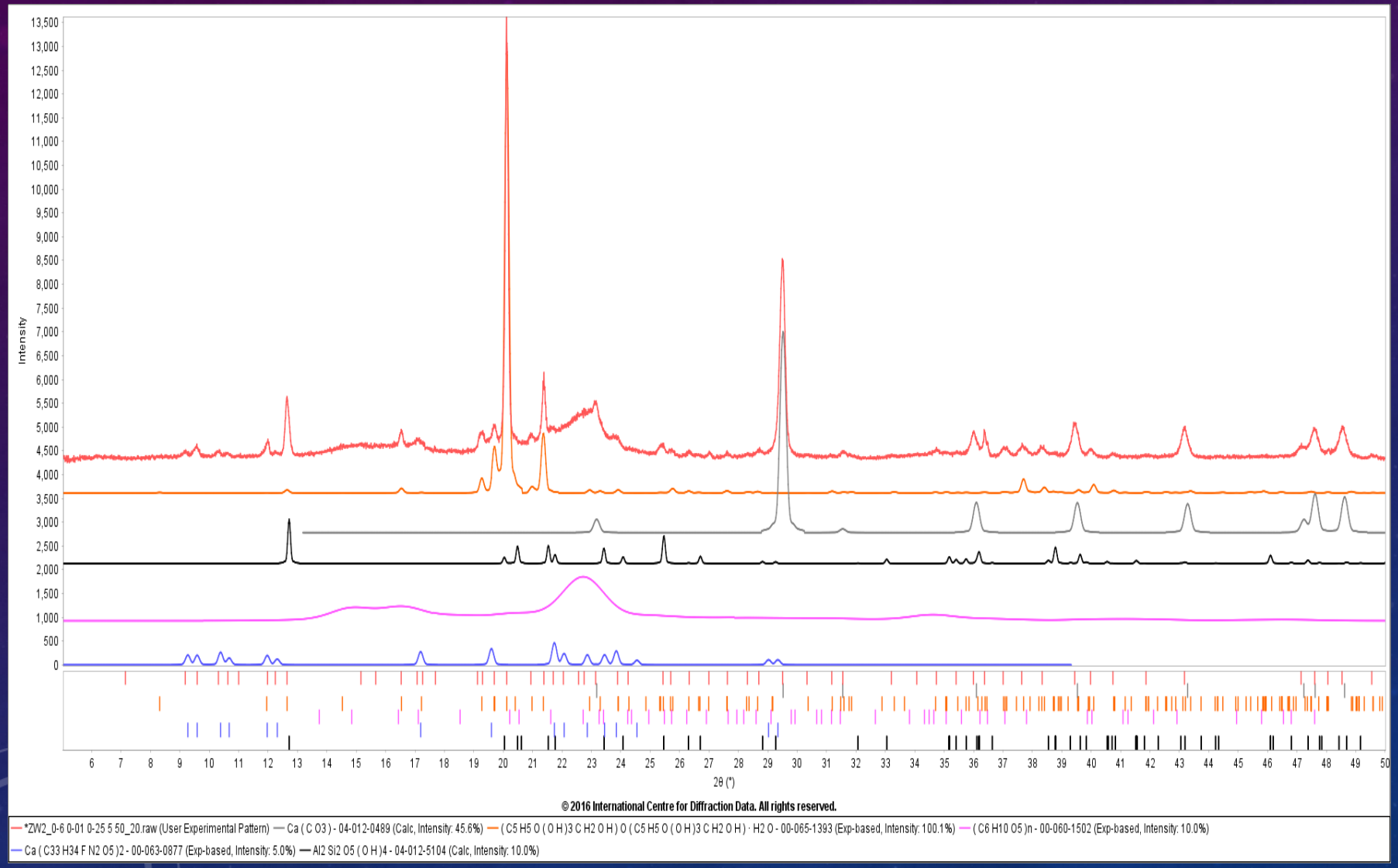
Figure 2: Lactose monohydrate crystals

Cavity Mount



Rotating Capillary Mount

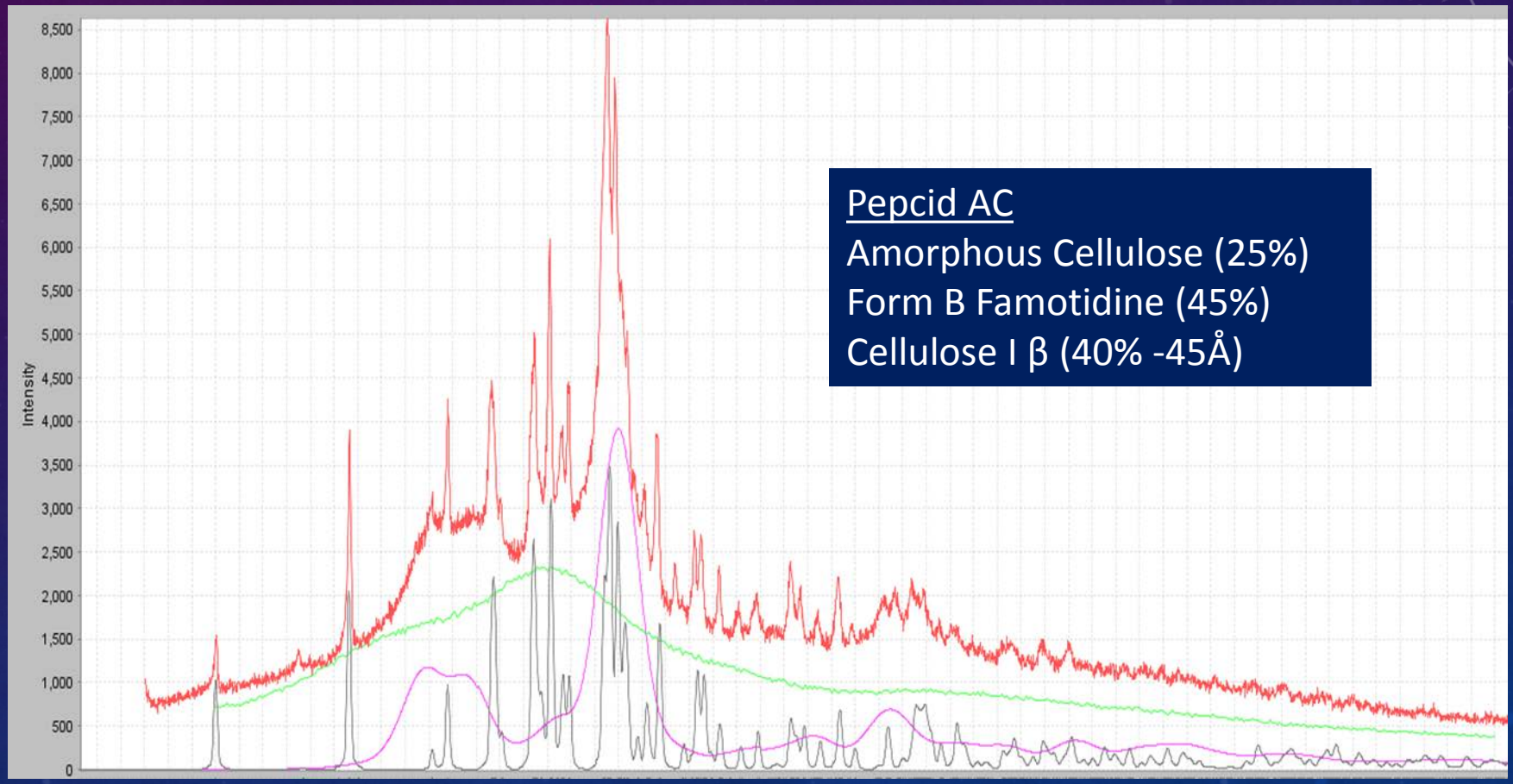
LIPITOR



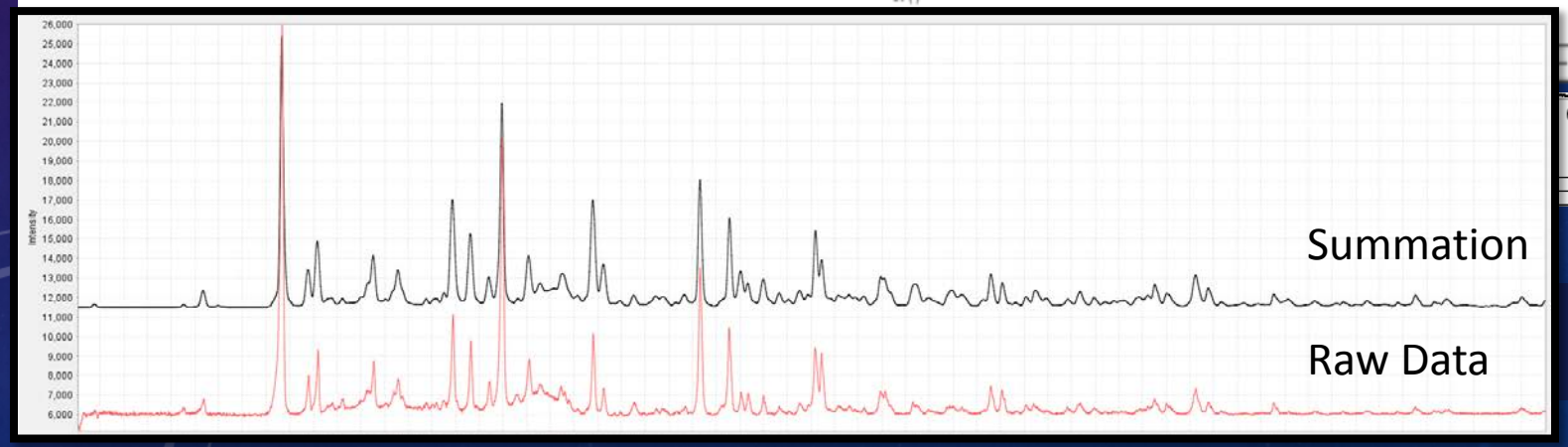
Raw Data

Lactose Monohydrate (oriented)
Calcite
Kaolinite 1A
Cellulose I β – 50 Å
Ca Atorvastatin – Form I

PEPCID AC


Intensity
8,500
8,000
7,500
7,000
6,500
6,000
5,500
5,000
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
Pepcid AC
Amorphous Cellulose (25%)
Form B Famotidine (45%)
Cellulose I β (40% -45Å)

DONNATAL



Raw Data

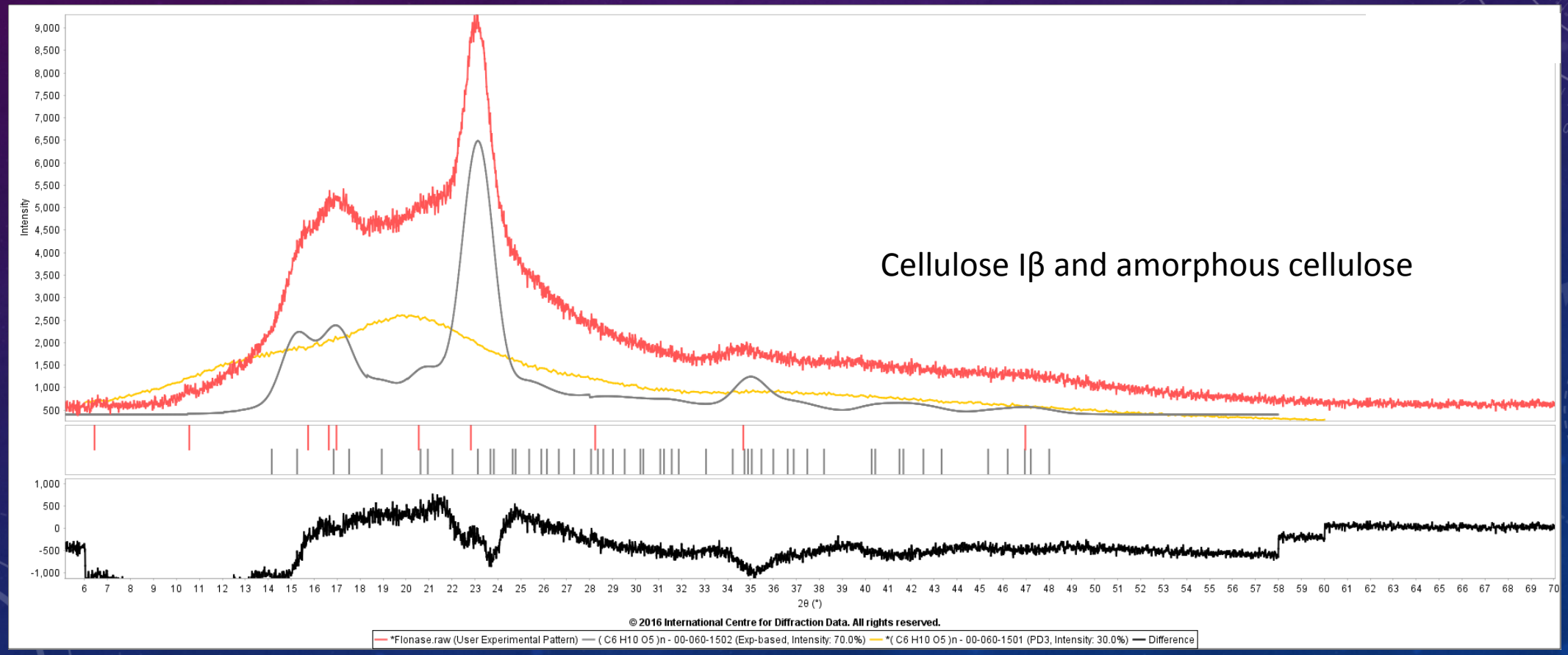
Cellulose I β – 50 Å

$Ca(PO_3)(OH)$ dihydrate

Phenobarbital

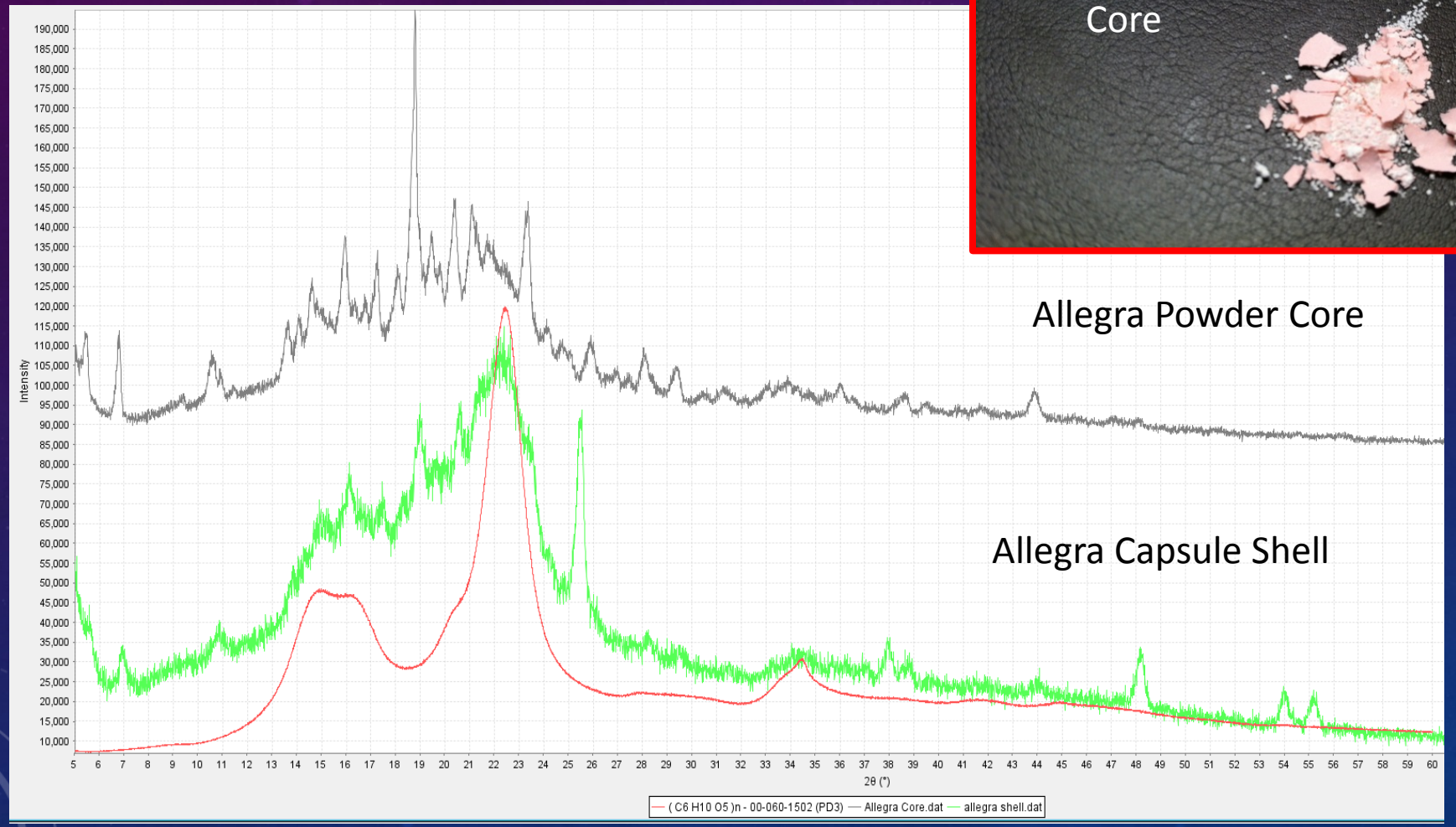
Sucrose

FLONASE


Cellulose Iβ and amorphous cellulose
Intensity
9,000
8,500
8,000
7,500
7,000
6,500
6,000
5,500
5,000
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
1,000
500
0
-500
-1,000
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70
2θ (°)
© 2016 International Centre for Diffraction Data. All rights reserved.
*Flonase.raw (User Experimental Pattern)
(C6 H10 O5)n - 00-060-1502 (Exp-based, Intensity: 70.0%)
*(C6 H10 O5)n - 00-060-1501 (PD3, Intensity: 30.0%)
Difference

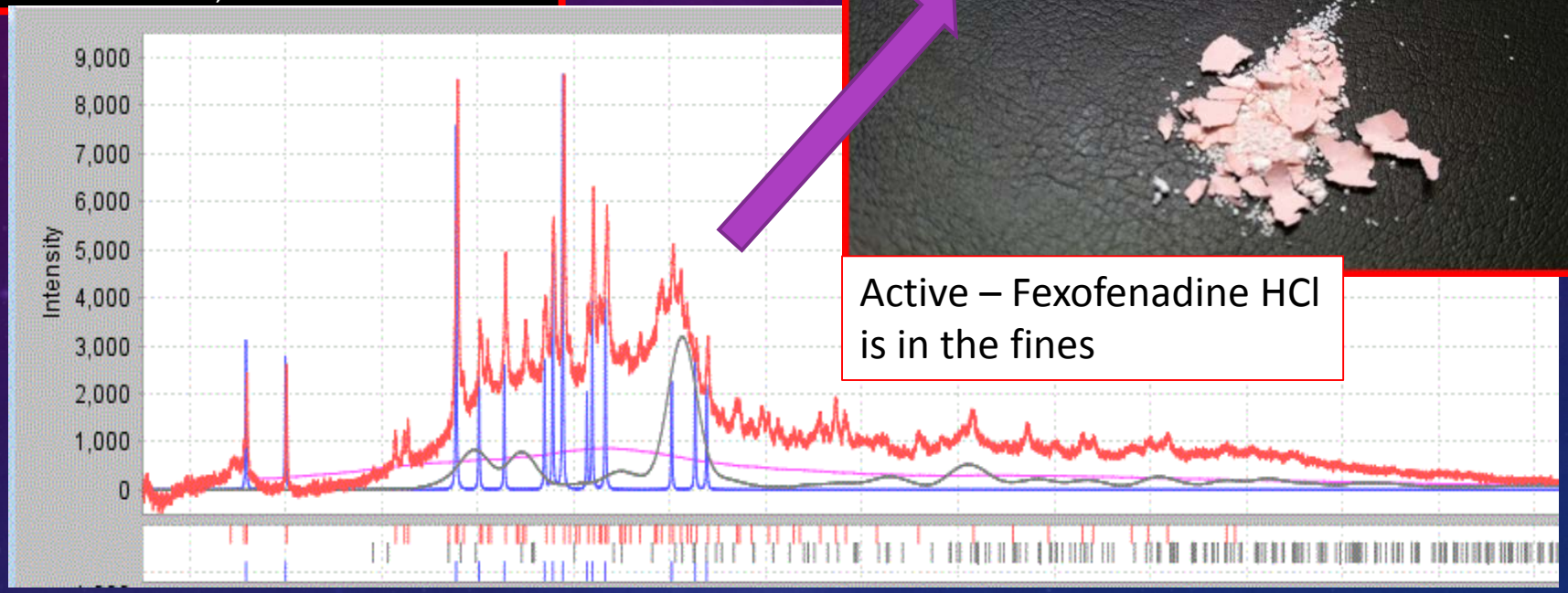
ALLEGRA


Core
Shell


Intensity
2θ (°)
Allegra Powder Core
Allegra Capsule Shell
(C6 H10 O5)n - 00-060-1502 (PD3)
Allegra Core.dat
allegra shell.dat

ALLEGRA
- SYNCHROTRON DATA

ARGONNE NATIONAL LIGHT SOURCE
THANKS TO KAI ZHONG, JIM KADUK

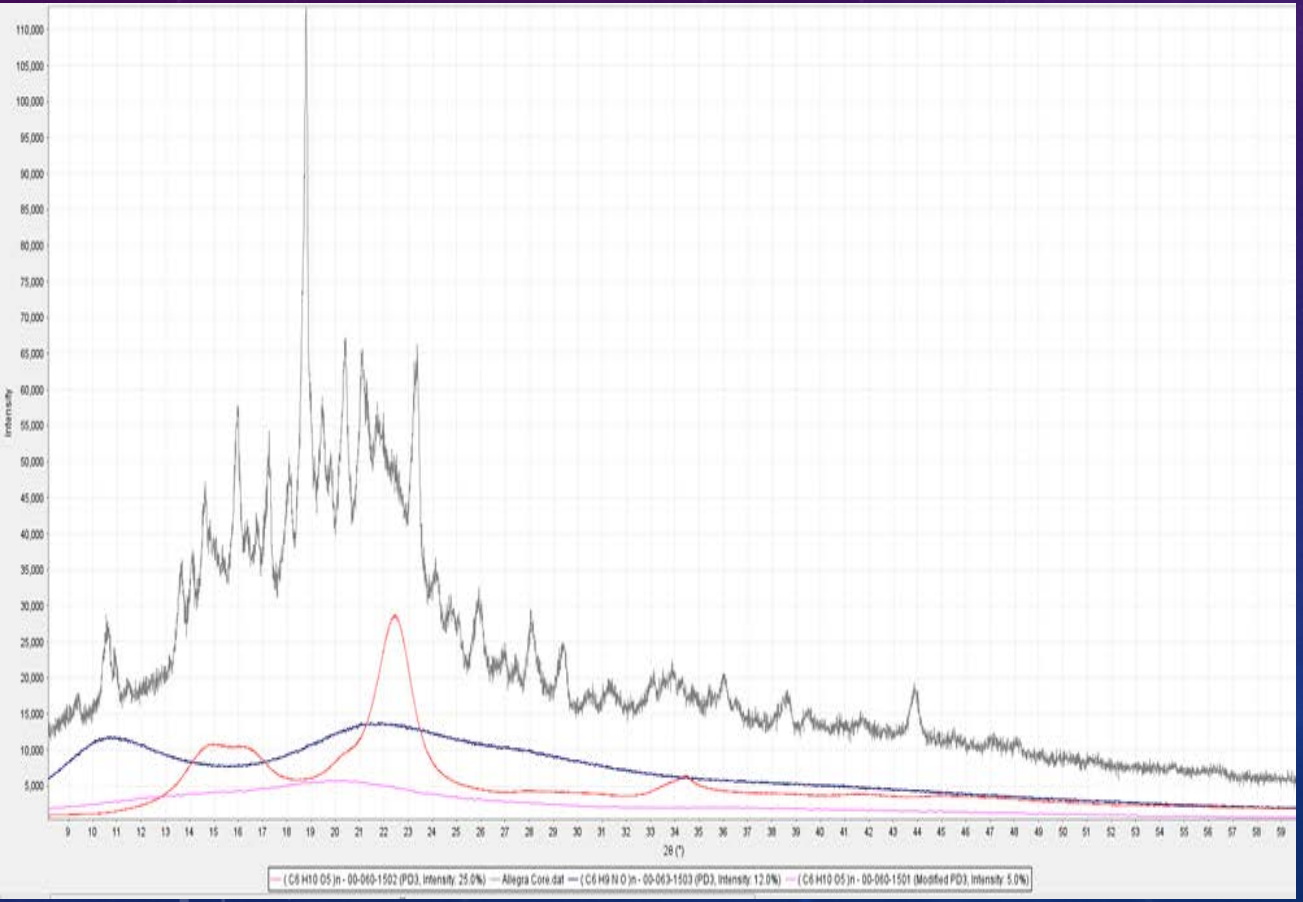


Active – Fexofenadine HCl is in the fines

Matched PDF 00-064-1548
"Fexofenadine hydrochloride." Kumar, L., Shahnwaj Alam, Md., Lal Meena, C., Jain, R., Bansal, A. Profiles Drug Subst., Excipients, Relat. Methodol. 34, 153 (2009). – unfortunately cut data off at 30 degrees

Not PDF 00-058-1149- "Fexofenadine polymorphs and processes of preparing the same." Rao, D., Kankan, R., Gangrade, M., Birari, D., WO 019175 A1. PCT Int. Appl. (2005).

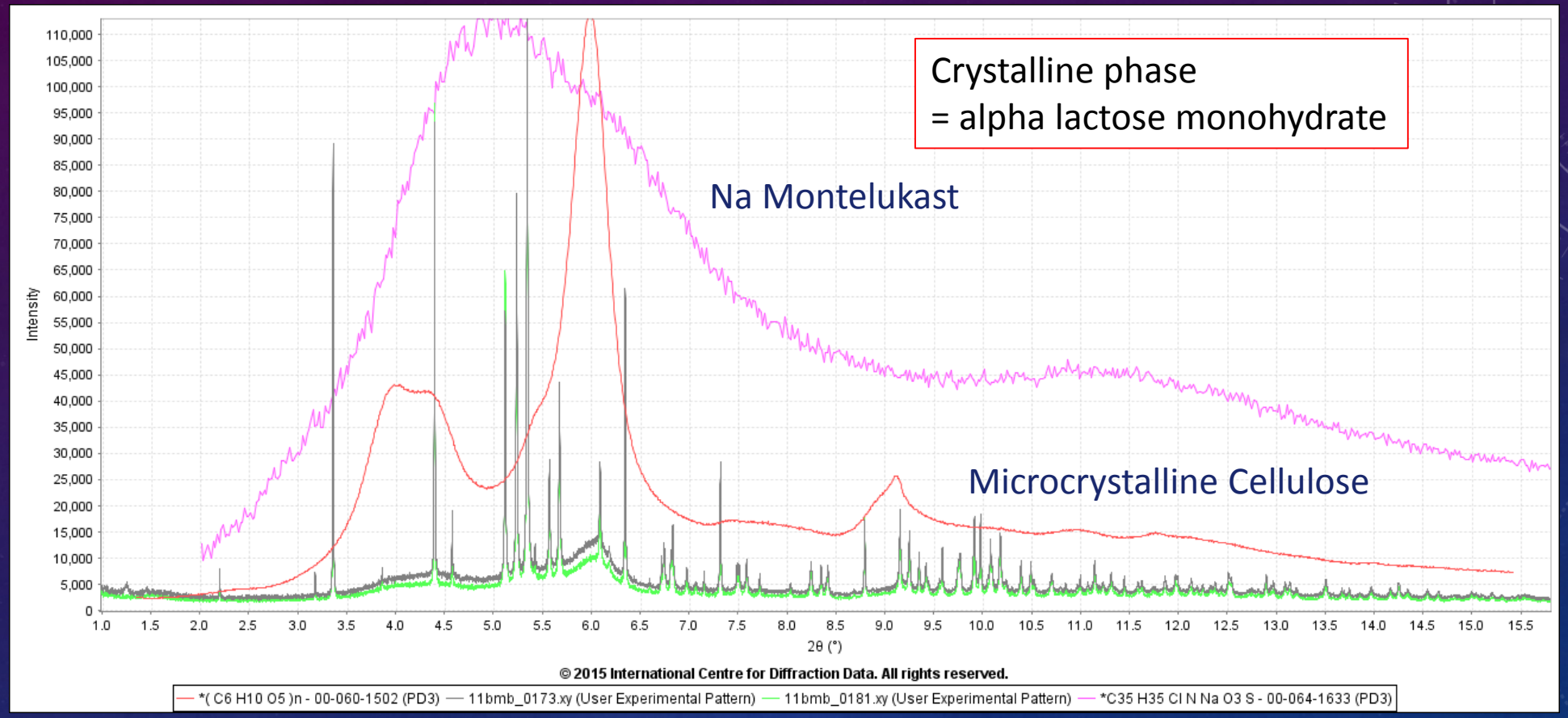
ALLEGRA
IDENTIFIED INGREDIENTS



Povidone - Amorphous
Cellulose I β – Nanocrystalline (shell)
Starch - Amorphous

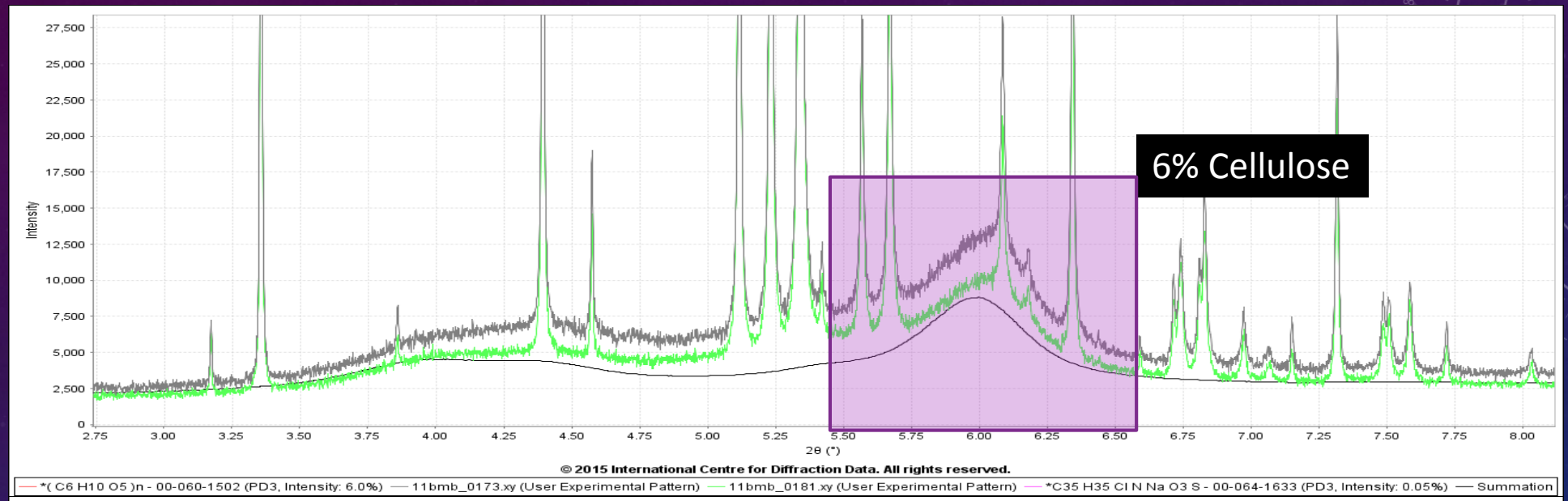
TiO2 (Shell)
Fexofenadine hydrochloride
(Core fines)
Magnesium Stearate Dihydrate
Citric Acid
D-Mannitol

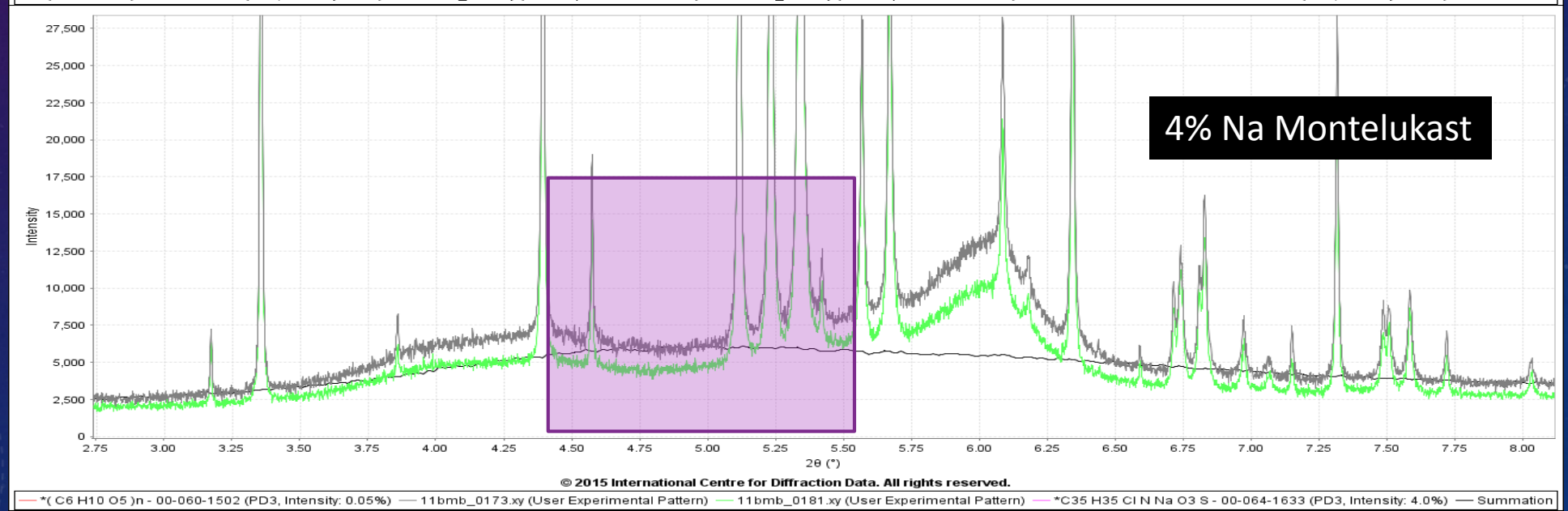
SINGULAIR



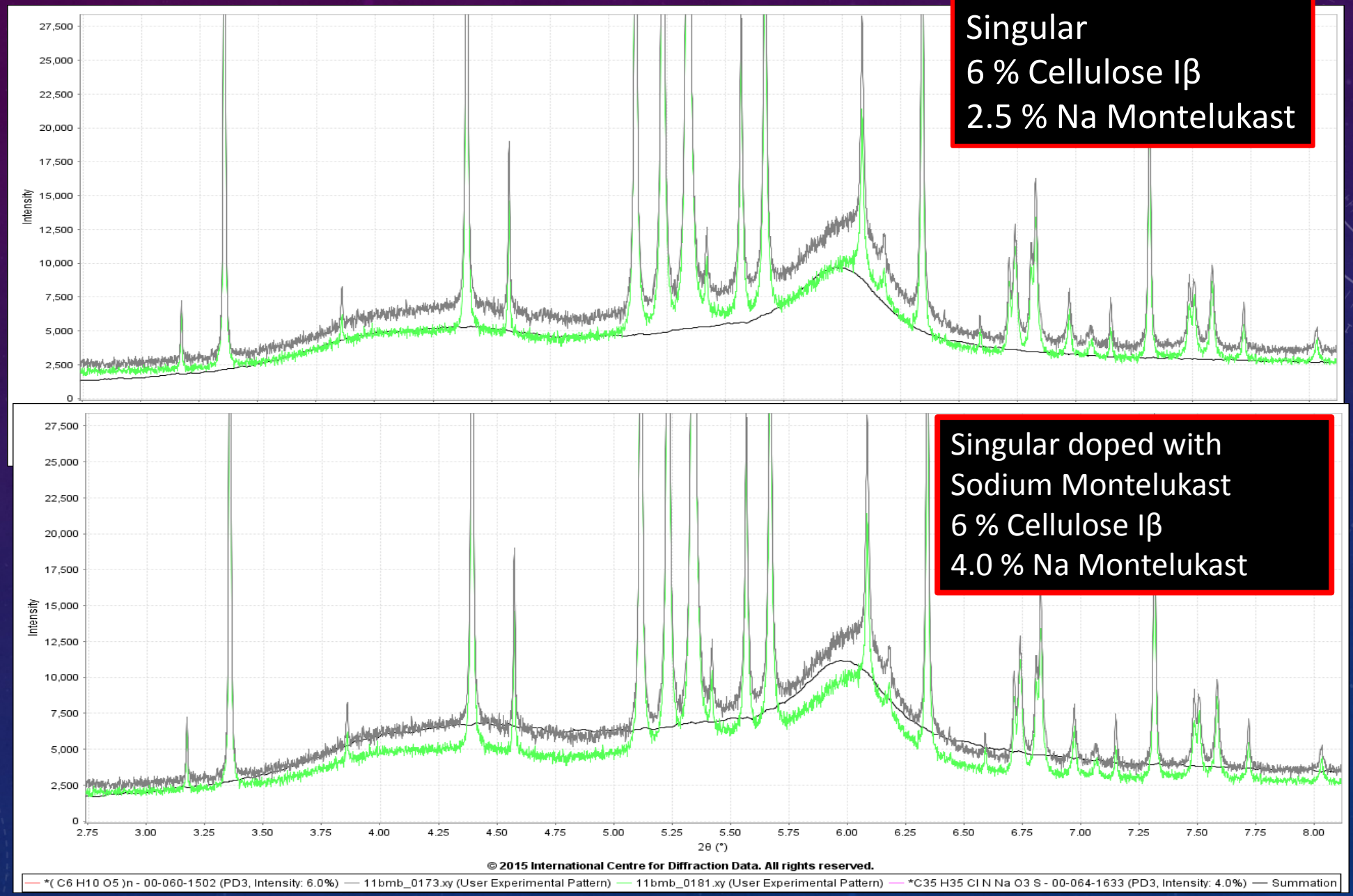
Singulair
Singulair plus 5% Na Montelukast

SINGULAR FIT

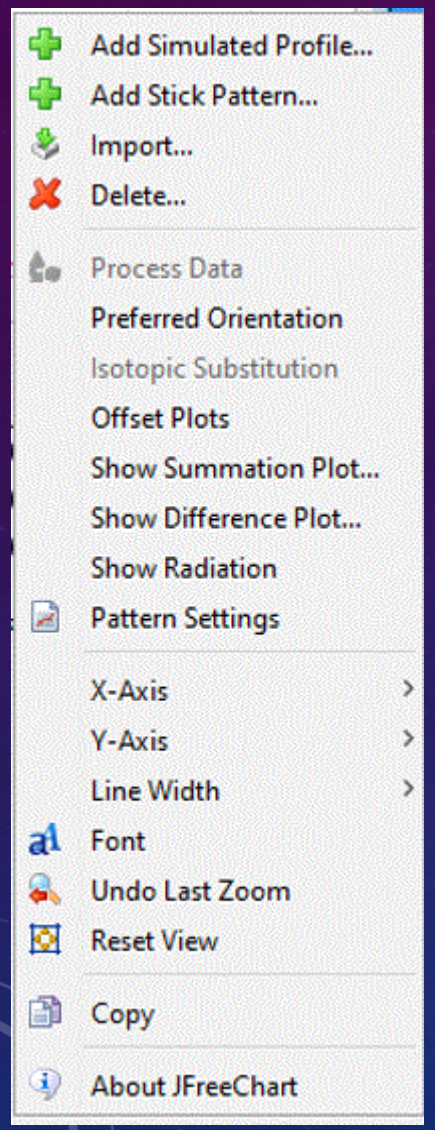




SINGULAR FIT 1



ANALYSIS SOFTWARE MENU



Ability to add any reference or any experimental pattern from the database

Import experimental data

Apply March-Dollase orientation function

Apply crystallite size and size distribution, scaling factors

Drop down menus for both x and y axis choices

Font and line widths for publication quality graphics

ALL MATERIALS AS NANOMATERIALS

6 Algorithms convert published data into a digital pattern

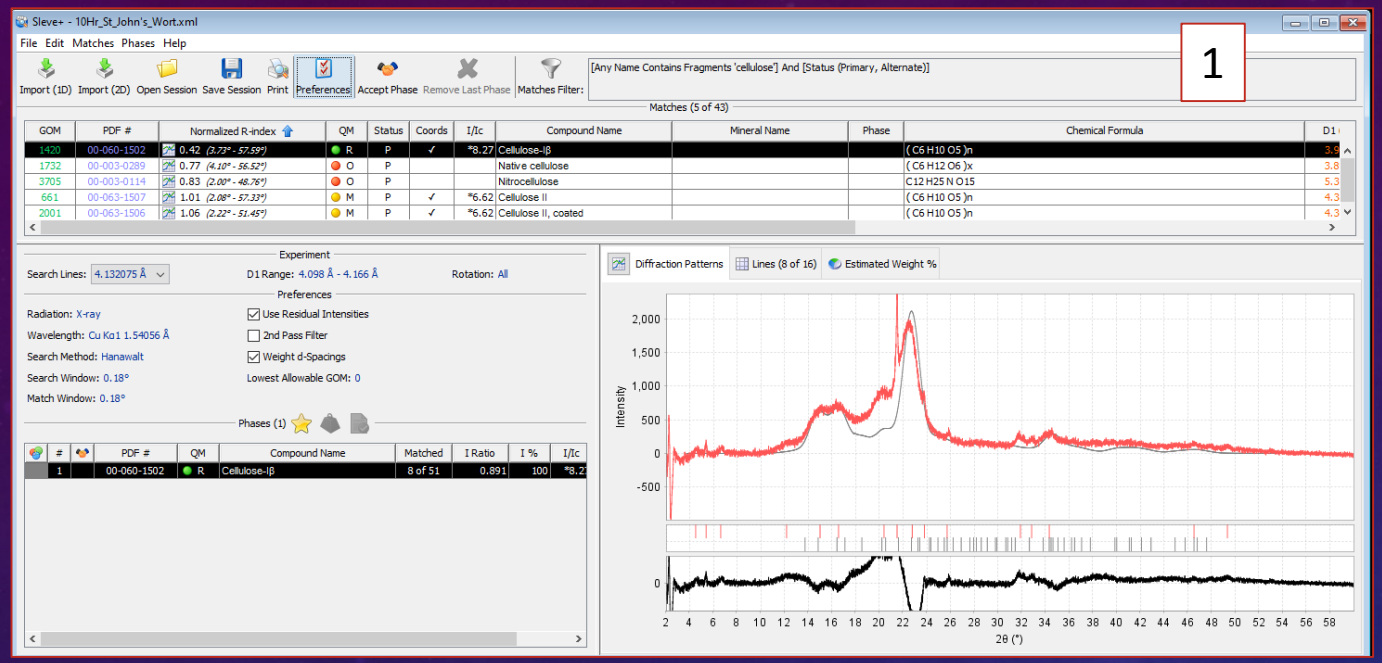
1) Old powder data sets without atomic coordinates
2) Data sets with atomic scattering factors
3) Data sets with atomic coordinates
4) Modulated structures (superspacegroups)
5) Neutron Diffraction (constant wavelength)
6) Neutron Diffraction (time of flight)

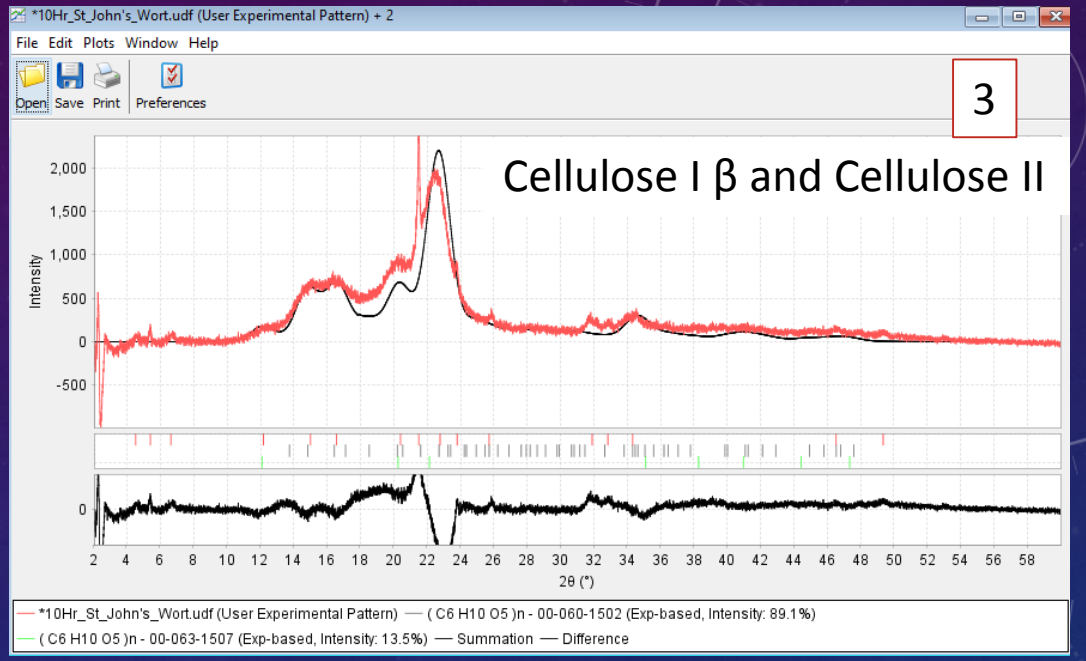
+

Experimental digital patterns

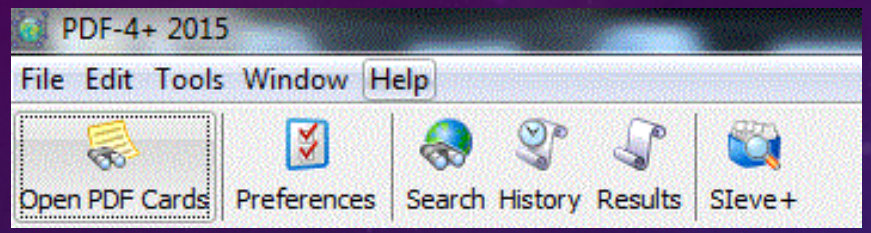
All data as a digital Pattern

INTEGRAL INDEX MATCH – NORMALIZED R INDEX





Created a reference file with 45 Å references



Preferences

General | Search | PDF Card | Simulated Profile | Bond Lengths/Angles | Electron | Ring Pattern | SIeve+

Simulation Sets: ICDD Defaults | Add... | Rename... | Delete | Import Instrument Parameters

Radiation

X-ray Diffraction

Type: Kα1+2

Anode: Cu

Kα1 (Å): 1.54056 (66.67%)

0.5

Kα2 (Å): 1.54439 (33.33%)

Kβ (Å): 0 (0%)

Neutron Diffraction (CW)*

Wavelength (Å): 1.5406

Electron Diffraction

Energy (keV) 100.0

Geometry

Bragg-Brentano: Fixed Slit

Polarization Fraction*: 0.5

Sample Thickness (mm)*: 0.1

Debye-Scherrer*

Packing Factor: 0.6

Sample Can Diameter (mm): 8.0

Profile

Crystallite Size

Mean Crystallite Diameter (Å): 825.0

Crystallite Variance: 50.0

Significance Limit: 0.01

Range

Step Width (°): 0.02 (To properly simulate synchrotron data, this value should be 0.005 or less.)

Start 2θ

Longest Line Minus (°): 10.0

Fixed Value (°): 2.0

Stop 2θ

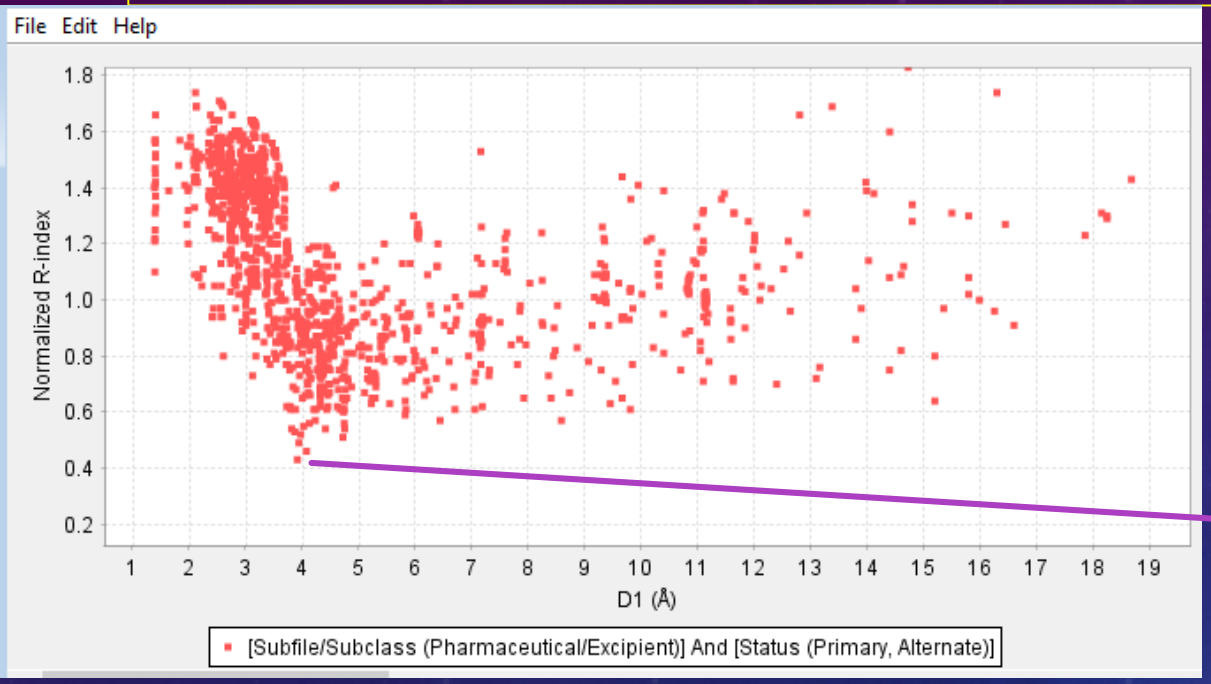
Shortest Line Plus (°): 10.0

Fixed Value (°): 150.0

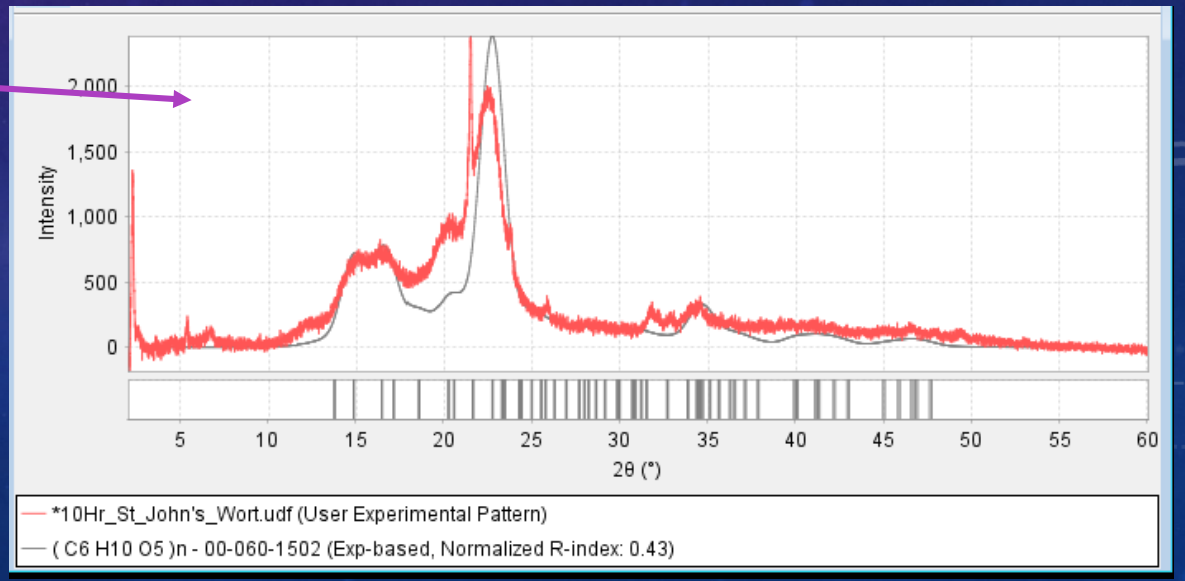
*Patterns require atomic coordinates or structure factors.

OK | Cancel | Apply | Reset Page | Reset All | Help

INTEGRAL INDEX – NORMALIZED R INDEX MATCH RAW DATA TO *ALL EXCIPIENTS*

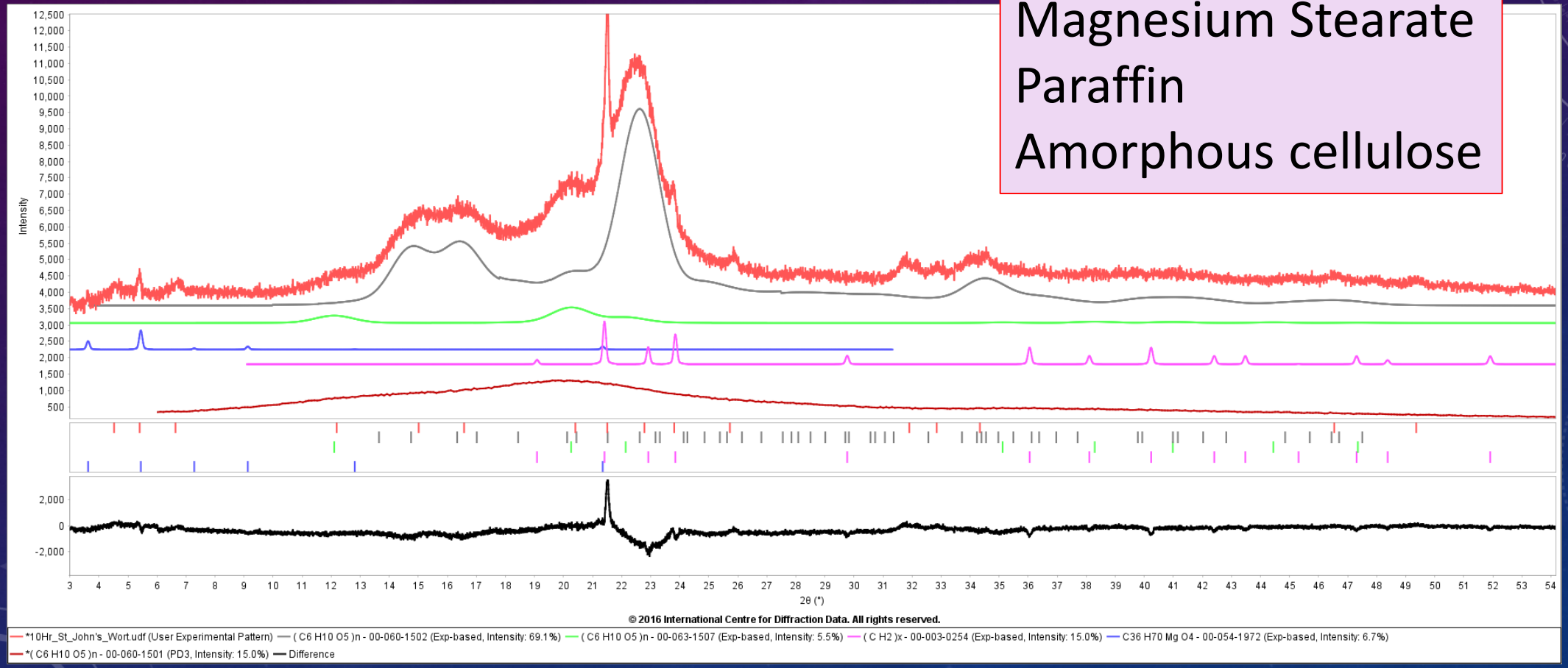


Normalized R-index	Empirical Formula	Compound Name
0.43 *(3.73° - 57.59°)*	C6 H10 O5	Cellulose-Iβ
0.46 *(2.00° - 59.97°)*	C6 H10 O5	Cellulose Iα
0.49 *(3.98° - 56.54°)*	C5 H12 O5	Xylitol
0.51 *(2.00° - 59.97°)*	C6 H14 O6	β-D-Mannitol
0.52 *(2.90° - 53.90°)*	C6 H14 O6	D-Sorbitol
0.53 *(2.00° - 59.97°)*	C6 H10 O5	Cellulose Iβ
0.54 *(2.00° - 59.97°)*	C12 H24 O12	D-Maltose hydrate
0.54 *(2.00° - 57.75°)*	C6 H14 O6	Mannitol
0.54 *(2.00° - 59.97°)*	C6 H14 O6	D-Sorbitol
0.55 *(2.00° - 53.01°)*	C6 H14 O6	D-Sorbitol
0.56 *(2.00° - 57.46°)*	C6 H14 O6	D-Mannitol



ST. JOHNS WORT

Cellulose I β
Cellulose II
Magnesium Stearate
Paraffin
Amorphous cellulose



SUMMARY

- ICDD has developed a total pattern analysis method for formulation analyses
- The method uses libraries of amorphous and nanocrystalline reference materials that are common excipients and active pharmaceutical ingredients
- A series of programs have been developed to perform search/match, crystallinity, crystallite size and orientation analyses to compliment the use of non-crystalline references

THANK YOU !

Singular, Allegra and all 15 amorphous API's

ACKNOWLEDGEMENTS

Use of the Advanced Photon Source at Argonne National Laboratory was supported by the US Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02–06CH11357.

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ICDD – ITT – Argonne National Laboratory Research Project

Crystal structure of atomoxetine hydrochloride (Strattera), $C_{17}H_{22}NOCl$

James A. Kaduk,[1,a] Cyrus E. Crowder,[2] Kai Zhong,[2] Timothy G. Fawcett,[2] and Matthew R. Suchomel[3]

[1]*Illinois Institute of Technology, 3101 S. Dearborn Street, Chicago, Illinois 60616*

[2]*ICDD, 12 Campus Boulevard, Newtown Square, Pennsylvania, 19073-3273*

[3]*Advanced Photon Source, Argonne National Laboratory, 9700 S. Cass Avenue, Argonne, Illinois 60439*

(Received 26 December 2013; accepted 21 April 2014)

Crystal structure of citalopram hydrobromide, $C_{20}H_{22}FN_2OBr$

James A. Kaduk,[1,a] Kai Zhong,[2] Amy M. Gindhart,[2] and Thomas N. Blanton[2]

[1]*Illinois Institute of Technology, 3101 S. Dearborn St., Chicago, Illinois 60616*

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(Received 24 October 2015; accepted 23 March 2016)

Diffraction line profile from a disperse system: A simple alternative to Voigtian profiles

P. Scardi and M. Leoni

Department of Materials Engineering and Industrial Technologies, University of Trento, 38050 via Mesiano 77, Trento, Italy

J. Faber

International Centre for Diffraction Data, 12 Campus Boulevard, Newtown Square, Pennsylvania 19073-3273

Full pattern comparison of experimental and calculated powder patterns using the Integral Index method in PDF-4+

John Faber[a] and Justin Blanton

International Centre for Diffraction Data, Newtown Square, Pennsylvania 19073-3273

Reference materials for the study of polymorphism and crystallinity in cellulosics

T. G. Fawcett,[1,a] C. E. Crowder,[1] S. N. Kabekkodu,[1] F. Needham,[1] J. A. Kaduk,[2] T. N. Blanton,[3] V. Petkov,[4] E. Bucher,[5] and R. Shpanchenko[6]

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[2]*Illinois Institute of Technology, Naperville, Illinois*

[3]*Eastman Kodak Company, Rochester, New York*

[4]*Central Michigan University, Mt. Pleasant, Michigan*

[5]*International Paper Company, Loveland, Ohio*

[6]*Moscow State University, Moscow, Russia*

ICDD Member Task Team