BEST PRACTICES IN FORMULATION ANALYSES BY X-RAY DIFFRACTION

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Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

About the Authors

- Suri Kabekkodu – editor in chief, pharmaceutical and excipients subfiles
- Stacy Gates – senior editor, polymers, non-crystalline materials
- Amy Gindhart – senior editor, pharmaceuticals
- Justin Blanton – senior programmer, JAVA, data mining, pattern simulations
- Cyrus Crowder – principle scientist, embedded software and method developments

Determining Best Practices – Key References

- Fawcett, T. G., McDonnell, H., Higginson, R., (**2006, 2009, 2012**) "ICDD Global Customer Survey", private communication, International Centre for Diffraction Data. Three separate surveys taken three years apart with over ***2,000 responses*** from scientists working in the field of diffraction and material analysis.

- Fawcett, T. G., Needham, F., Faber, J., Crowder, C. E., (**2010**), "International Centre for Diffraction Data round robin on quantitative Rietveld phase analysis of pharmaceuticals", *Powder Diffraction*, 25(1), pp 60-67.

- Fawcett, T. G., Hubbard, C. R., (**2004**), "Formulation Analyses of Off-the-shelf Pharmaceuticals", *American Pharmaceutical Review,* Vol. 7, pp 80-83.

- Fawcett T. G., Faber, J., Needham F., Kabekkodu S. N., Hubbard C. R. and Kaduk J. A. , **(2006),** "Developments in formulation analyses by powder diffraction analysis", *Powder Diffraction*, 21, pp 105-110.

About the data

- Y. Ososkov and Z. Cherbanyk Beti, Exova, Mississauga, Canada
- A. Patel, Bristol-Myer Squibb, New Brunswick, NJ, USA
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- H. Brusova, Zentiva AS, Prague, Czech Republic

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- J. Kaduk, Illinois Institute of Technology, Il, USA

Outline

Specimen Preparation-
Round Robin, Experience

- General issues – low scattering power, absorption difference in ingredients, crystallinity
- Asymmetric Crystals
- Particle size
- Granularity
- Orientation
- Separation Techniques

Methods of Analysis –
Customers Survey Data

- Experience
- Databases
- Noncrystalline Materials
- Reference Quality
- Elemental Filters
- Subfiles
- Pattern Simulations
- Rietveld Analysis
- Combined Techniques – DXC/XRD
- Complimentary Analytical Techniques

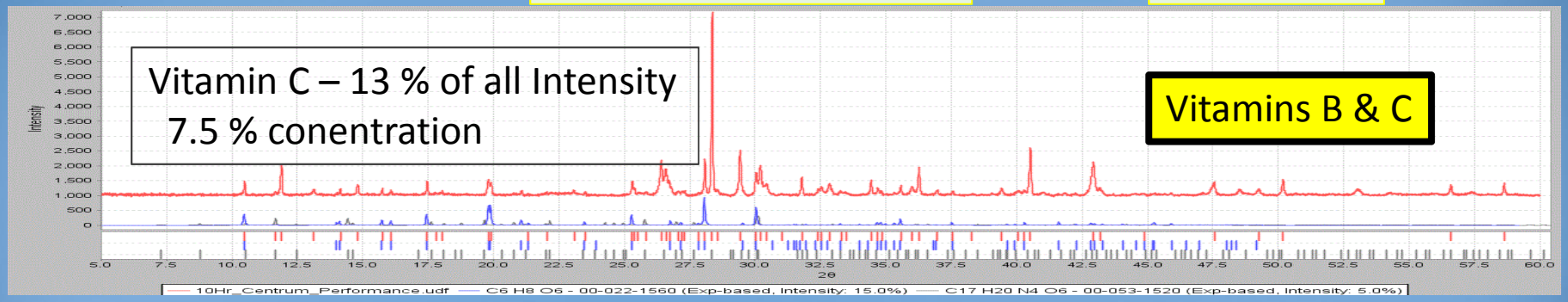
Centrum Performance

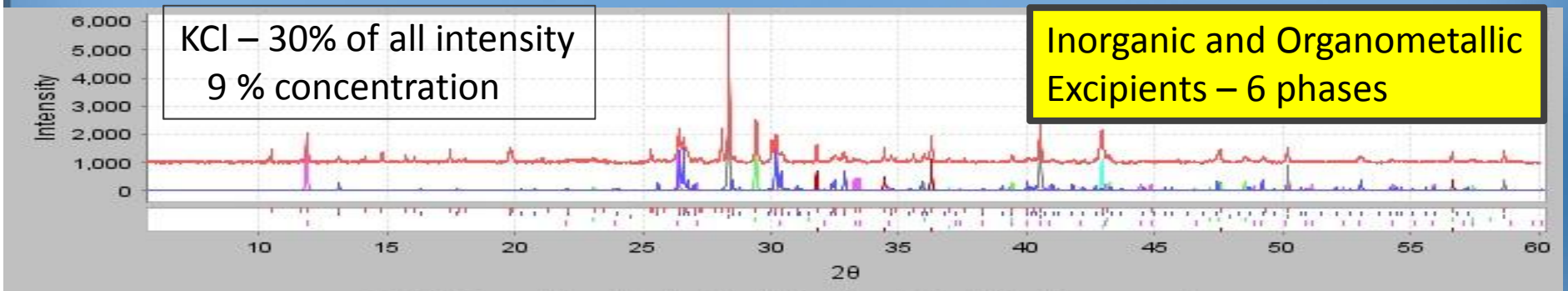
General Issues

$$I_{(hkl)\alpha} = \left[\frac{I_0 \lambda^3}{64\pi r}\left(\frac{e^2}{m_e c^2}\right)^2\right]\left[\frac{M_{hkl}}{V_\alpha^2}\left|F_{(hkl)\alpha}\right|^2\right]\left(\frac{1+\cos^2 2\theta \cos^2 2\theta_m}{\sin^2\theta\cos\theta}\right)\left[\frac{X_\alpha}{\rho_\alpha(\mu/\rho)_s}\right].$$

Low scattering factor (Z)

Low density





10Hr_Centrum_Performance.udf — Ca P O3 (O H) - 00-009-0080 (Exp-based, Intensity: 32.1%)
K Cl - 01-075-0296 (Calc, Intensity: 75.1%) — Ca (C O3) - 04-012-0489 (Calc, Intensity: 29.9%)
Fe (C4 H2 O4) - 00-062-1294 (Exp-based, Intensity: 31.8%) — Mg O - 04-001-7295 (Calc, Intensity: 18.0%)
Zn O - 04-007-9627 (Calc, Intensity: 18.3%)

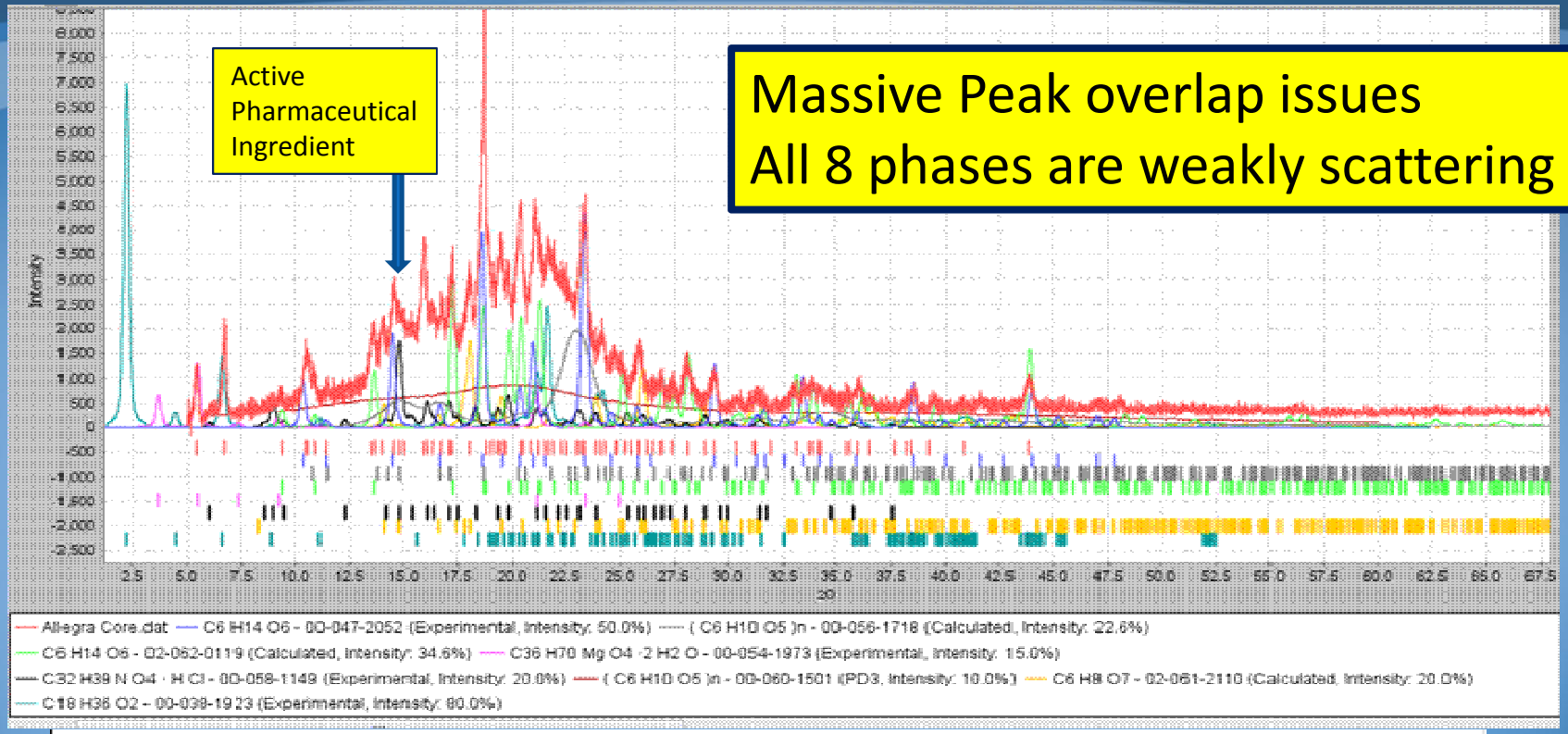
Consequences

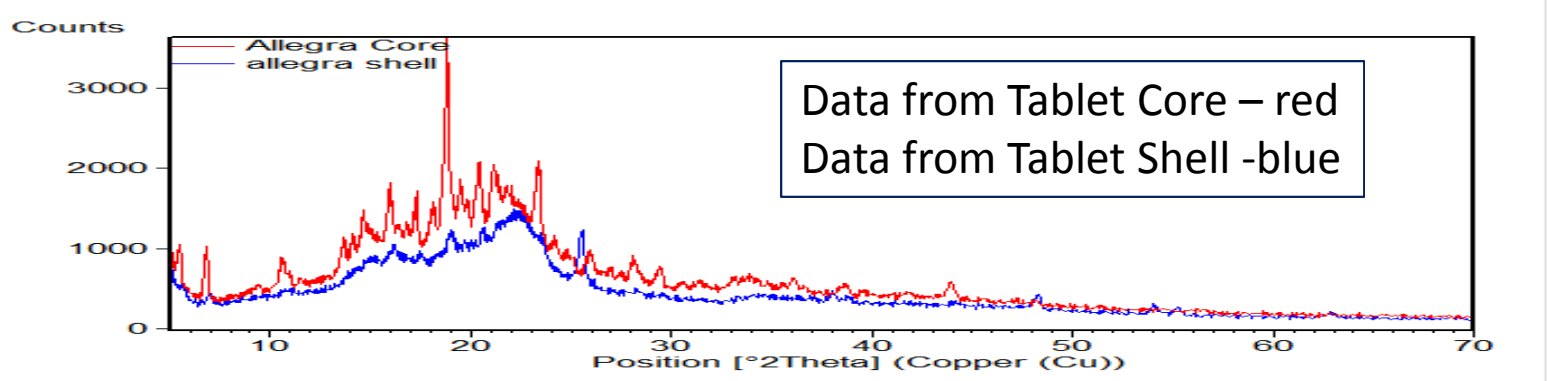
In Formulation analyses the API is often a low scattering low density material that is masked by highly scattering higher density materials often used as excipients

Identify excipients first and then identify the API

Allegra

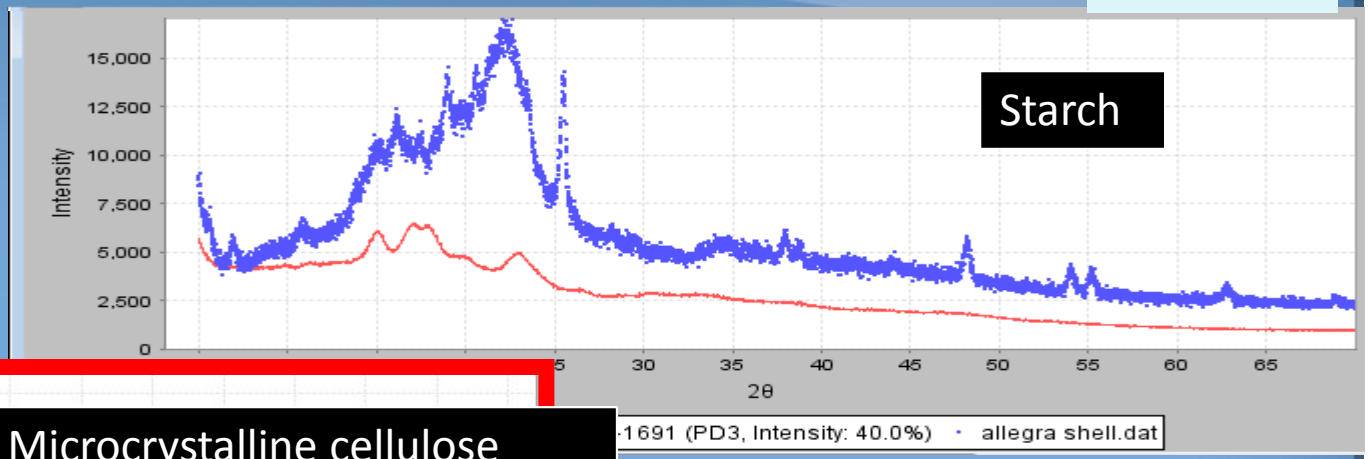
General Issue - Crystallinity

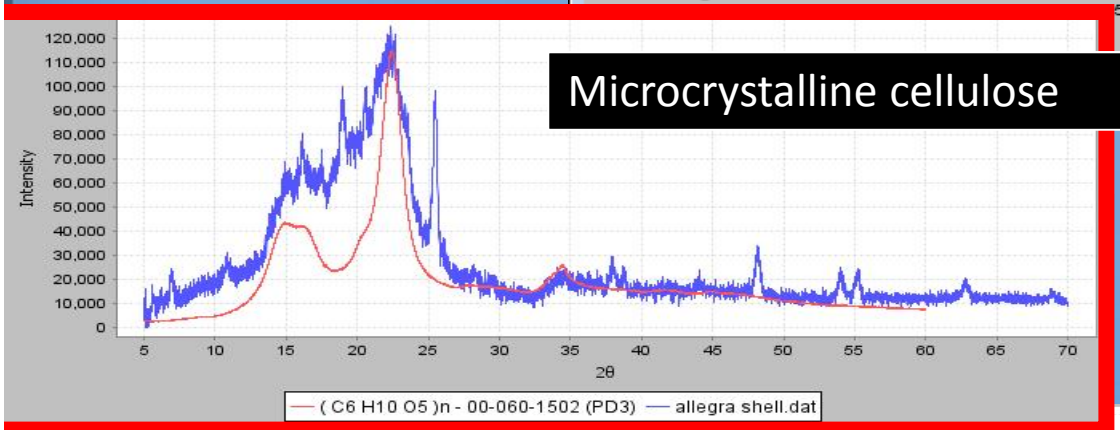




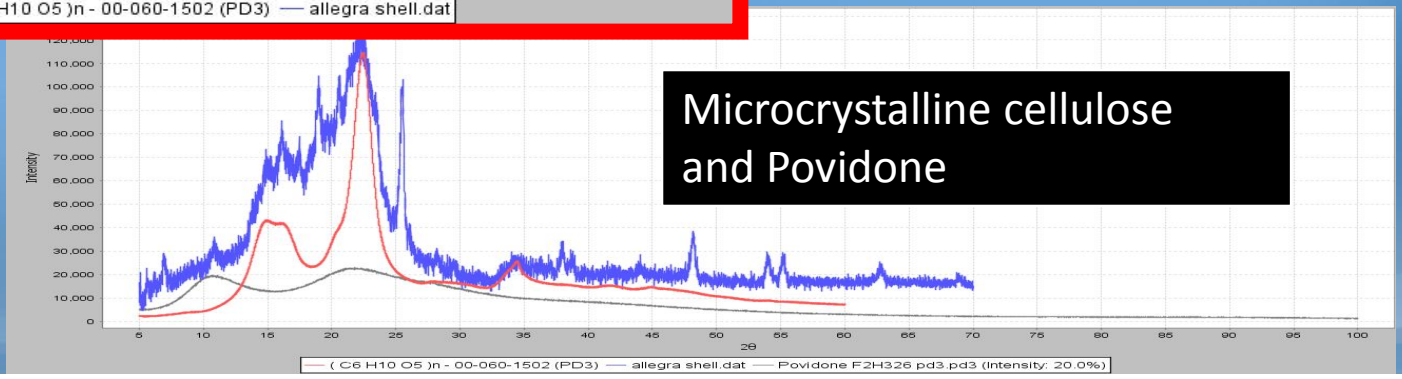
Experimental digital patters for Nanocrystalline and non-crystalline materials

Allegra





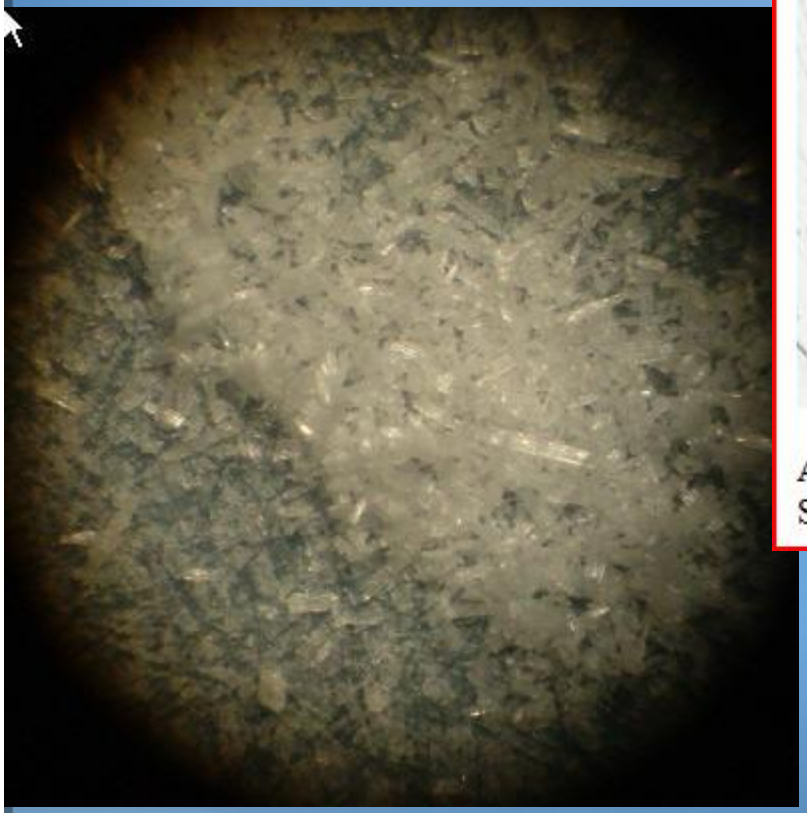
Microcrystalline cellulose
Gelatinized Starch
Povidone



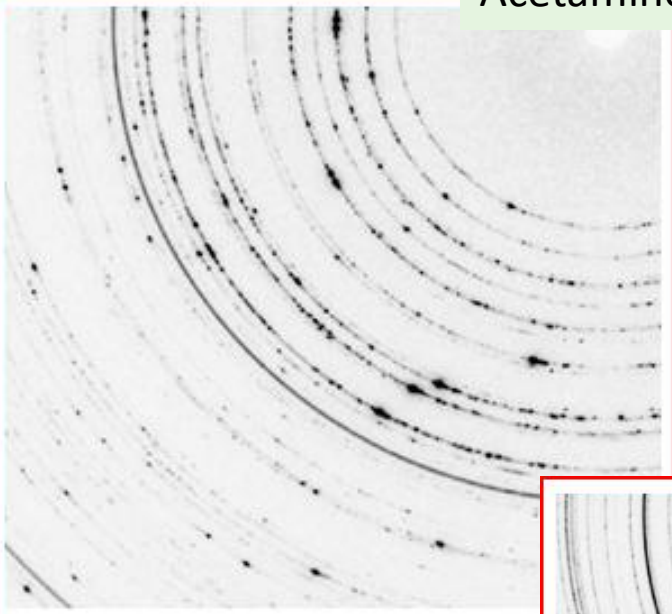
Pharmaceutical Round Robin

Assymmetric Crystals

ICDD Round Robin Data

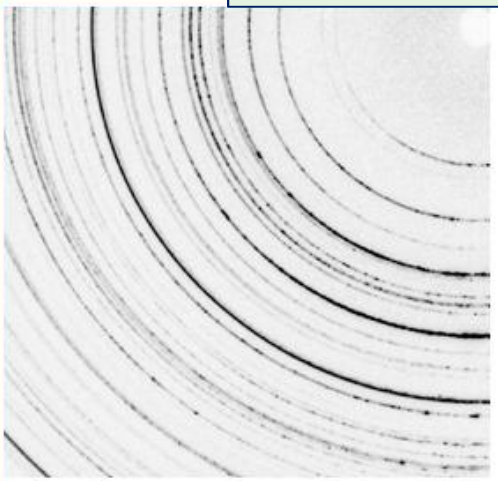


Acetaminophen & Si



ASi - A + Silicon
Spotty rings.

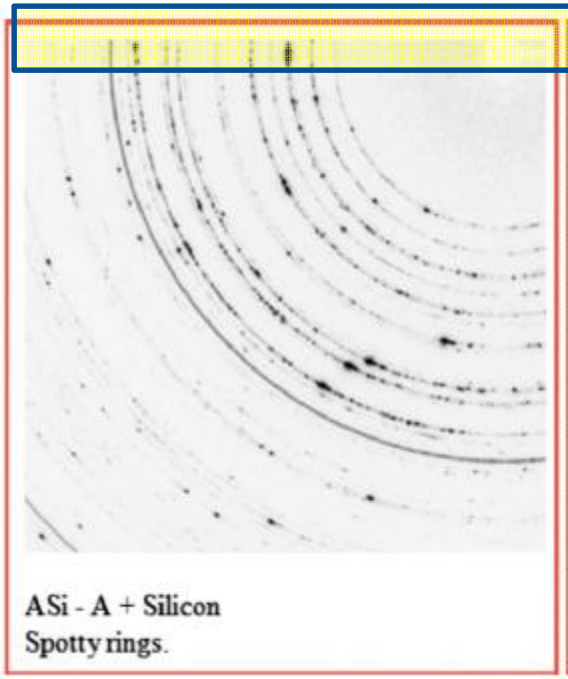
Mannitol & Si

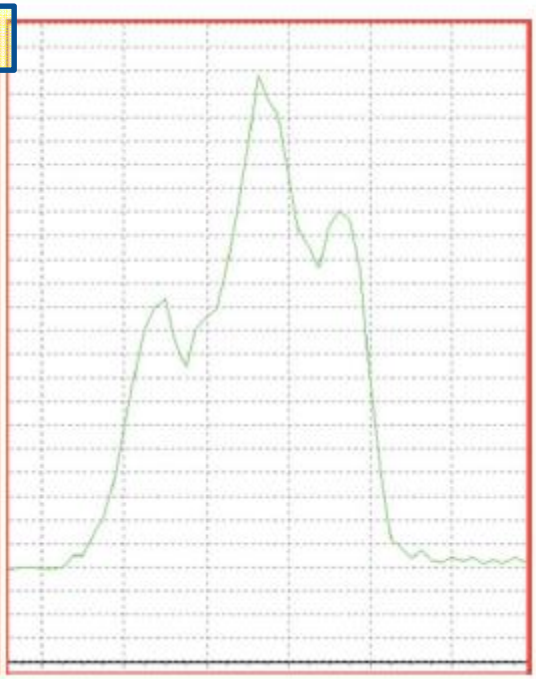


MSi - M + Silicon
Strong texture and some spottiness.

Pharmaceutical Round Robin

Large grains – capillary mount



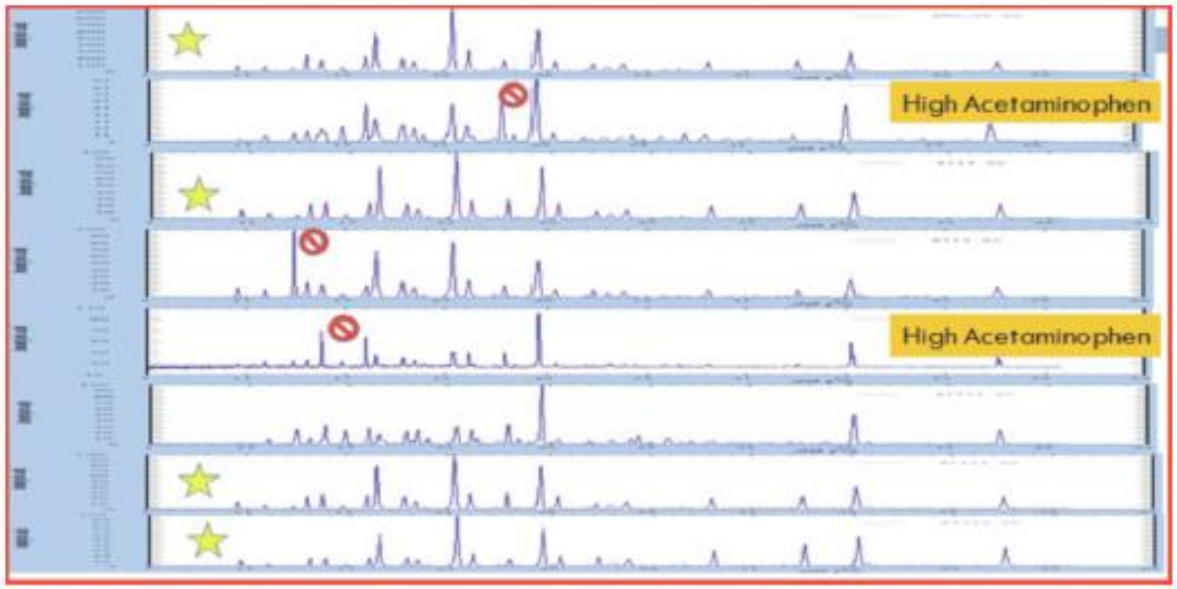


2D Detector

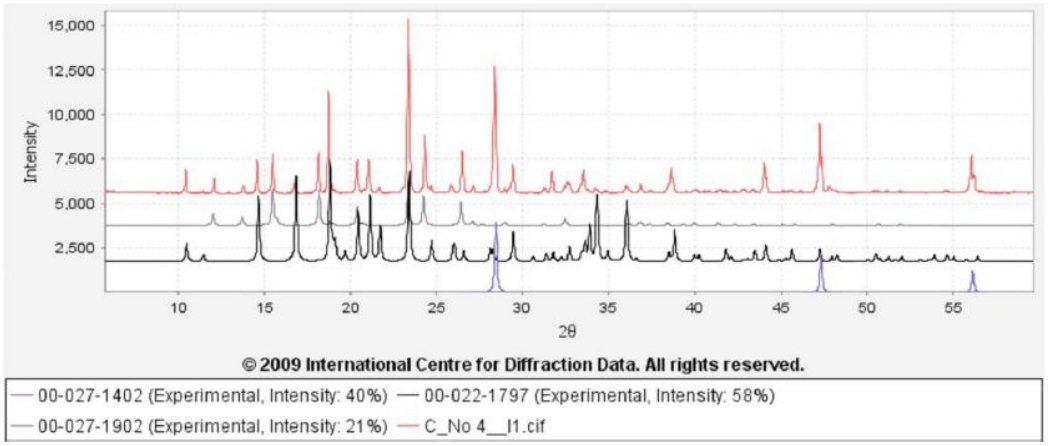
1D Detector

Pharmaceutical Round Robin

Particle Size/Granularity



Only 4/8 Laboratories produced a randomly oriented powder – only 3/11 produced the correct quantitative results.

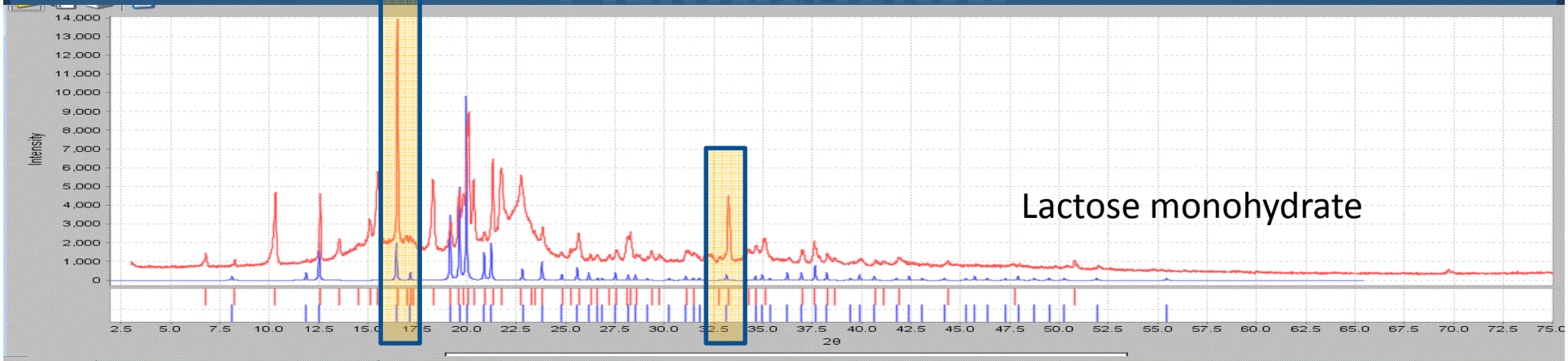


Grind the sample to eliminate the particle size effect in the original material

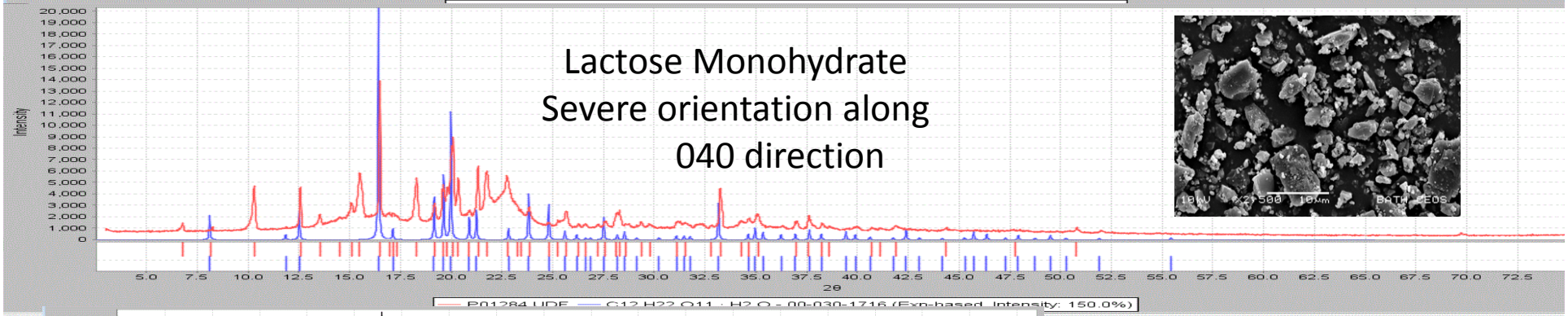
Acetaminophen, D-mannitol and NIST silicon

Orientation

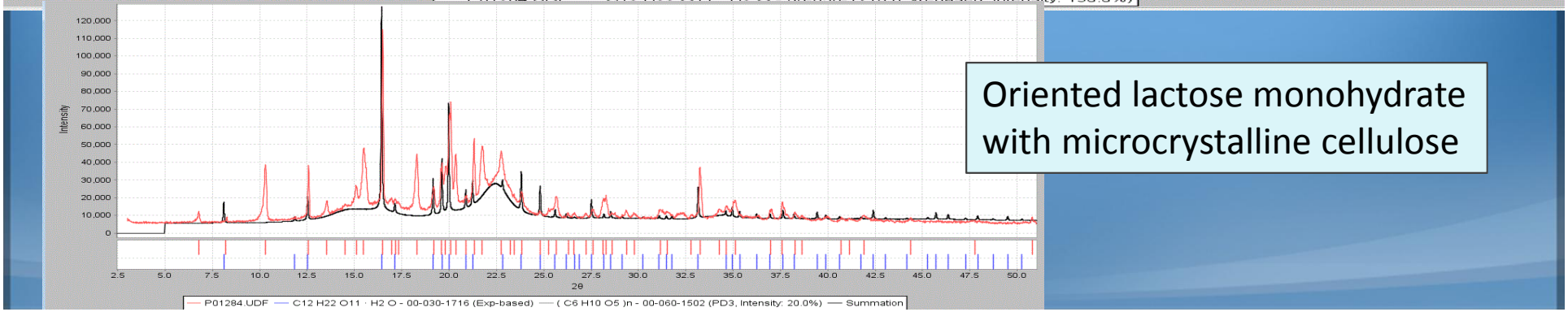
Effexor



Lactose monohydrate



Lactose Monohydrate
Severe orientation along
040 direction



Oriented lactose monohydrate
with microcrystalline cellulose

Pharmaceutical Round Robin

Impact on Intensities

Severe orientation will prevent both identification and quantitation

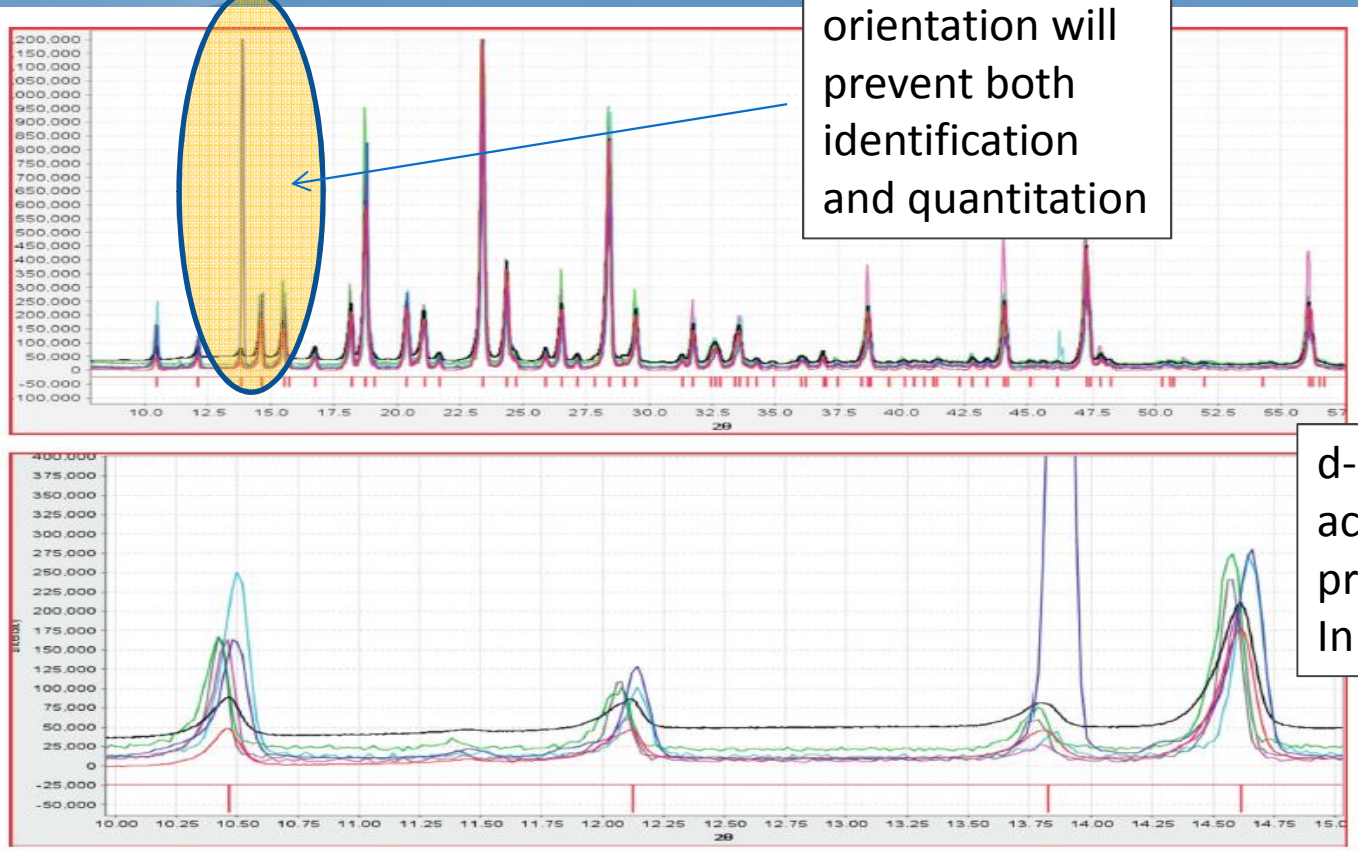


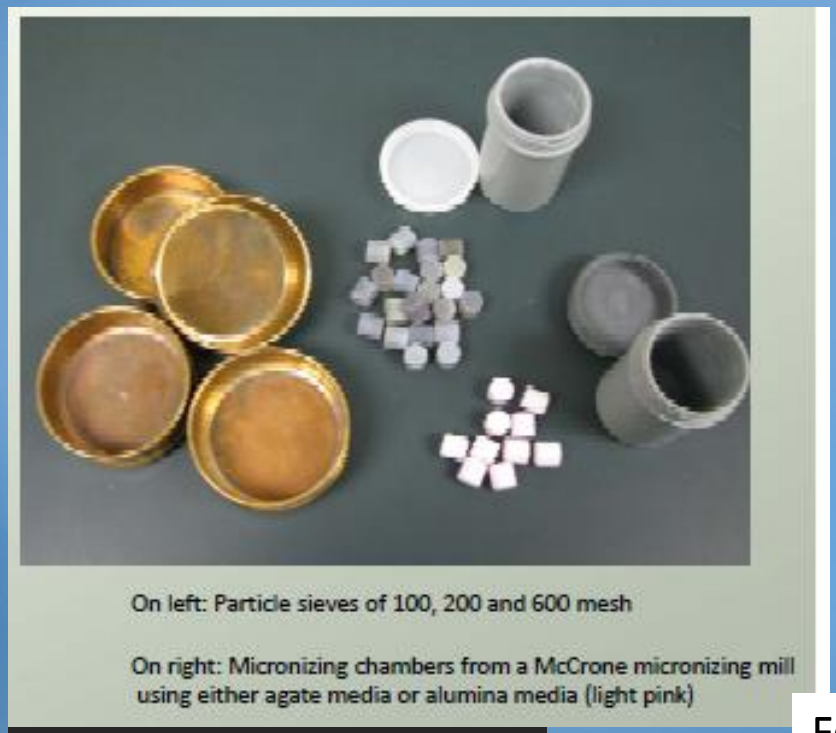
Figure 8. (Color online) (a) Superimposed data from seven laboratories for the three component mixture that were all scaled to the maximum peak. (b) Data from seven laboratories are superimposed for the three component mix. The outside two peaks are due to mannitol and the inside two peaks to acetaminophen. The off-scale peak is characteristic of severely oriented acetaminophen.

d-spacings relatively accurate, intensities and profiles vary considerably In poorly prepared samples

Best Practices

- Grind or attrite to product random oriented specimens without specimen damage
- Increase collection times and optimize S/N for low Z, low density materials
- Use zero background holders especially if you are analyzing amorphous and non-crystalline components
- Analyze peak shapes to detect granularity (*know your instrumental peak shape by running a NIST standard*)
- Analyze relative peak intensities to detect orientation
- Run multiple specimens and /or separations (compare or cluster the data)

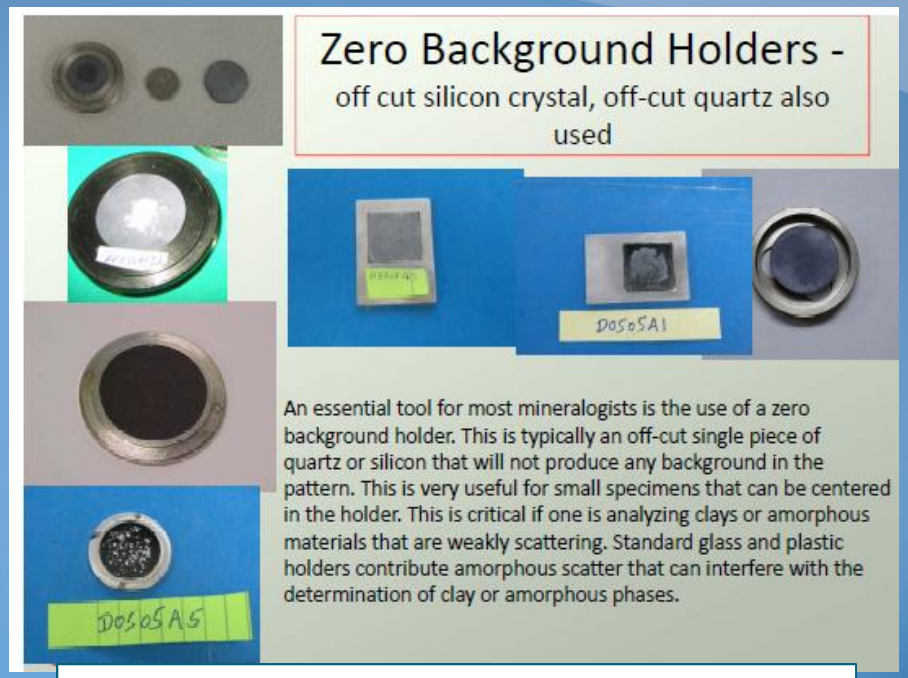
Tutorial – How to Analyze Drugs (www.icdd.com/resources/tutorials)



On left: Particle sieves of 100, 200 and 600 mesh

On right: Micronizing chambers from a McCrone micronizing mill using either agate media or alumina media (light pink)

How to Analyze Minerals



Kaptan capillaries for capillary mounts

For pharmaceuticals polymeric attrition media (Polystyrene, Polyethylene) used for soft materials

METHODS OF ANALYSIS

ICDD Global User Surveys

	Responses	Queries	
2012 Survey	1031	9956	10.3%
2009 Survey	811	6950	11.6 %
2006 Survey	220	1305	6 %

All survey data are in a relational database format for data mining purposes – We can correlate responses to methods used with responses to success in particular analyses

Success in Material Identification

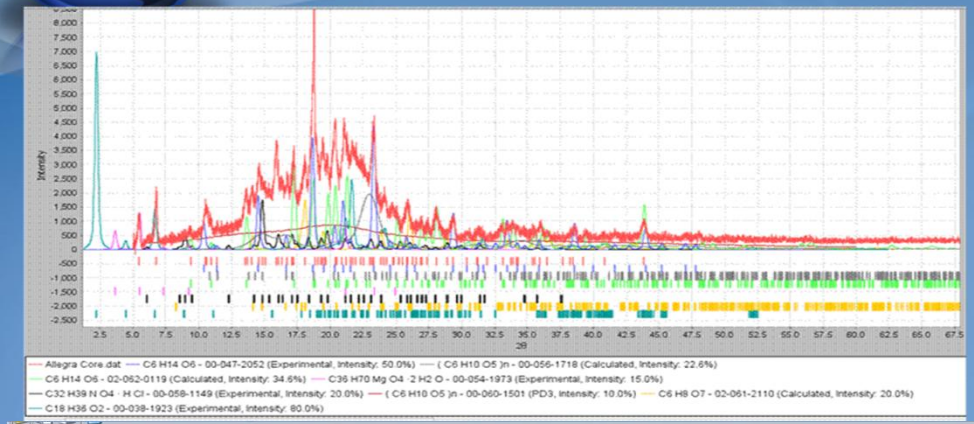
	PDF-4+	Good	Average	Bad	Ugly
	>95 %	>95	>90 %	75-90 %	75% <
Number of Reponses	63	132	351	192	61
Age					
Age >50	42.9	43.2%	41.6%	35.9%	41
21-30	4.8	7.6%	11.7%	10.4%	18
Experience					
Primary XRD Analysis	91.8	87.3%	82.9%	78.7%	73.7%
Frequency Phase ID	88.7	81.0%	79.6%	68.6%	70.0%
Tools					
PDF-2 Usage	20.6	48.8%	61.3%	61.8%	61.8%
PDF-4+ Usage	100.0	48.8%	39.6%	34.9%	38.2%
Technique					
Element Filters	74.0	64.6%	65.9%	51.9%	45.0%
Subfiles	*53.3*	*50.0%*	*48.6%*	*27.1%*	*31.3%*
GOM	48.7	40.0%	32.9%	24.8%	35.7%
d- Match	37.8	41.1%	31.4%	23.1%	40.0%
Frequently Don't Use Filters	32.4	38.2%	36.7%	34.0%	40.0%
Frequently do pattern simulations	30.0	32.2%	14.8%	12.3%	10.0%

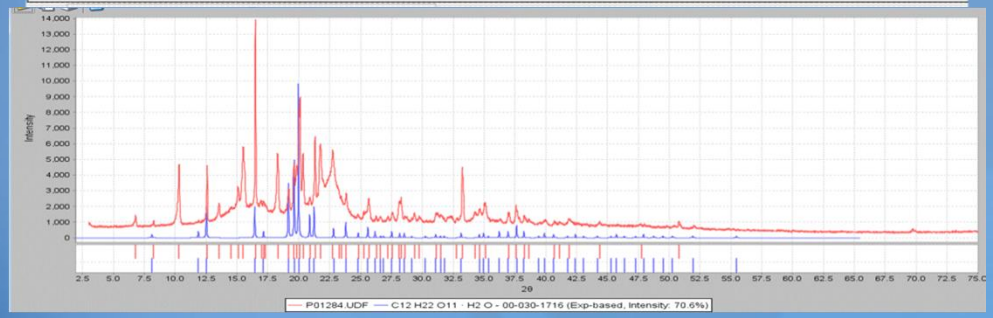
Database Users

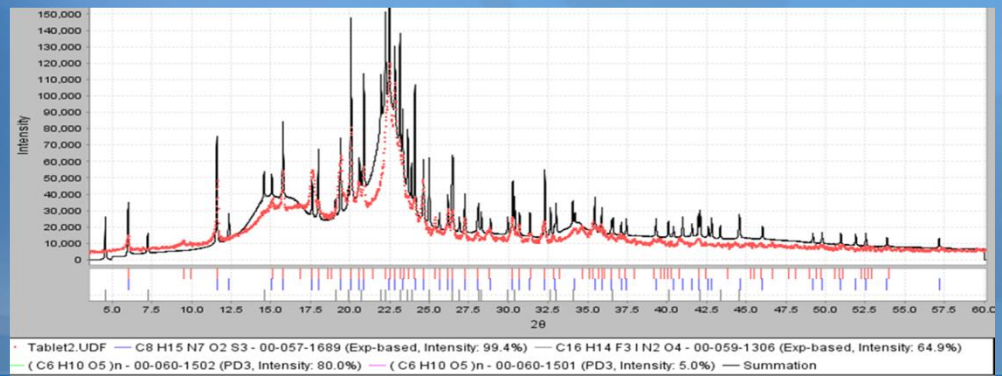
Analyzing Organics is more difficult

	PDF-4+	PDF-4/Organics	PDF-4/Minerals	PDF-2	PDF-2 Best	PDF-4+ Best
Total Responses	314	54	94	468	63	63
Q3						
Academic	41.1	24.1	36.1	45.7	41.9	34.9
Industrial/Man/serv.	29.9	38.9	25.5	29.7	36.5	31.8
Q7						
Primary XRD	83.6	87.5	79.5	80.1	85.2	91.8
Primary ED	31.4	22.2	23.4	28.4	27.8	40.0
Q 10						
Phase ID	59.2	54.0	60.9	61	63.8	58.6
Quant Rietveld	9.9	4.0	6.9	6.8	5.2	13.8
Rietveld Structure	5.1	6.0	3.4	6.4	3.4	0.0
Q 11						
Freq XRD Phase ID	73.0	64.0	65.9	69.4	82.3	86.4
Rietveld Quant	35.0	29.3	30.3	22.4	26.7	40.0
Crystallinity	21.8	20.9	13.6	14.8	22.4	36.7
Crystallite Size	24.4	15.2	15.6	18.9	13.5	36.5
Q 18						
Phase ID						
>95%	21.1	18.4	24.2	14.1	100.0	100.0
>90	45.3	40.8	49.5	46.8		
>75	21.8	32.7	18.7	25.7		
75<	7	6.1	3.3	7.6		
Q 19						
Elements	67.7	60.5	54.8	61.3	67.3	74.0
Subfiles	46.4	43.2	58.6	41	55.8	53.3
GOM	35.2	35.5	38.8	30.7	40.0	48.7
Ref qual	39	48.6	40.4	31.3	40.5	37.8

Difficult Problems







Allegra

- Complex Formulation
- Heavy Peak Overlap
- Contains amorphous and nano crystalline materials

Effexor (and Lipitor)

- Major phase (lactose monohydrate) is heavily oriented
- Nanocrystalline material

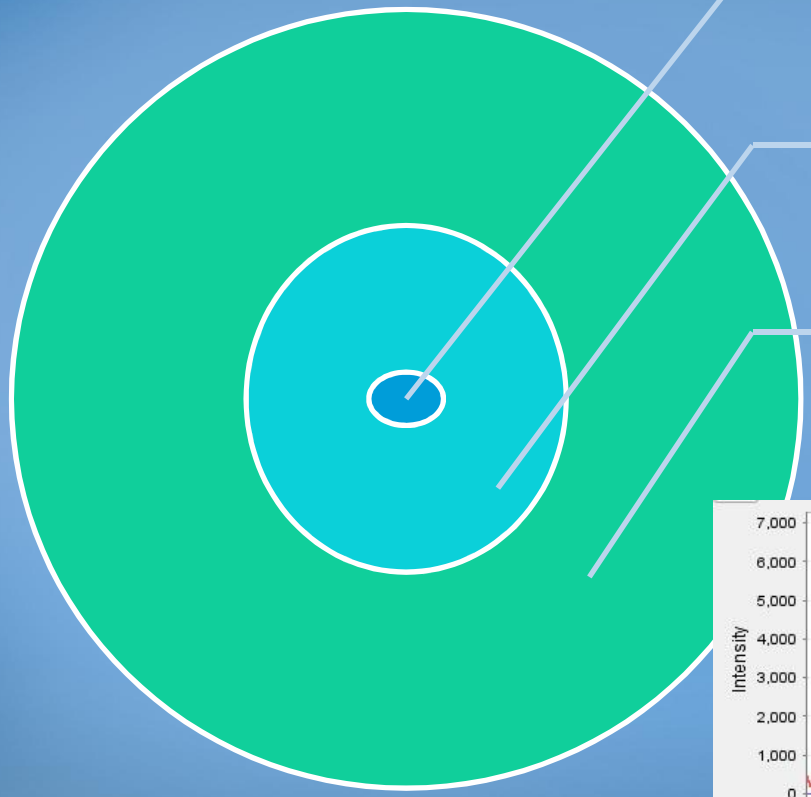
Pepcid AC

Due to nano and amorphous content this is difficult to analyze with PDF-2, easy to analyze with PDF-4

Database
Tools for improved formulation analysis

- *Subfiles on Excipients and Pharmaceuticals*
- Elemental Filters - All data expressed in atomic and weight %'s
- *Full experimental digital patterns for mircocrystalline polymers and amorphous materials*
- *Common inorganic salts and oxides*
- *Evaluate and correct disordered structures*
- *Actively collect new pharmaceutical materials through grants*

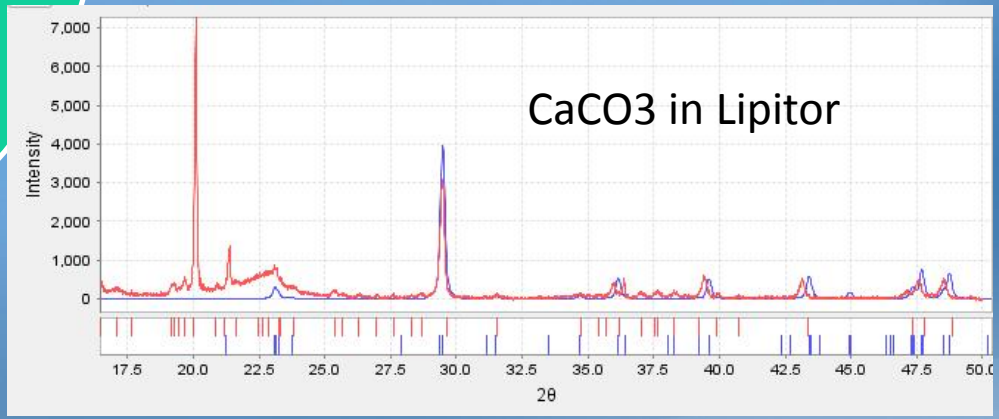
Use of Filters



Element 293 entries (Ca)

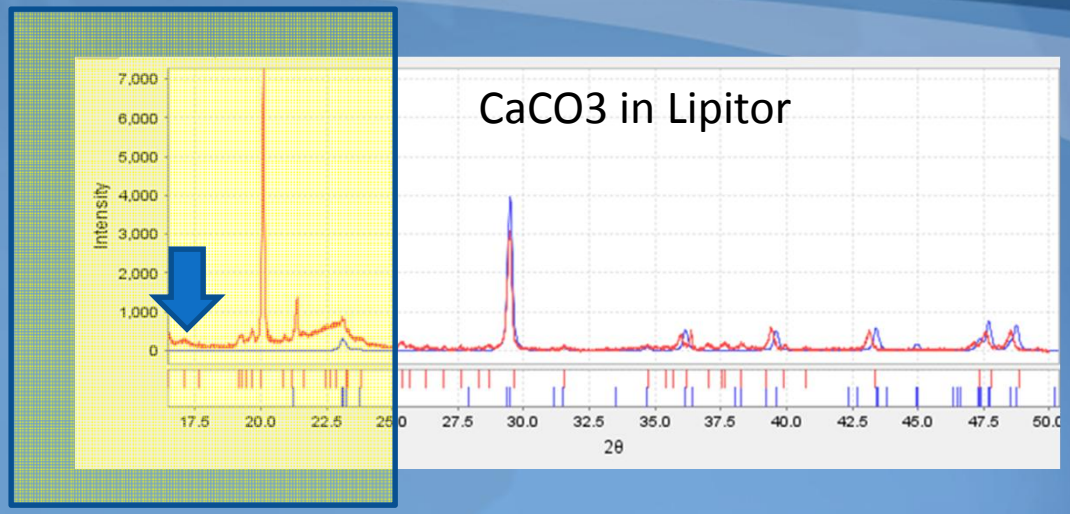
Pharmacuetical and Excipients 6,967 entries

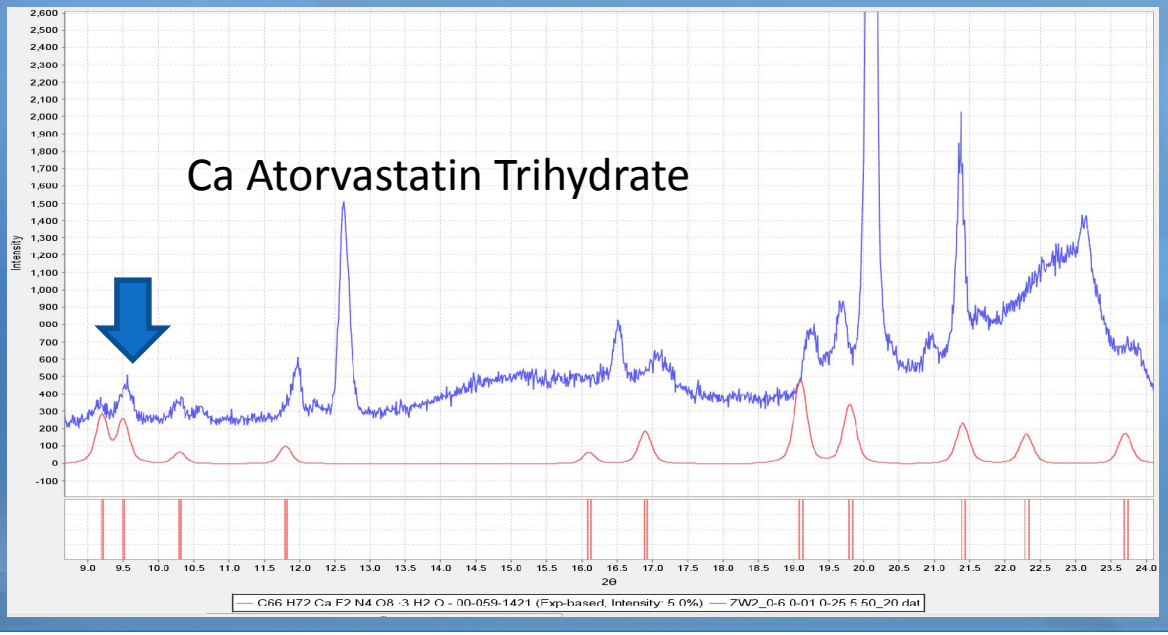
Database 471,257 entries



Use of Filters - Lipitor

Subfile and Element Filter

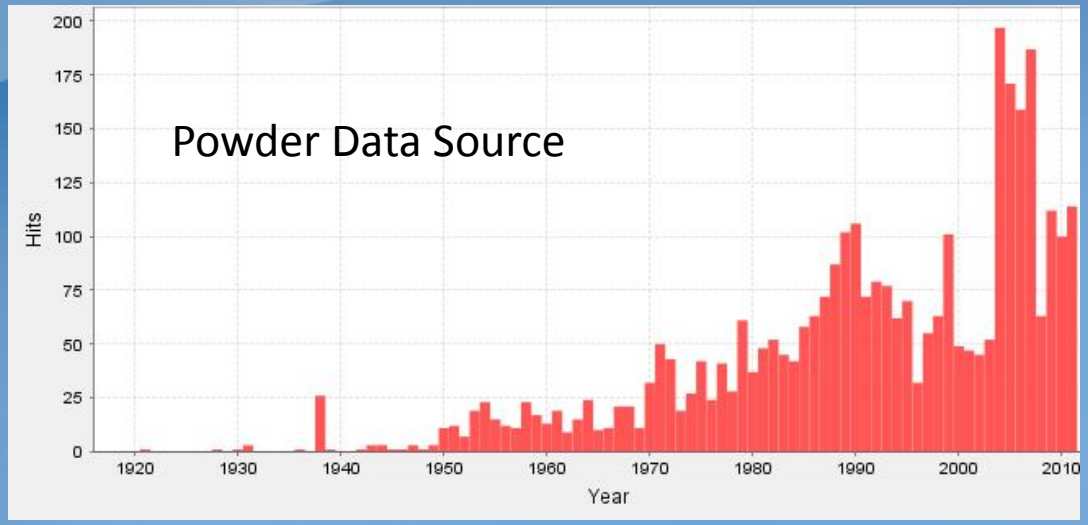




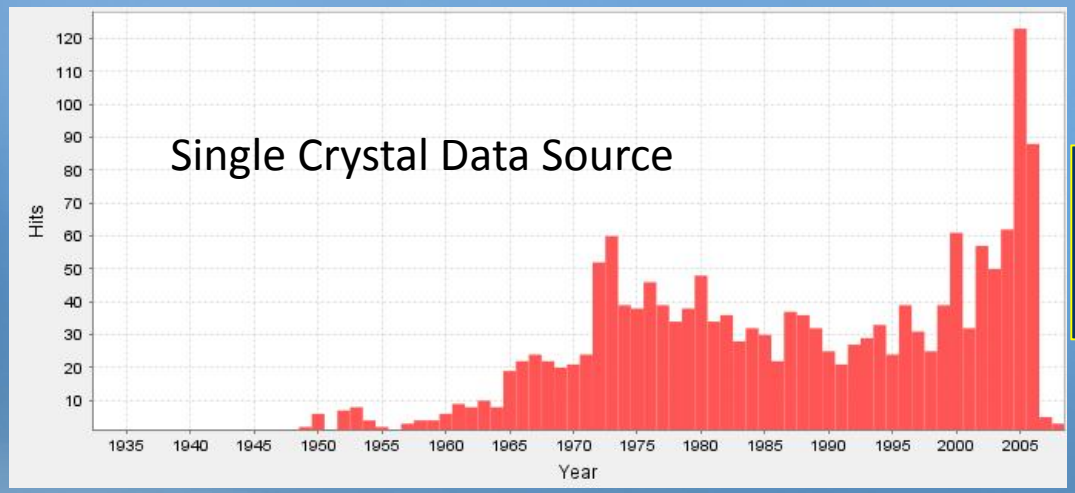
d-spacing filter – 9.66 Å
293 Entries

8 Entries
4 are Ca Atorvastatin

Subfiles - Pharmaceuticals



ICDD data sourced from powder diffraction experiments – many grants and donations

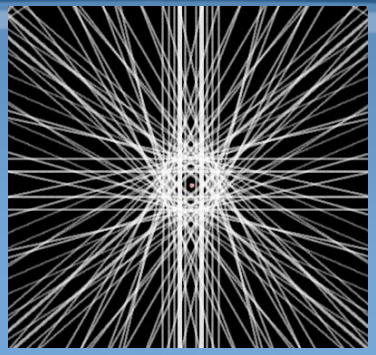


ICDD data sourced from CSD single crystal data – primarily literature publications

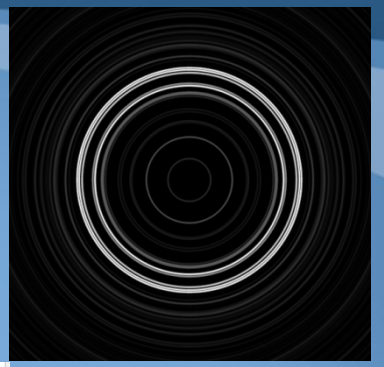
Pattern Simulation

Shao-Fan Lin Dropropizine

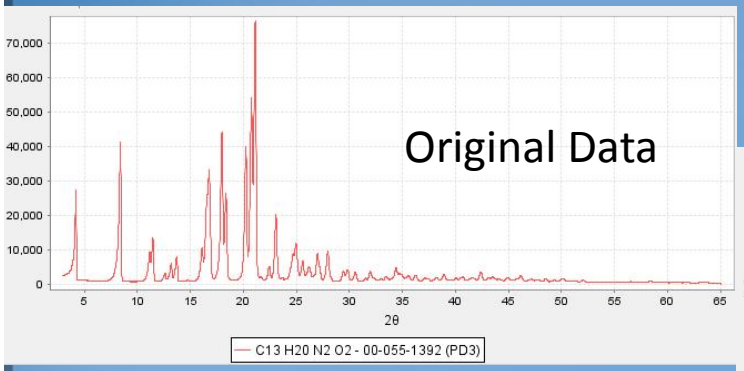
53 % of PDF-4/Organics users have a 2D detector

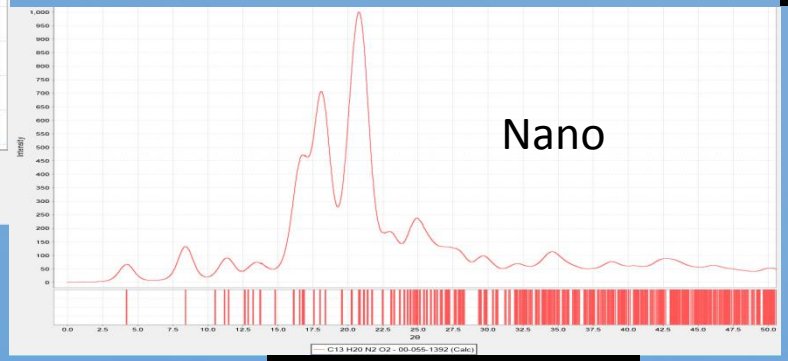


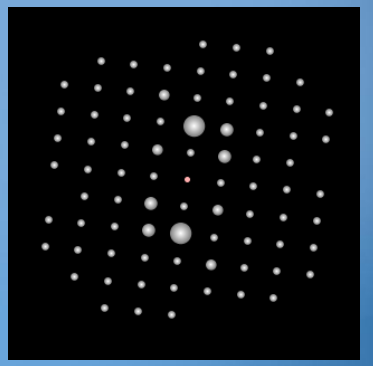
EBSD Pattern



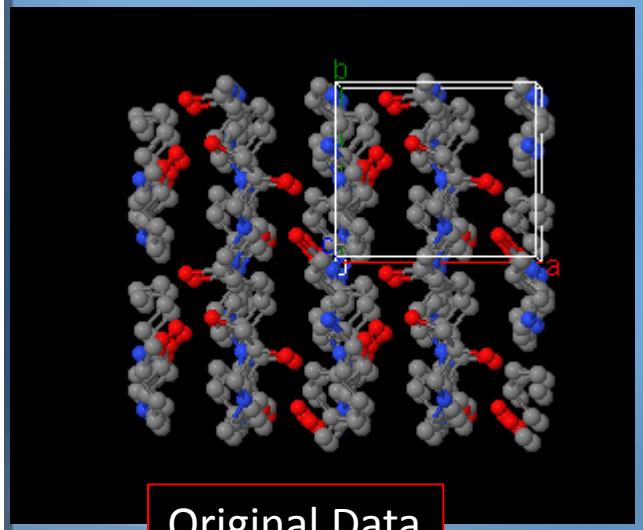
2D XRD



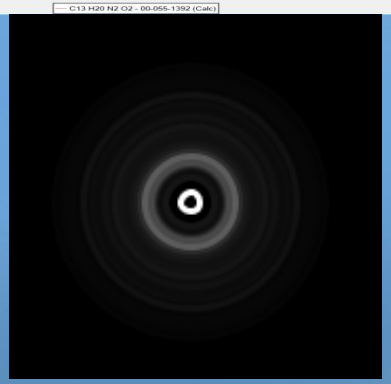




Electron Diffraction Spot Pattern (001)

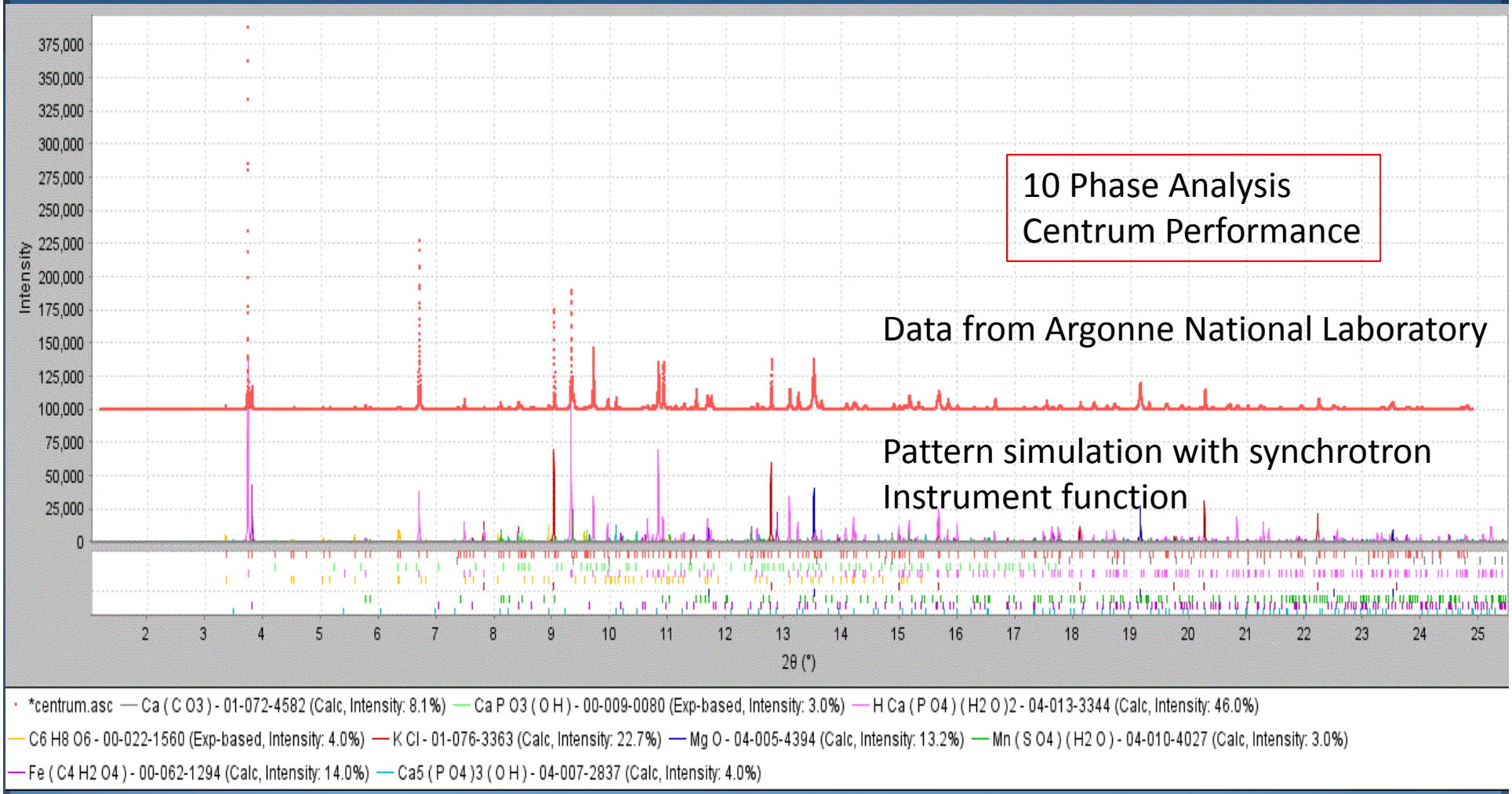


Original Data



Electron Diffraction (100 KeV)

Synchrotron Analyses



~ 30% of PDF-4/Organics users use both a laboratory XRD unit and a synchrotron

Centrum Performance- Goodness of Merit (GOM)

High quality lab data

GOM

Vit C	6159	C	1
Calcite	6145	I	2
Monetite	6143	I	3
KCl	5884	I	4
Fe Fumarate	5334	B	5
Brushite	2640	S	8
Nicotinamide	2517	I	15

95 d-spacings in the pattern

GOM maximum = 8000
High scores better fit

Synchrotron Data

GOM

Calcite	7519	I	1
Monetite	7477	I	2
Brushite	7469	S	3
Vitamin C	7384	C	4
KCl	7166	A	5
MgO	6779	I	12
MnSO4 Hydrate	5230	I	2
Fe Fumarate	4321	R	8
Hydroxyapatite	4892	I	2
Nicotinamide	3161	I	8

More intensity and resolution
203 d-spacings in the pattern
Peaks are well separated

Success in Identification

Technique	Greater than 95 %			Less than 75 %
Element Filters	74.0	64.6%		45.0%
Subfiles	*53.3*	*50.0%*		*31.3%*
GOM	48.7	40.0%		35.7%
d- Match	37.8	41.1%		40.0%
Frequently Don't Use Filters	32.4	38.2%		40.0%
Frequently do pattern simulations	30.0	32.2%		10.0%

Best Methods

Use elemental filters
Use subfiles
Use GOM
Use pattern simulation

Rietveld Refinements for improved phase identification

J. Kaduk, "A Rietveld Tutorial – mullite"
Powder Diffr., Vol. 24, No. 4, December 2009

T. G. Fawcett, C. E. Crowder, S. N. Kabekkodu, **J. A. Kaduk**, "Improved Material Identification through Targeted Data Mining" Advances in X-ray Analysis, 2010 (with on-line tutorial, icdd.com)

J. Kaduk, "Crystallographic Databases and Powder Diffraction" Volume H, International Tables, IUCr, in progress.

Routinely identifies phases in 0.1-5 weight % concentration with good quality laboratory data

Rietveld Refinements for improved phase identification

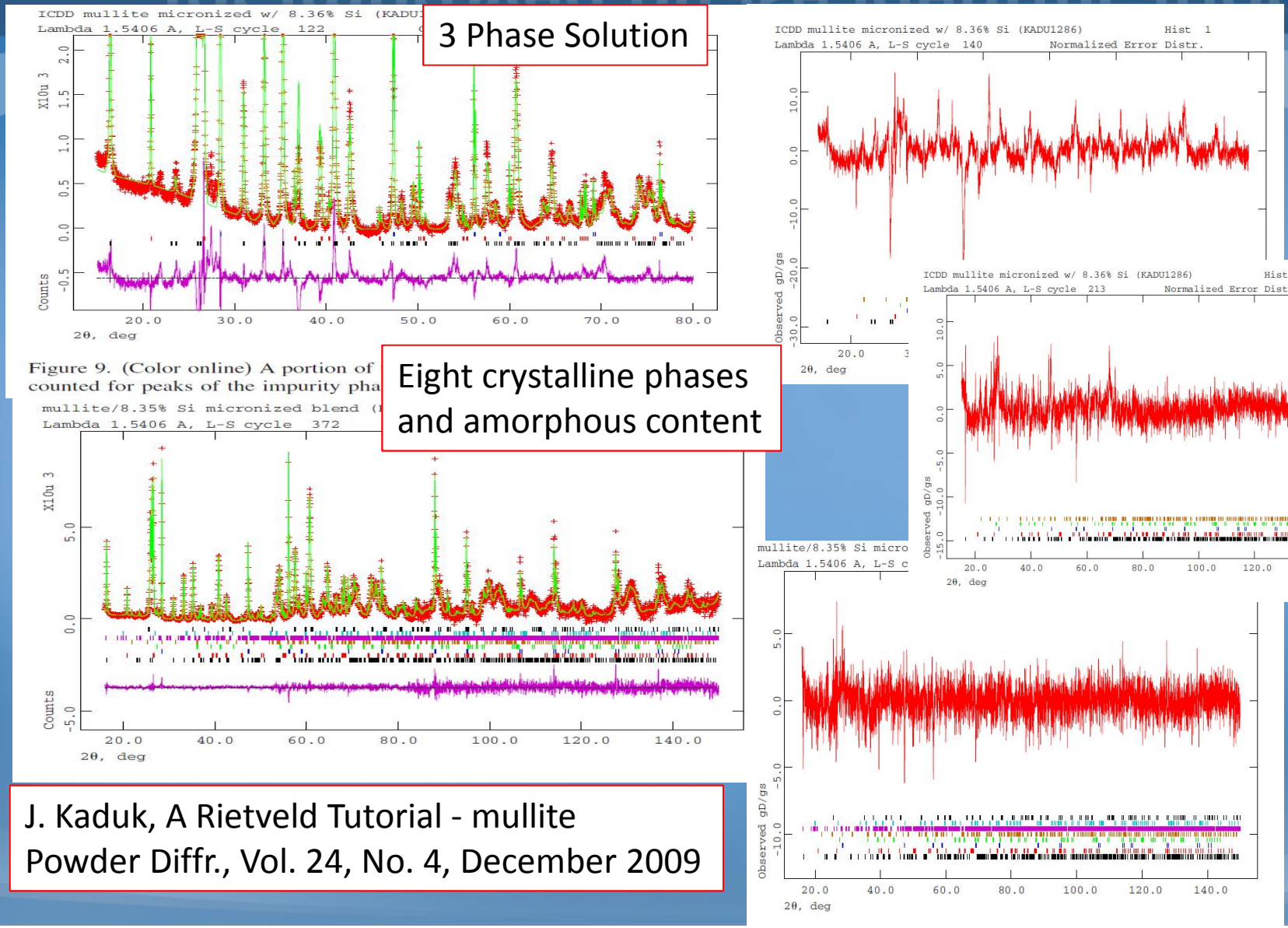
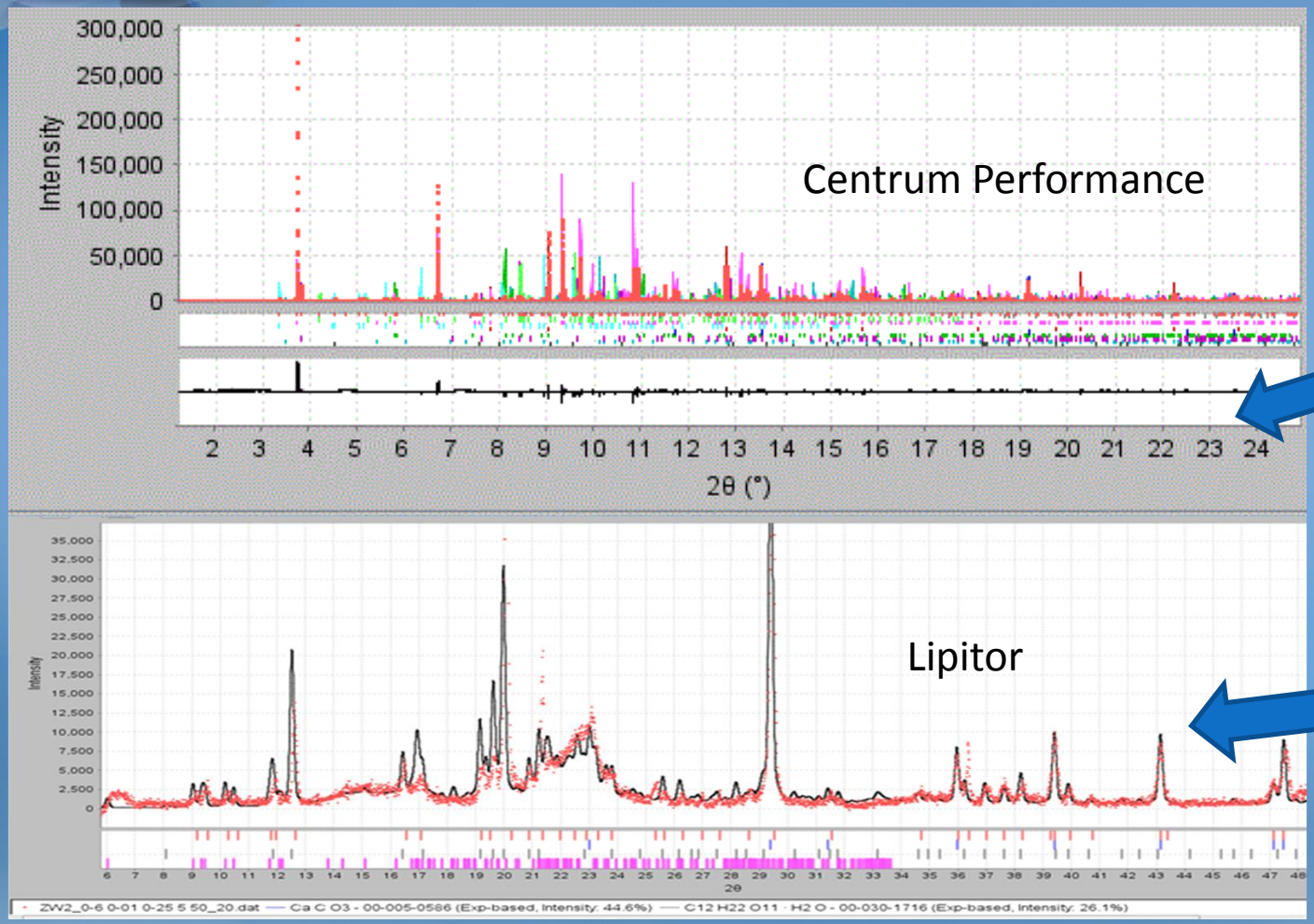


Figure 9. (Color online) A portion of
counted for peaks of the impurity pha

J. Kaduk, A Rietveld Tutorial - mullite
Powder Diffr., Vol. 24, No. 4, December 2009

Pattern Simulations (not a refinement)



Difference Plot
New in 2013

Summed component
Plot (New in 2012)

Cluster Analyses

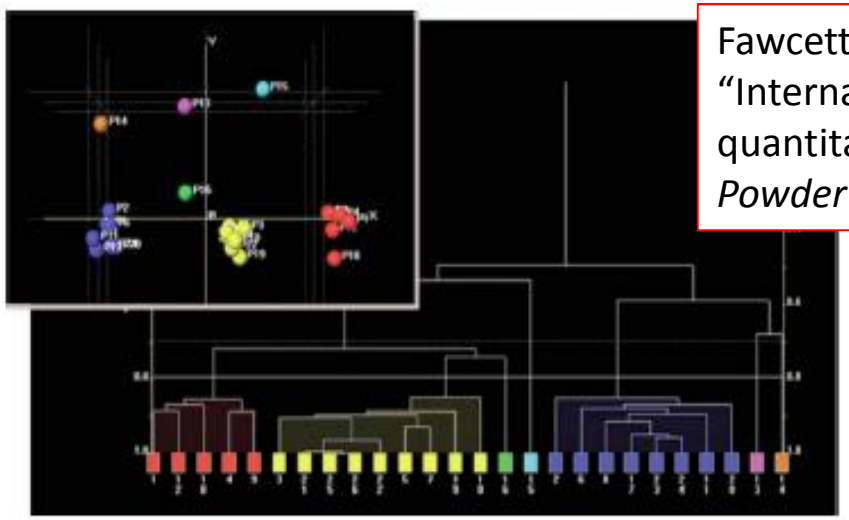


Figure 3. (Color online) Dendrogram and principal component analysis of 21 data sets from seven laboratories.

Fawcett, T. G., Needham, F., Faber, J., Crowder, C. E., (**2010**), "International Centre for Diffraction Data round robin on quantitative Rietveld phase analysis of pharmaceuticals", *Powder Diffraction*, 25(1), pp 60-67.

APPLICATION OF HIGH-THROUGHPUT CLUSTER ANALYSIS TO MULTIPLE DATA TYPE – COMBINING DATASETS

G.J. Cunningham, G. Barr, W. Dong, C.J. Gilmore, WestCHEM, Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, Scotland; C. Frampton, Pharmorphix Limited, 250 Cambridge Science Park, Milton Road, Cambridge, CB4 0WE

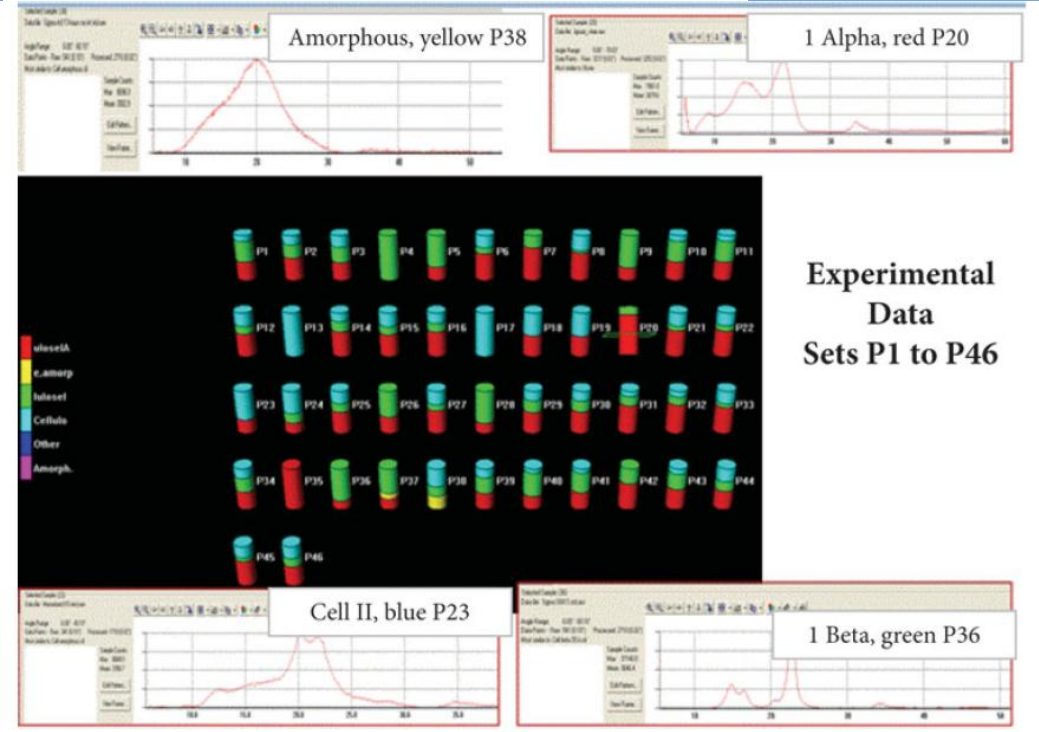
HIGH-THROUGHPUT POWDER DIFFRACTION - THE SEARCH FOR POLYMORPHS	PPXRD-2	65,348
HOW TO COMBINE PXRD, RAMAN AND OTHER 1-D DATA IN HIGH THROUGHPUT POLYMORPH/SALT/CO-CRYSTAL STUDIES	PPXRD-6	23,954
MANY PATTERNS AND MANY METHODS: NEW METHODS UTILISING MULTIPLE ANALYSIS TECHNIQUES IN POLYMORPH AND SALT SCREENING SYSTEMS	PPXRD-8	6,478
PXRD WITH RAMAN SPECTROSCOPY, DSC AND IR DATA	PPXRD-9	18,973
QUANTITATIVE ANALYSIS OF MIXTURES USING HIGH THROUGHPUT INSTRUMENTATION WITHOUT THE USE OF STANDARDS	PPXRD-6	120,457

Cluster Analyses

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]
[1]*International Centre for Diffraction Data, Newtown Square, Pennsylvania*
[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*

Powder Diffr., Vol. 28, No. 1, March 2013



Polymorphs Identified

Cellulose
AZT
Carbamazepine
Heroin
Calcium Phosphates
Glycine
Codeine
Famotidine
Cocaine
Cimetidine

Cluster analysis doesn't depend on the specimen being crystalline !

Cluster Analyses

MAPPING DRUG CHEMISTRY FOR AZT AND CARBAMAZEPINE BY COMBINING CLUSTER ANALYSIS AND DIFFRACTION DATABASES

Timothy G. Fawcett, Soorya N. Kabekkodu

International Centre for Diffraction Data
Newtown Square, PA, 19073

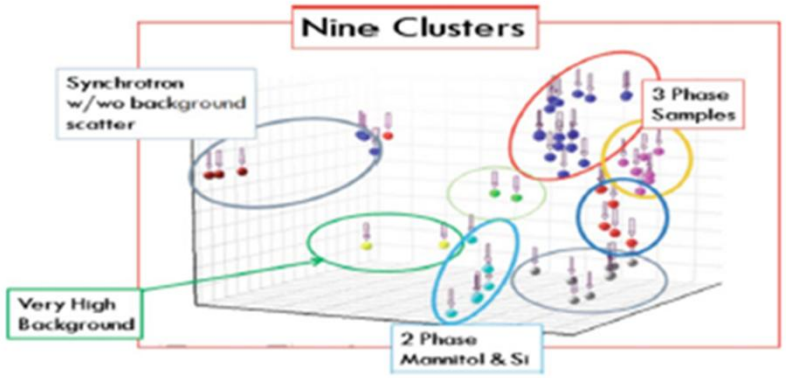


Figure 4. (Color online) PCA of 63 data sets from nine laboratories. The comments were added by the authors.

Declustering multiple data sets to get component contributions

Invited – CRYSTAL STRUCTURE SOLUTION FROM POWDER MIXTURES: THE PXRD-BTEM-RIETVELD METHOD

Marc Garland*, L.Guo, M. Schreyer, S. Thirunahari
ICES, Jurong Island, Singapore

Outline – Best Practices

- Specimen Preparation-
- Round Robin, Experience

- General issues – low scattering power, absorption difference in ingredients, crystallinity
- Asymmetric Crystals
- Particle size
- Granularity
- Orientation
- Impact on Intensities
- Separation Techniques

- Methods of Analysis –
- Customers Survey Data

- Experience
- Databases
- Noncrystalline Materials
- Reference Quality
- Elemental Filters
- Subfiles
- Pattern Simulations
- Rietveld Analysis
- Combined Techniques – DXC/XRD
- Complimentary Analytical Techniques

Best Practices

- Focus on specimen preparation – good data lead to good analyses
- Formulation analyses are difficult – use all your tools
  - Subfiles
  - Complimentary analytical data – Element filters
  - Data analysis tools – Figures of Merit, Reference quality, Intensity and d-spacing matches
  - Data processing techniques (Rietveld reinteration, different search/match algorithms, cluster analyses, simulations especially with non-crystalline materials)

Ingredients

Dibasic Calcium Phosphate , Potassium Chloride , Ascorbic Acid (Vit. C) , Microcrystalline Cellulose , Calcium Carbonate , Dl-Alpha Tocopheryl Acetate (Vit. E) , Magnesium Oxide , Ginkgo Biloba Leaf (Ginkgo Biloba) Standardized Ex , Gelatin , Ginseng Root (Panax Ginseng) Standardized Extract , Ferrous Fumarate , Niacinamide , Crospovidone , Starch , Zinc Oxide , Calcium Pantothenate , Silicon Dioxide , Manganese Sulfate , Pyridoxine Hydrochloride (Vit. B6) , Riboflavin (Vit. B2) , Thiamin Mononitrate (Vit. B1) , Cupric Oxide , Vitamin A Acetate , Beta Carotene , Chromium Chloride , Folic Acid , Potassium Iodide , Sodium Molybdate , Sodium Selenate , Boron , Biotin , Phytonadione (Vit. K) , Sodium Metavanadate , Nickelous Sulfate , Stannous Chloride , Cyanocobalamin (Vit. B12) , Ergocalciferol (Vit. D2) , Acacia Gum , Ascorbyl Palmitate , Butylated Hydroxytoluene (BHT) , Citric Acid , Dl-Alpha Tocopherol (Vit. E) , FD&C Red No. 40 Aluminum Lake , FD&C Yellow No. 6 Aluminum Lake , Glucose , Hydroxypropyl Methylcellulose , Lactose , Magnesium Stearate , Polyethylene Glycol , Polysorbate 80 , Potassium Sorbate , Sodium Aluminum Silicate , Sodium Ascorbate , Sodium Benzoate , Sodium Citrate , Sorbic Acid , Sucrose , Titanium Dioxide , Tribasic Calcium Phosphate , Water , Maltodextrin , Maltodextrin May Also Contain

Vitamin A (20% as Beta Carotene)	70.0%	%
Vitamin C 120.0 mg	200.0%	%
Vitamin D	100.0%	%
Vitamin E	200.0%	%
Vitamin K 25.0 mcg	31.0%	%
Thiamin 4.5 mg	300.0%	%
Riboflavin 5.1 mg	300.0%	%
Niacin 40.0 mg	200.0%	%
Vitamin B6 6.0 mg	300.0%	%
Folic Acid 400.0 mcg	100.0%	%
Vitamin B12 18.0 mcg	300.0%	%
Biotin 40.0 mcg	13.0%	%
Pantothenic Acid 10.0 mg	100.0%	%
Calcium 100.0 mg	10.0%	%
Iron 18.0 mg	100.0%	%
Phosphorus 48.0 mg	5.0%	%
Iodine 150.0 mcg	100.0%	%
Magnesium 40.0 mg	10.0%	%
Zinc 15.0 mg	100.0%	%
Selenium 70.0 mcg	100.0%	%
Copper 2.0 mg	100.0%	%
Manganese 4.0 mg	200.0%	%
Chromium 120.0 mcg	100.0%	%
Molybdenum 75.0 mcg	100.0%	%
Chloride 72.0 mg	2.0%	%
Potassium 80.0 mg	2.0%	%
Ginseng Root (Panax Ginseng) Standardized Extract 50.0 mg	%	%
Ginkgo Biloba Leaf (Ginkgo Biloba) Standardized Extract 60.0 mg	%	%
Boron 60.0 mg	%	%
Nickel 5.0 mcg	%	%
Silicon 4.0 mg	%	%
Tin 10.0 mcg	%	%
Vanadium 10.0 mcg	%	%

Vitamin C	120 mg
Niacin (B3)	40 mg
Root Extracts (Celluloses)	>100 mg
Riboflavin (B2)	5.1 mg
Folic Acid	400 mcg
K,Cl *in KCl*	147 mg
Ca *in CaCO3,CaHPO4*	100 mg
P *in CaHPO4*	48 mg
Fe *in Iron Fumarate*	18 mg
Zn *in ZnO*	15 mg
Mg *in MgO, MgStearate*	40 mg
Si *in SiO2*	4 mg
Mn *in MnSO4*	4 mg
TiO2	

<u>4-10 mg</u>
Vit B6 HCl
Calcium Pantothanate
(overlap with Vit C)

<u>60 mg</u>
Boron