EXPANDING THE SCOPE OF PDF-4/ORGANICS™ IN PHARMACEUTICAL PXRD ANALYSIS

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International Centre for Diffraction Data, Newtown Square, PA, USA

ICDD®
International Centre for Diffraction Data

ISO 9001:2008
QUALITY ASSURED COMPANY
CERT.NR. 11409.1

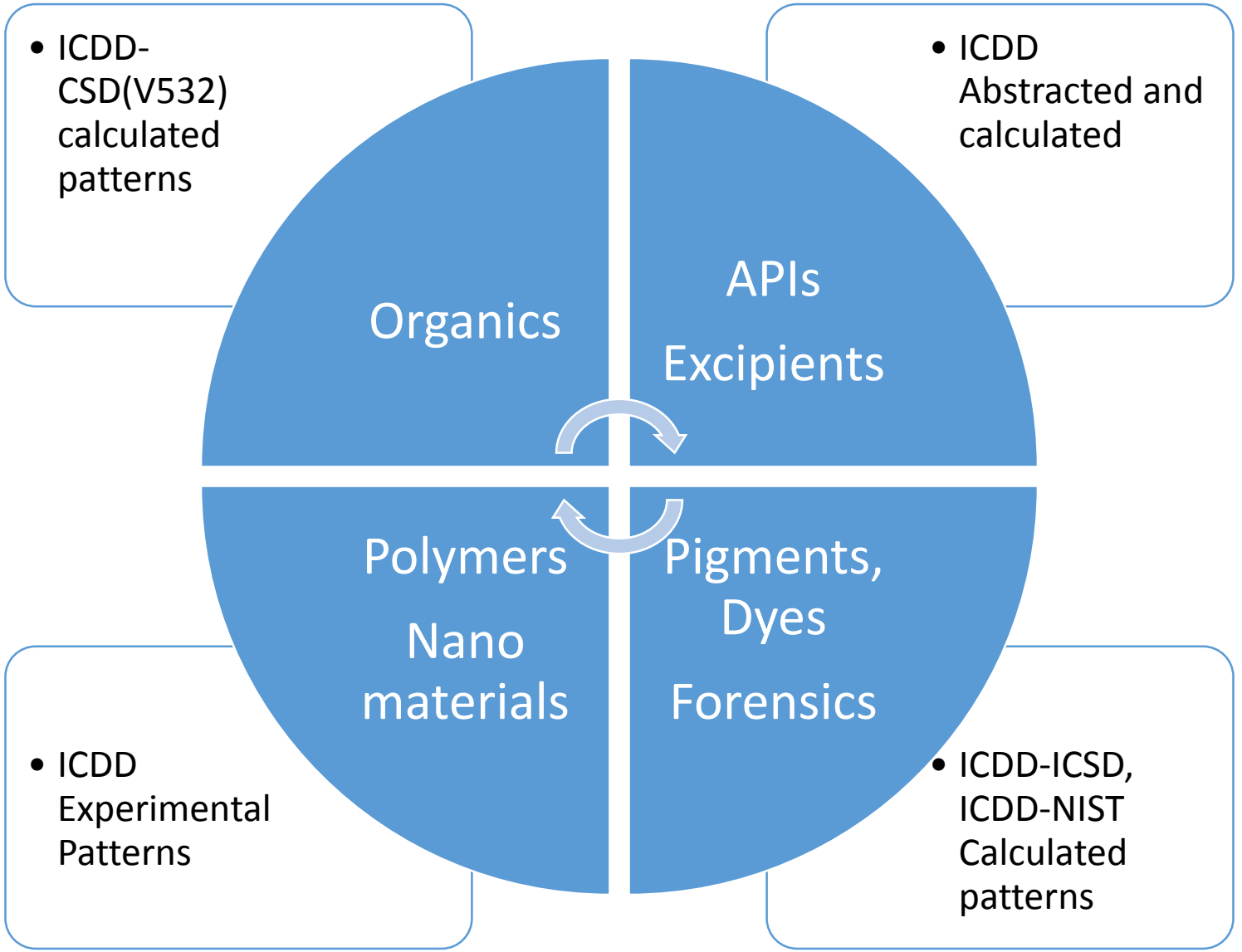
This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

PDF-4/Organics



Release 2016 will have 501,964 entries

PDF-4/Organics

- Database specially designed to target Pharmaceutical and Forensic sample analysis using powder X-ray diffraction methods.
- Atomic coordinates
- Does contain editorially chosen inorganic phases
- Targeted subfiles
- Top 200 pharmaceuticals by US sales
- Raw diffraction patterns
- Amorphous and poorly crystalline patterns
- Trade names where available
- Editorially reviewed organic nomenclature

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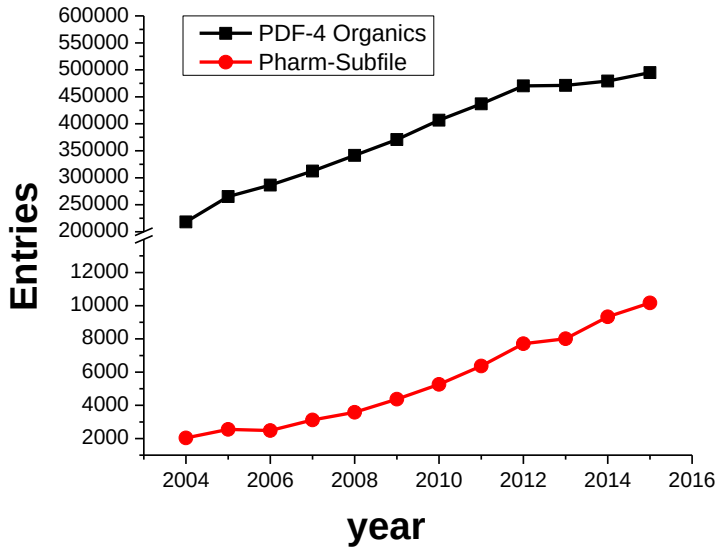
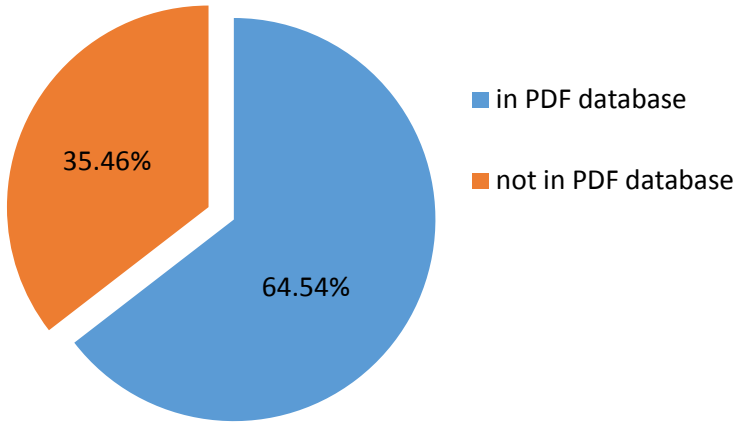
Top 200 Pharamceuticals





- PDF4- Organics database continually expanded in recent years to cover commercially important pharmaceuticals and other phases like polymer

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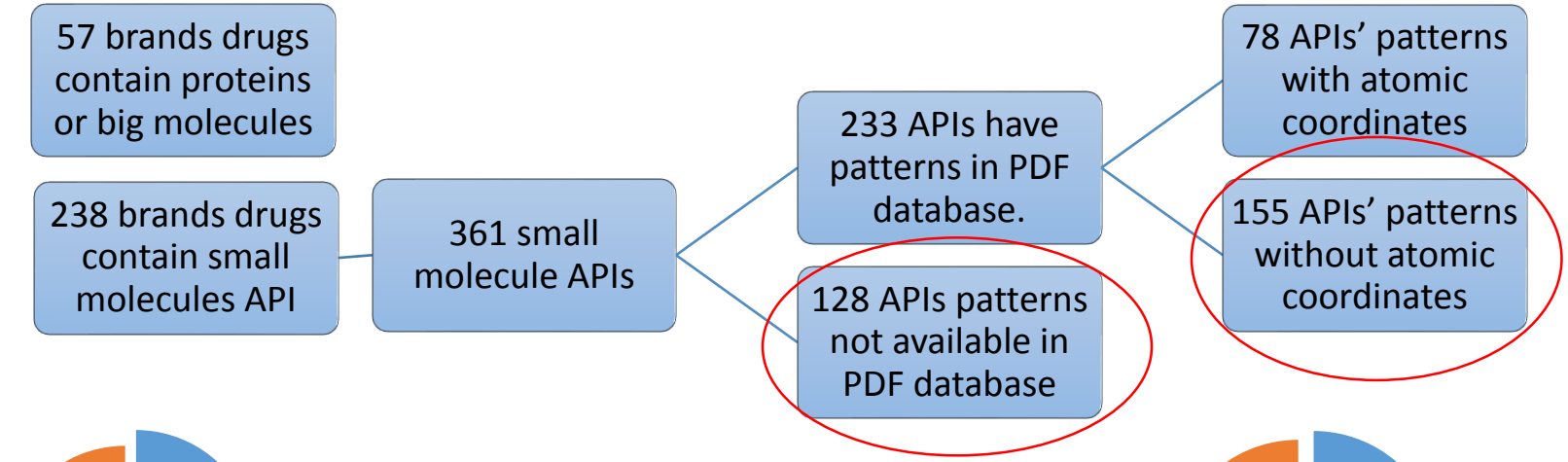
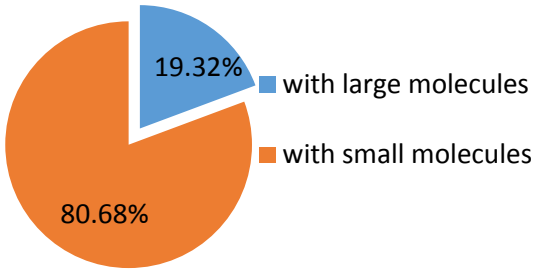
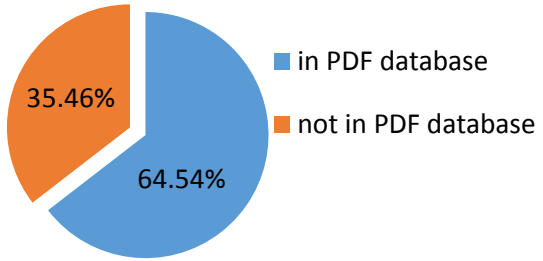
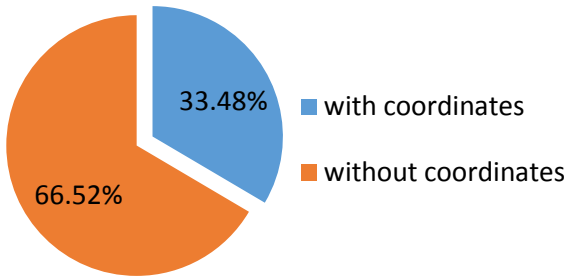
How do we select materials?









- Reviewed top 200 drug list based on 2011/2012 prescriptions/sales
- 295 brands drugs (361 small molecule APIs) were investigated
- 79 APIs materials patterns were collected

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ICDD-Argonne-IIT cooperative work

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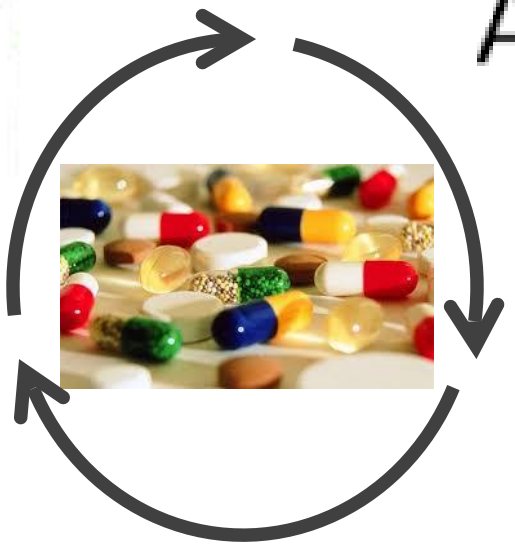
Dedicated to collecting, editing, publishing, and distributing powder diffraction data for the identification of crystalline materials.



Argonne
NATIONAL LABORATORY

ILLINOIS INSTITUTE OF TECHNOLOGY 1890

	Pharmaceutical	PDF #
1	Tazobactam Sodium	64-1626
2	Atomoxetine Hydrochloride (Strattera®) ★	64-1490
3	Piperacillin Sodium (Pipracil®)	64-1631
4	Rabeprazole Sodium (AcipHex®)	64-1632
5	Montelukast Sodium (Singulair T®)	64-1633
6	Valsartan (Diovan®)	64-1634
7	Daptomycin	64-1635
8	Octreotide Acetate (Sandostatin®)	64-1636
9	Rosuvastatin Calcium (Crestor®)	64-1637
10	Iohexol (Omnipaque®)	64-1638
11	Bivalirudin Trifluoroacetate	64-1639
12	Vancomycin Hydrochloride (Vancocin®) ★	64-1640
13	Risedronate Sodium Hemipentahydrate ★	64-1491
14	Ziprasidone Hydrochloride Monohydrate (Geoden®) ★	64-1492
15	Capecitabine (Xeloda®)	64-1493
16	Levalbuterol Hydrochloride (Xopenex®) ★	64-1494
17	Fingolilmod Hydrochloride (FTY-720) ★	64-1495
18	Ibandronate Sodium Monohydrate (Bonivaa®) ★	64-1496
19	Paliperidone (Invega®) ★	64-1497
20	Dutasteride (Avodart®) ★	64-1498
21	Raltegravir Potassium (Isentress®) ★	64-1499
22	Sitagliptin Phosphate Monohydrate (Januvia®)	64-1500
23	Rivastigmine Hydrogen Tartrate (Exelon®)	64-1501
24	Darunavir Ethanolate (Prezista®) ★	64-1502
25	Norgestimate	64-1503
26	Metoprolol Succinate (Toprol XL®)	64-1504
27	Salbutamol Sulfate (Albuterol sulfate) ★	64-1505
28	Levothyroxine Sodium Pentahydrate (Pestanal®) ★	64-1506
29	Escitolopram Oxalate Oxalic Acid Hydrate (Lexapro®)	64-1507
30	Bendamustine Hydrochloride Monohydrate (Cytostatsan®) ★	64-1508

SET 64

7 publications

7 rapid communications

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	Pharmaceutical	PDF #
1	Folic Acid Dihydrate ★	65-1262
2	Rilpivirine (Edurant®) ★	65-1406
3	Beta 17alpha-Estradiol Hemihydrate	65-1407
4	Naproxen Sodium (Aleve®)	65-1408
5	Everolimus (Certican®)	65-1532
6	Abiraterone (Zytiga®)	65-1409
7	Choline Fenofibrate (Trilipix®)	65-1410
8	Lacosamide (Vimpat®) ★	65-1411
9	Methylprednisolone (Medrol®)	65-1412
10	Nilotinib (Tasigna®)	65-1413
11	Solifenacin (VESIcare®)	65-1414
12	Tamsulosin (Flomax®)	65-1415
13	Tramadol Hydrochloride (Tramal®) ★	65-1416
14	Cephalexin Hydrate (Keflex®)	65-1417
15	Saxagliptin Hydrochloride Dihydrate (Onglyza®) ★	65-1418
16	Azithromycin (Zithromax®)	65-1419
17	Fluoxetine (Prozac®)	65-1420
18	Warfarin	65-1421
19	Pravastatin (Pravachol®)	65-1533
20	Atazanavir (Reyatez®)	65-1426
21	Bortezomib (Velcade®)	65-1427
22	Formoterol (Symbicort®)	65-1428
23	Metoprolol (Lopressor®)	65-1429
24	Salmeterol (Severent diskus®)	65-1430
25	Telaprevir (Incivek®)	65-1431
26	Pantoprazole (Protonix®)	65-1424
27	Citalopram (Cipramil®)	65-1422
28	Mupirocin (Bactroban®)	65-1423
29	Rifaximin (Xifaxan®)	65-1425

SET 65

4 publications

1 rapid communication

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Minerals in the Pharmaceutical Industry

Out of ~4,500 mineral species, ~30 are used in the Pharmaceutical industry

- Active ingredients
- Excipients

- Synthetic analogues are more economical to synthesize than to extract and purify naturally occurring minerals except clay minerals (more difficult and expensive to synthesize)

Applied Clay Science 47 (2010) 171-181

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Minerals in the Pharmaceutical Industry

- Oxides (Rutile, Periclase, Zincite)
- Carbonates (Calcite, Magnesite, Hydrocincite, Smithsonite)
- Sulfates (Epsomite, Mirabilite, Melanterite, Chalcanthite, Alum)
- Chlorides (Halite, Sylvite)
- Hydroxides (Brucite, Gibbsite, Hydrotalcite)
- Sulfides (Greenockite)
- Phosphates (Hydroxyapatite)
- Phyllosilicates (smectite, palygorskite, sepolite, kaolinite, talc, mics)

Applied Clay Science 47 (2010) 171-181

Some Examples of Minerals as Active Ingredients

Mineral	Chemical Formula	Therapeutic activity
Periclase	Mg O	Antacid, mineral supplement
Zincite	Zn O	Antiseptic and disinfectant, solar protector
Rutile	Ti O2	Dermatological protector
Calcite	Ca CO3	Antacid
Melanterite	Fe SO4. 7H2 O	Antianemic
Chalcanthite	Cu SO4. 5H2 O	Antiseptic and disinfectant
Alum	K Al (SO4)2. 12 H2 O	Antiseptic and disinfectant
Brucite	Mg (OH)2	Antacid
Gibbsite	Al (OH)3	Antacid
Hydroxyapatite	Ca5 (PO4)3 (OH)	Mineral supplement
Montmorillonite	(Al1.67 Mg0.33) Si4 O10 (OH)2	Antacid, gastrointestinal protector
Kaolinite	Al2 Si2 O5 (OH)4	gastrointestinal protector, anti-inflammatory
Talc	Mg3 Si4 O10 (OH)2	Dermatological protector
Muscovite	K Al2 (Si3 Al) o10 (OH)2	Cosmetic creams

Searches Based on Mineral Classifications

Formula ▾

Any Formula

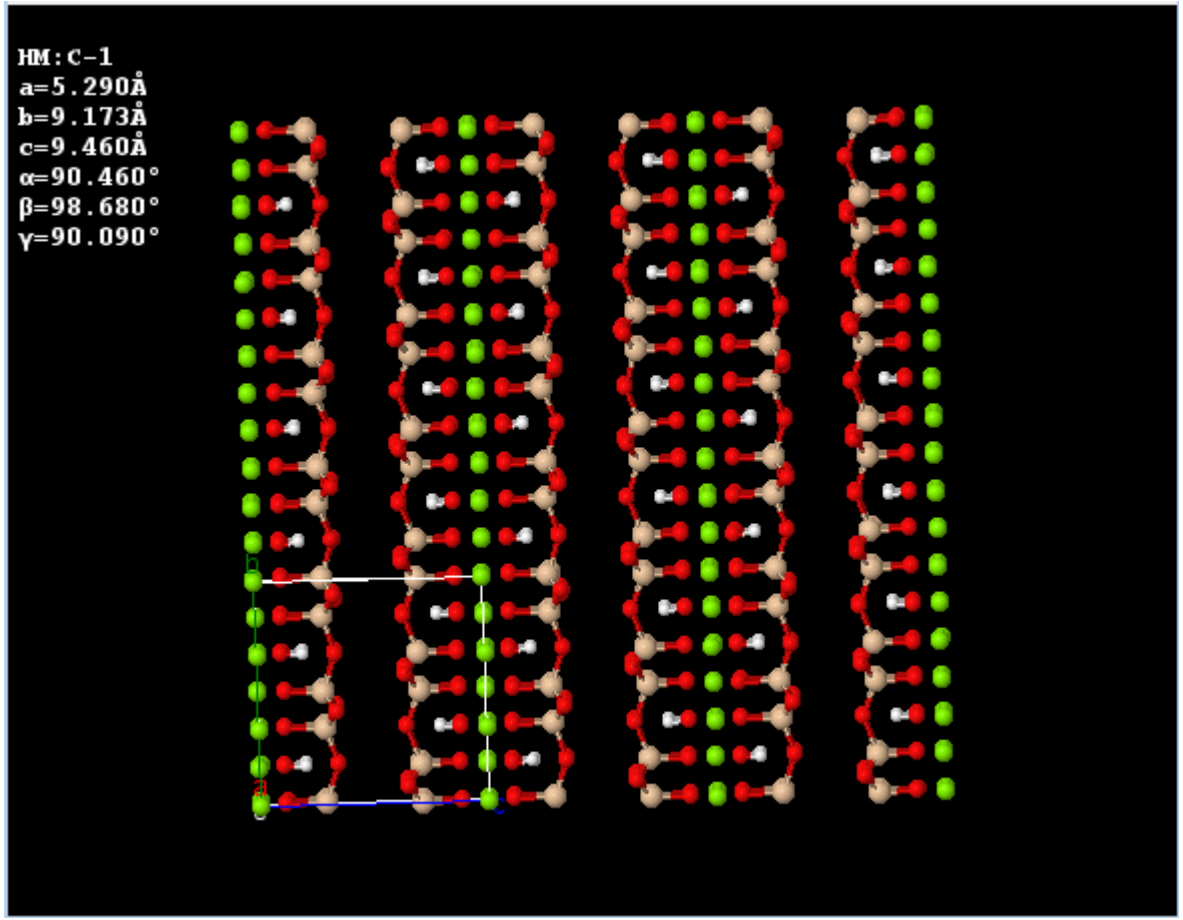
Formula Type (ANX) ▾

Name ▾

talc

Mineral Classification ▾

- RSA - Rosasite (Group)
- ROS - Roscherite (Supergroup)
- RSL - Roselite (Group)
- STK - Rozenite (Group)
- RUT - Rutile (Supergroup)
- SCA - Scapolite (Supergroup)
- SEI - Seidozerite (Group)
- SEP - Sepiolite (Family)
- SHC - Shcherbakovite (Group)
- SIL - Sillimanite (Group)
- SKU - Skutterudite (Group)
- SME - Smectite (Family)
- SMO - Smolyaninovite (Supergroup)
- SPA - Spangolite (Group)
- SPL - Spinel (Supergroup)
- STA - Staurolite (Group)
- STB - Stibnite (Supergroup)
- STL - Stilpnomelane (Family)
- SOH - Stottite (Supergroup)



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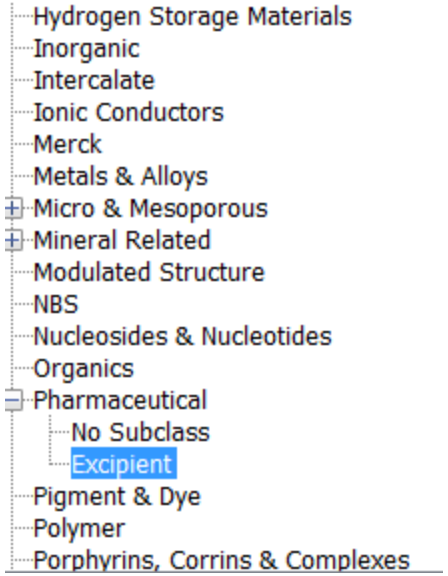
Populating Excipients

- Identifying and populating excipients in the database using United States Pharmacopeia
- Cross reference the entries with atomic coordinates to facilitate quantitative phase identification



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Quality Enhancements

- Poorly characterized patterns are replaced by better patterns wherever possible
- One such example is Iron Fumarate
- There was only one entry from 1968 based on visual intensities
- No better quality data was found in the published literature
- ICDD purchased this sample and with the help of Mathew Suchomel synchrotron data was collected at APS 11-BM

C4 H2 Fe O4 - 00-023-1730

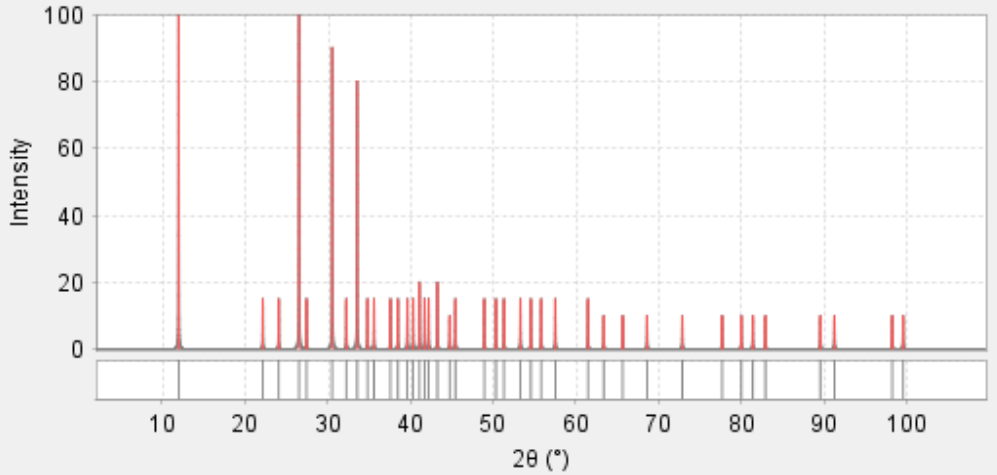
File Edit Plots Window Help

Save Print | Preferences | Temperature Series Toolbox Property Sheet | 2D 3D Bonds | SAED EBSD Ring | Simulated Profile Raw Diffraction Data

Cu Kα1 1.54056 Å ☑ Simulated Profile (Exp-based)

Fixed Slit Intensity ☐ Raw Diffraction Data (PD3)

2θ (°)	d (Å)	I	h	k	l	*
11.8532	**7.460000**	100	0	1	1	
22.0382	4.030000	15	2	0	0	
23.9661	3.710000	15	2	1	0	
26.4258	**3.370000**	100	1	1	3	
27.3344	3.260000	15	0	3	0	
30.4412	**2.934000**	90	1	3	1	
32.1482	2.782000	15	1	0	4	
33.4583	2.676000	80	3	0	0	



PDF | Experimental | Physical | Crystal | Optical | Structure | Miscellaneous | References | Comments

Status: Primary QM: Blank Pressure/Temperature: Ambient

Chemical Formula: C4 H2 Fe O4

Structural Formula: Fe C4 H2 O4

Empirical Formula: C4 H2 Fe O4

Weight %: C28.28 Fe32.87 H1.19 O37.67

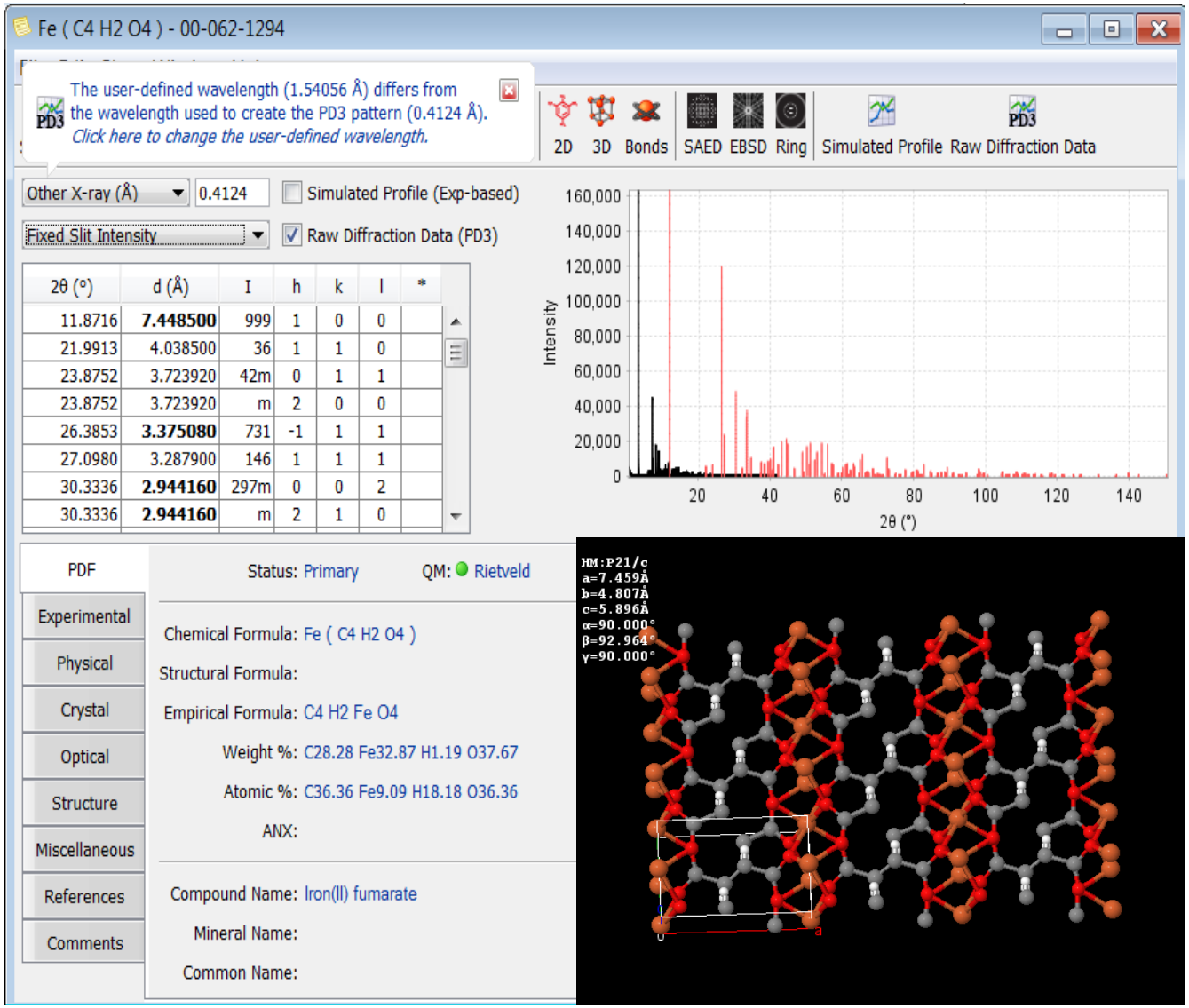
Atomic %: C36.36 Fe9.09 H18.18 O36.36

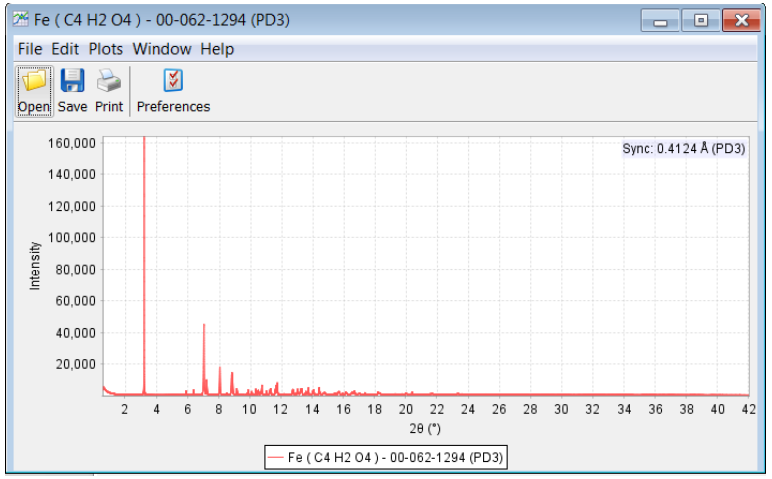
ANX:

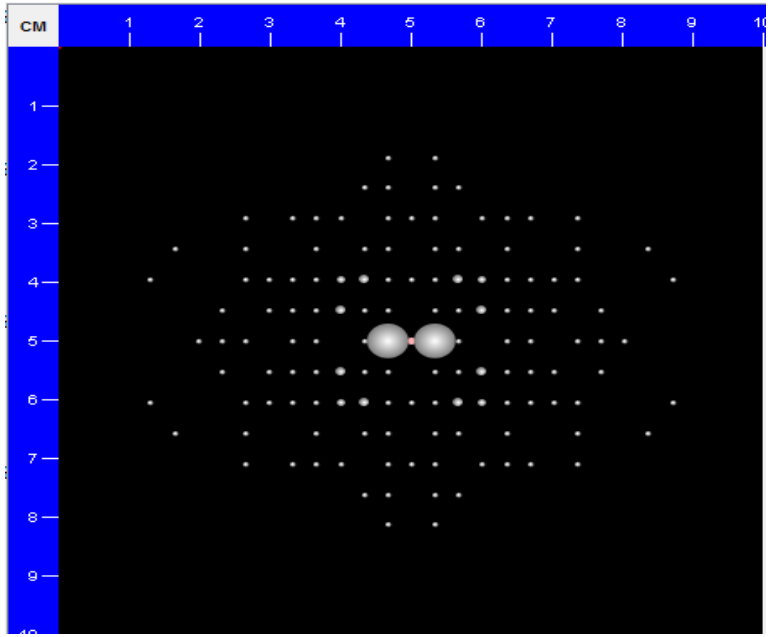
Compound Name: Iron fumarate

Mineral Name:

Common Name:







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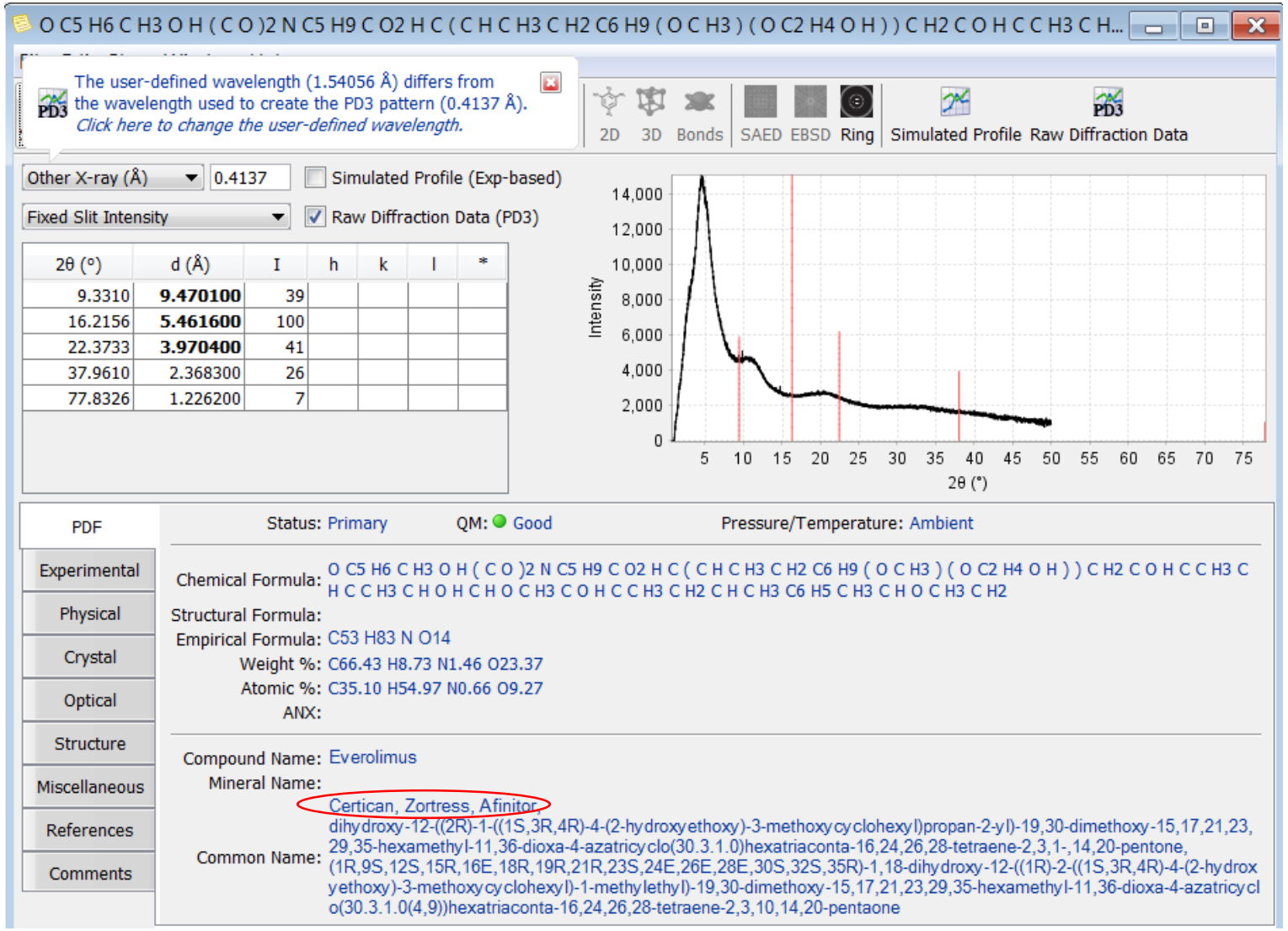
Common Names, Trade Names



Bioactivity: Used as an immunosuppressant to prevent rejection of organ transplants, also used for treatment of renal cell cancer and other tumors. **General Comments:** Pattern measured in 0.001° steps and rebinned to 0.02° steps; scattering from the Kapton capillary was subtracted. An "Al2 O3":"La B6" mixture was used as an external standard. Raw Data Comment: Pattern measured at beam line 11-BM, (goniometer radius 1000 mm) Advanced Photon Source, Argonne National Laboratory, Lement, Illinois, USA. Data collected using Debye-Scherrer geometry. **Sample Source or Locality:** Commercial material, purchased from Sigma-Aldrich. **Temperature of Data Collection:** Pattern taken at 300 K.

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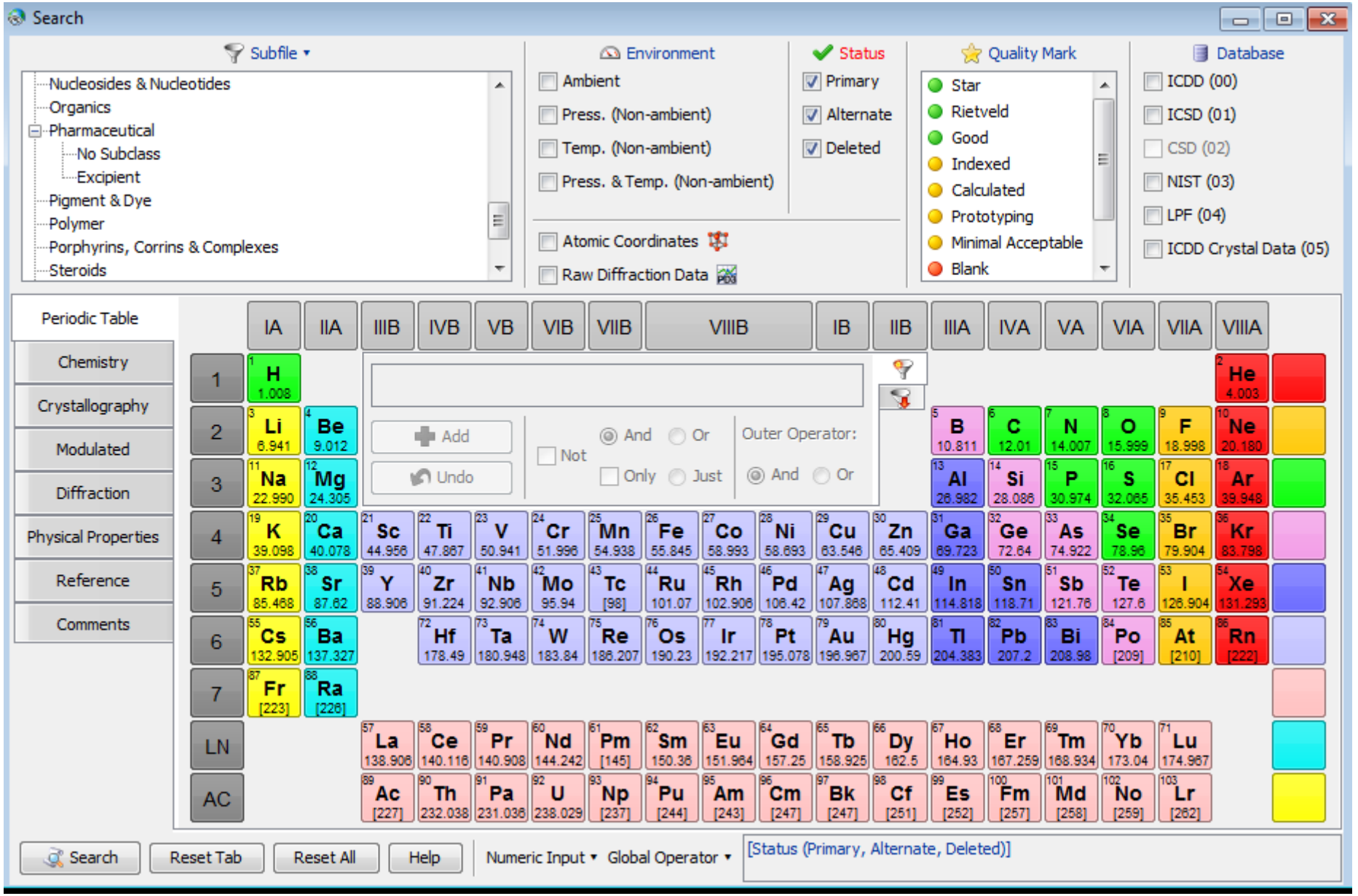
Quality Marks

- Quality marks are essential while working with larger database with similar diffraction patterns
- Data validation and the quality mark assignments is the most important step in the editorial process



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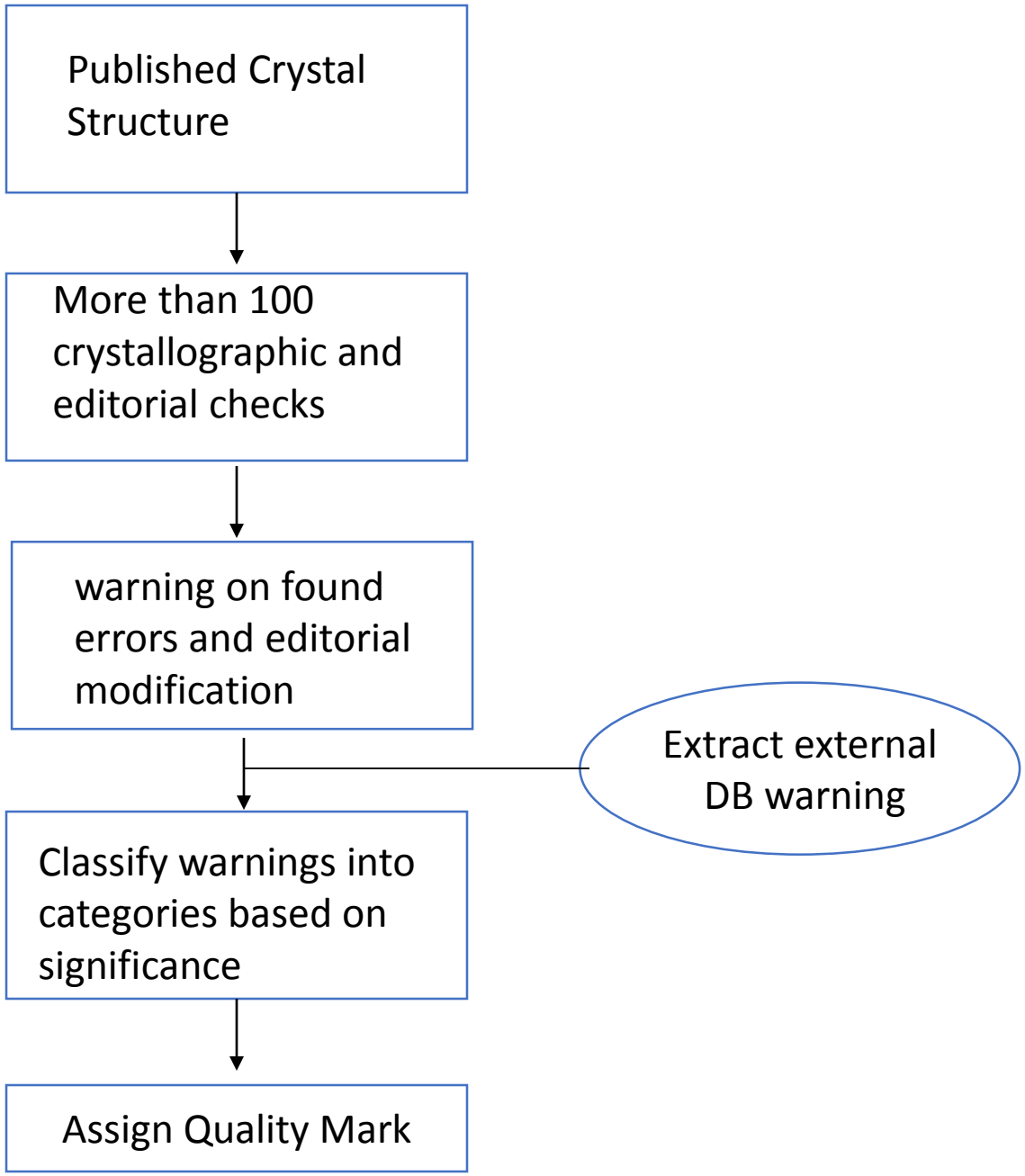
Quality Mark (QM) Types

- Experimental patterns
- Calculated Patterns (based on experimentally determined crystal structures)

QM for Experimental Patterns

- **Star** (Well characterized chemically and crystallographyically, No unindexed lines,$\Delta 2\theta \leq 0.03^{\circ}$)
- **R** (d values from whole pattern fitting, like Rietveld, Le Bail refinement)
- **I** (Well characterized chemically No unindexed strong lines,$\Delta 2\theta \leq 0.06^{\circ}$)
- **B** (Do not meet the criteria for *, I)
- **O** (Poorly characterized, with editorial comment explaining the reason)
- **C** (author calculated d values)
- **H** (Hypothetical)
- M (Minimally acceptable non crystalline pattern)
- G (Good non crystalline pattern, usually has additional characterization other than XRD)

Calculated Pattern Quality Mark assignment process



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Calculated Pattern QM Notations

Category	QM
No Warning	*
Minor Warning	I
Significant warning	B
Assigned structure (Prototype)	P
Hypothetical	H
Major warning	O

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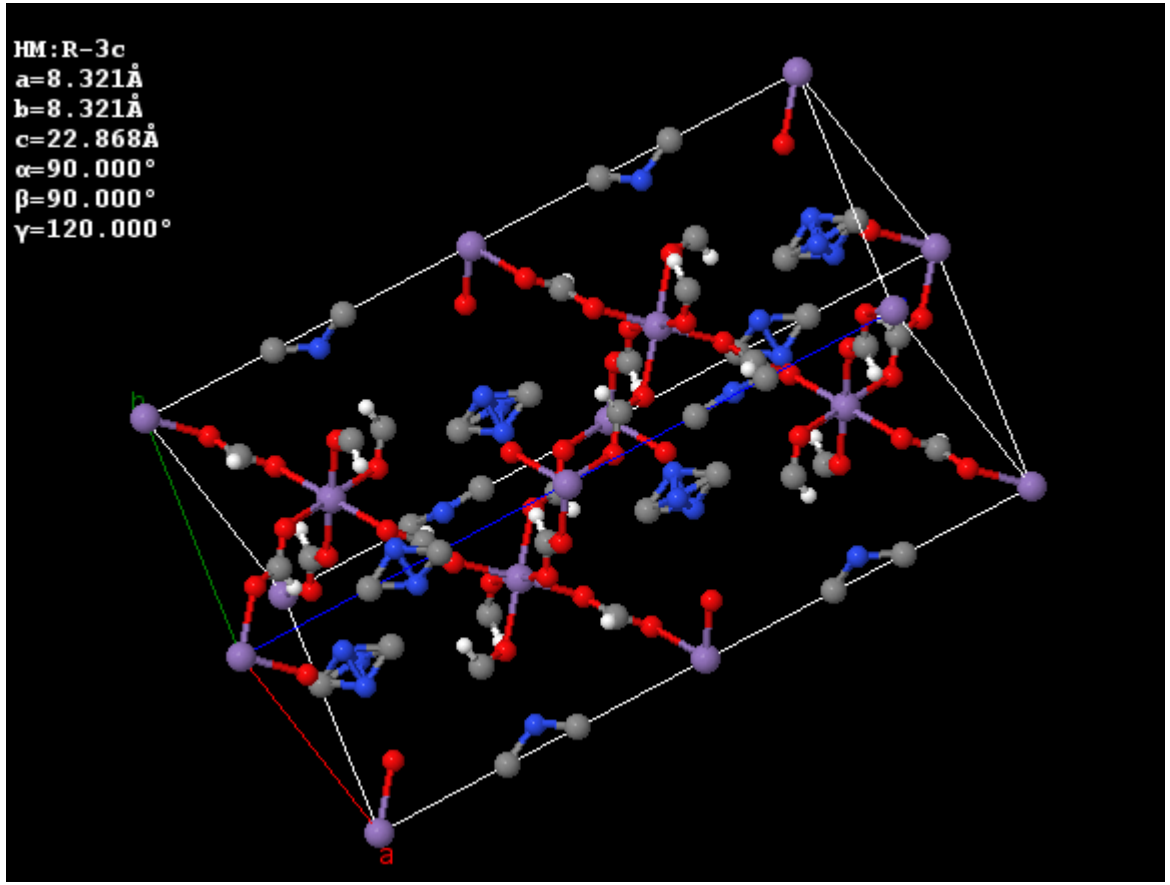
Disordered Structures

Poorly described disordered structures (missing site occupation factor) will lead to error in the calculated intensity and Reference Intensity Ratio

$I/I_c = \mu \gamma \rho_c / \mu_c \gamma_c \rho$

μ = Linear attenuation coefficient
γ = Absolute scale factor
ρ = Density
(Subscript “c “ corresponds to corundum)

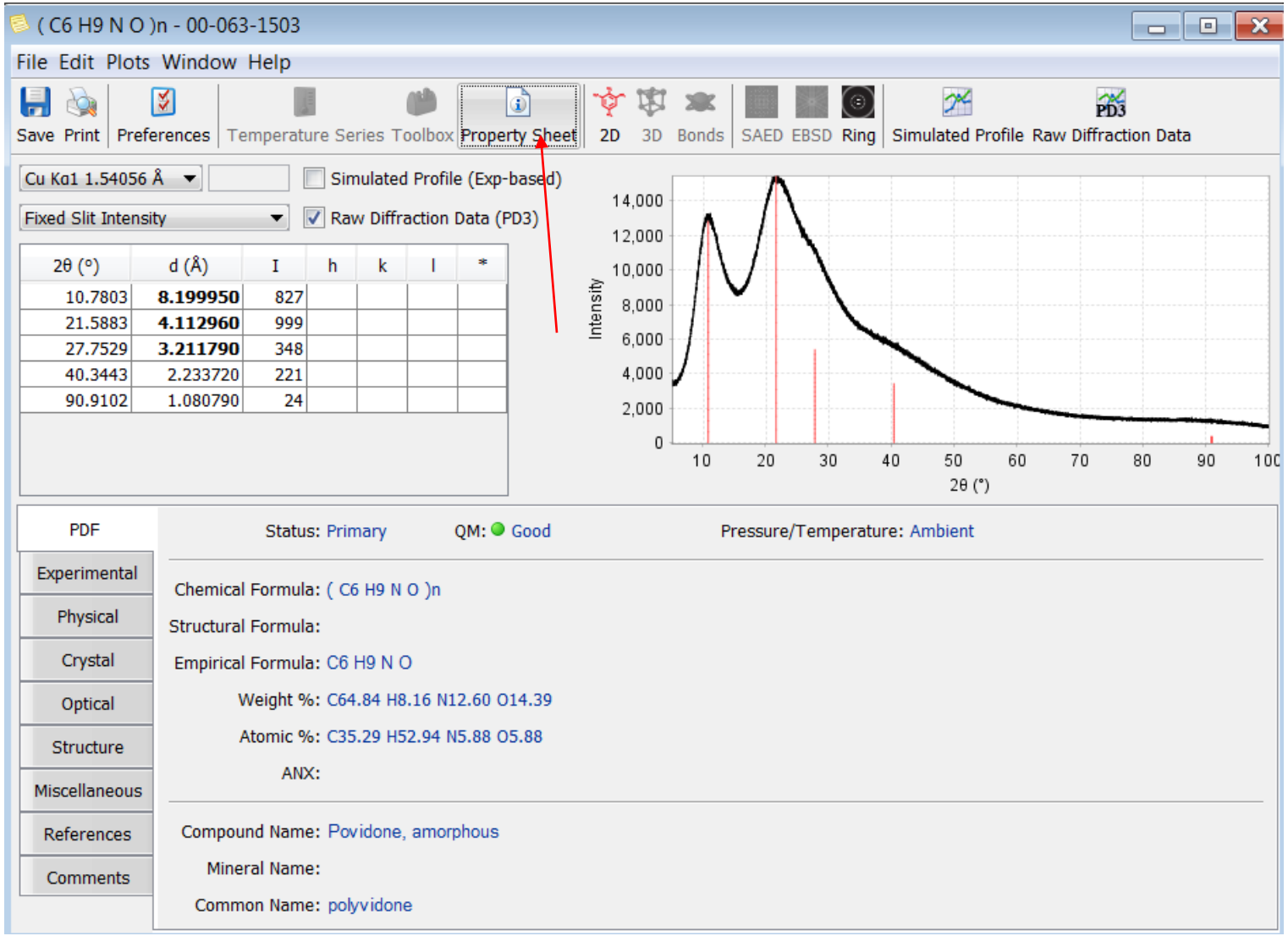
Error depends on the extent of disorder and the quality mark will be lowered accordingly

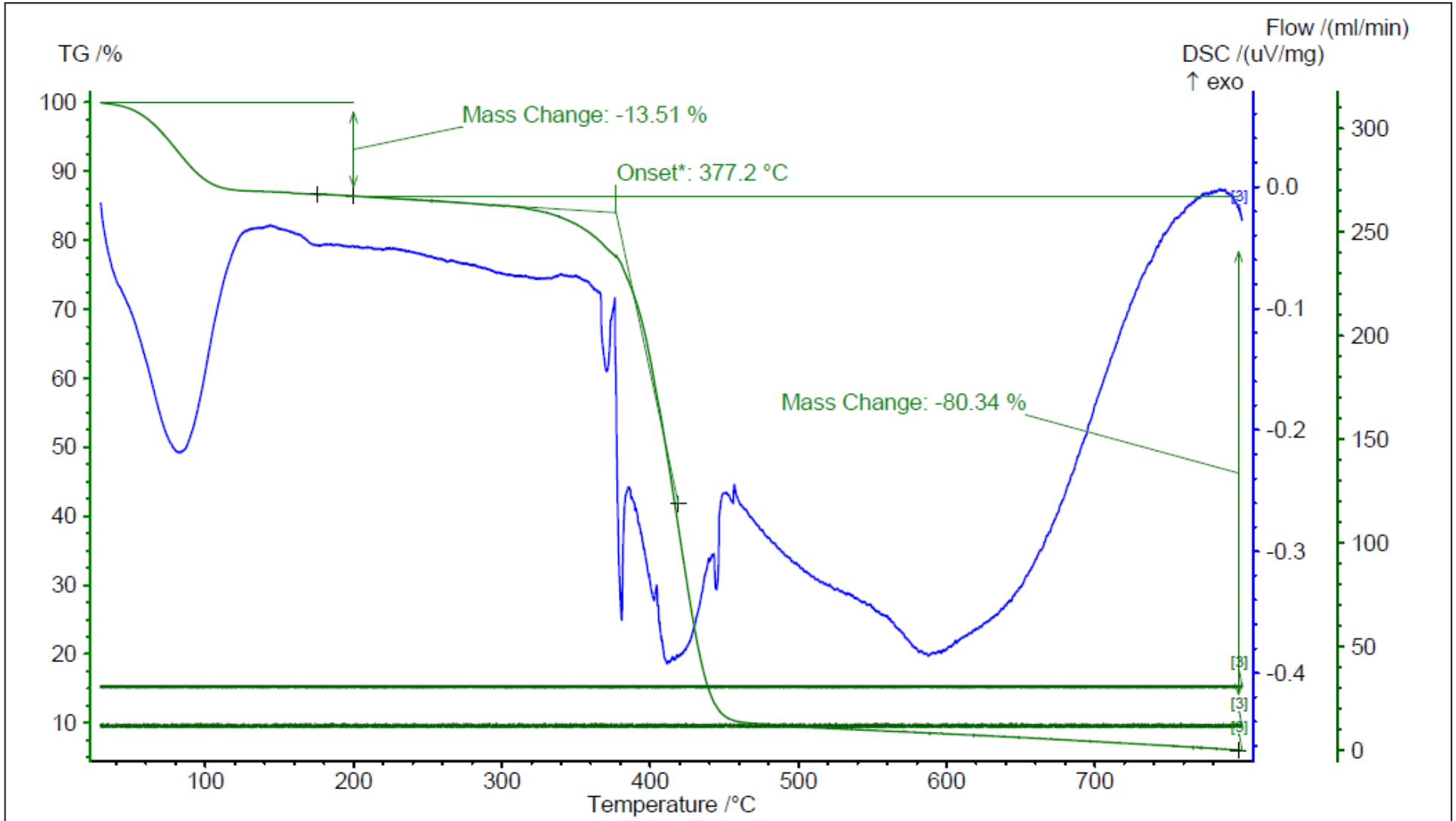


ICDD is re-abstracting targeted disordered crystal structures to improve the quality of the pattern

Dimethylammonium manganese formate

Data Content

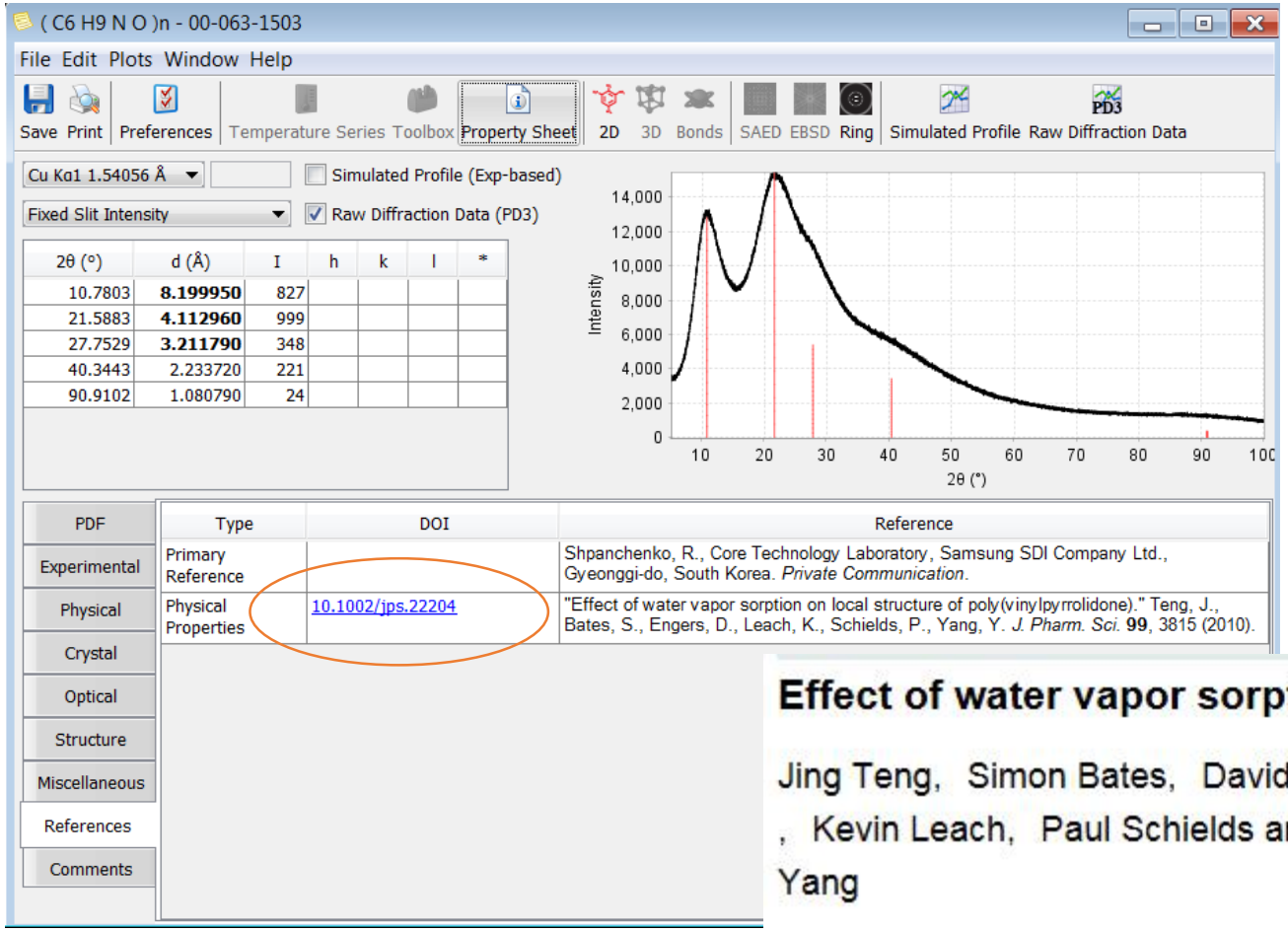




Main 2009-10-09 12:35 User: netzsch

Instrument :	NETZSCH STA 449 C	**File :**	C:\ngbwin\ta\data5\HKX\00062_Edik_LOTF2H326_05102009.dsu		
Project :	Коррекция	**Material :**	нет	**Segments :**	1/1
Identity :	00062	**Correction file :**	00047_correction_new_crucibales_170809.bsu	**Crucible :**	DSC/TG pan Al2O3
Date/time :	10/5/2009 13:25:28	**Temp.Cal./Sens. Files :**	Tcalzero.tcx / Senszero.exx	**Atmosphere :**	Ar / -- / Ar
Laboratory :	НКХ	**Range :**	30.0/3.0(K/мин)/800.0	**TG corr./m. range :**	020/5000 mg
Operator :	Истомин С.Я.	**Sample car./TC :**	DSC(/TG) HIGH RG 4 / S	**DSC corr./m. range :**	020/5000 µV
Sample :	LOTF2H326, 18.764 mg	**Mode/type of meas. :**	DSC-TG / Sample + Correction		

Digital Object Identifier



Effect of water vapor sorption on local structure of poly(vinylpyrrolidone)

FREE

Jing Teng, Simon Bates, David A. Engers*, Kevin Leach, Paul Schields and Yonglai Yang

Article first published online: 25 MAY 2010

DOI: 10.1002/jps.22204

Issue

Journal of Pharmaceutical Sciences

Special Issue: Dedicated to Stephen R. Byrn

Volume 99, Issue 9, pages 3815–3825, September 2010

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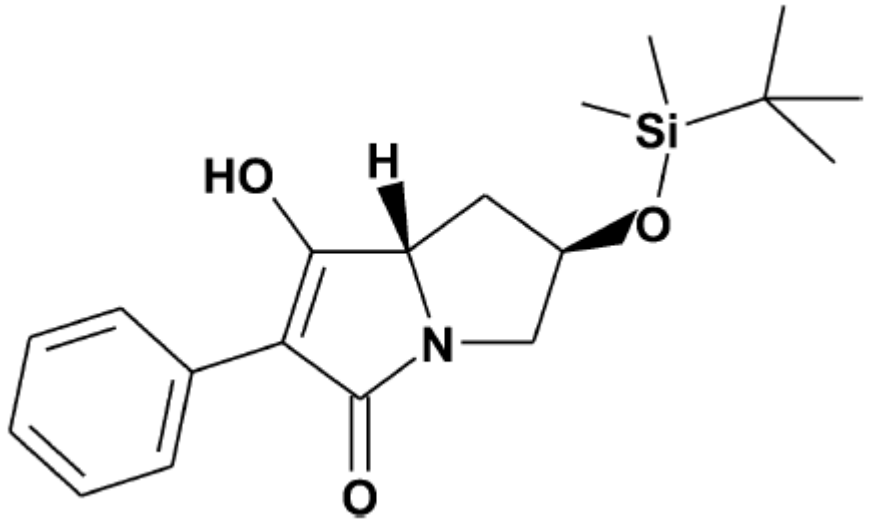
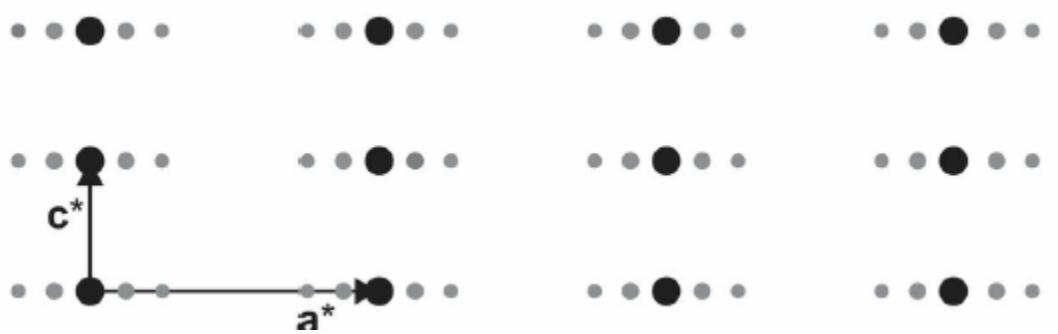
Modulated Structures in Pharmaceuticals

Satellite reflections around strong Bragg peaks can not be indexed in 3D using the conventional reciprocal lattice vectors



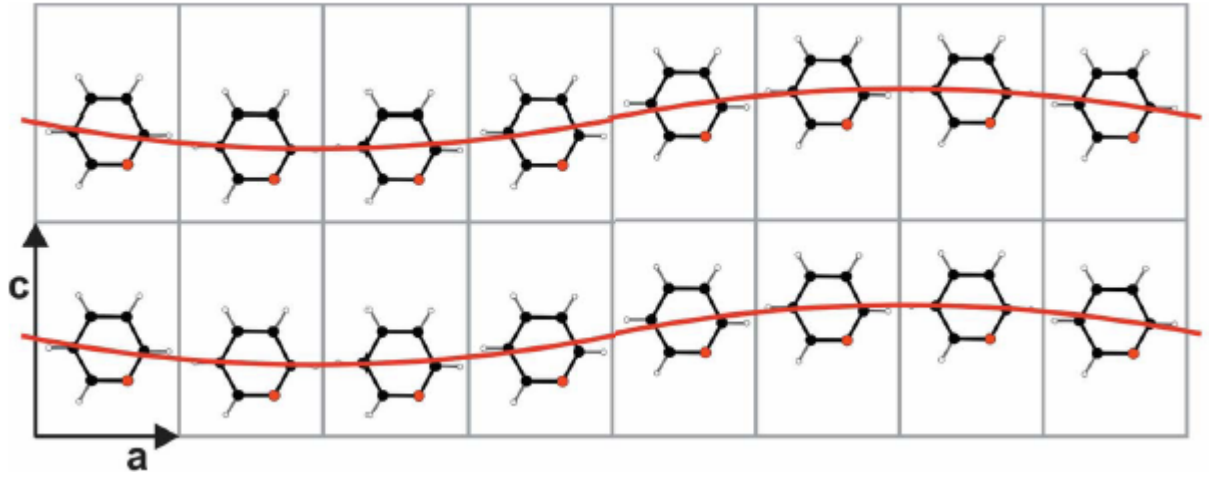
Tetrahydropyrrolizinone derivative



Acta Cryst. (2009). B65, 249–268

Modulated Structures in Pharmaceuticals

- Modulated structures form on account of perturbation in atomic position, occupation and/or thermal motion
- If period of fluctuation matches that of the 3D unit cell then a superstructure results otherwise an incommensurate modulated structure is obtained



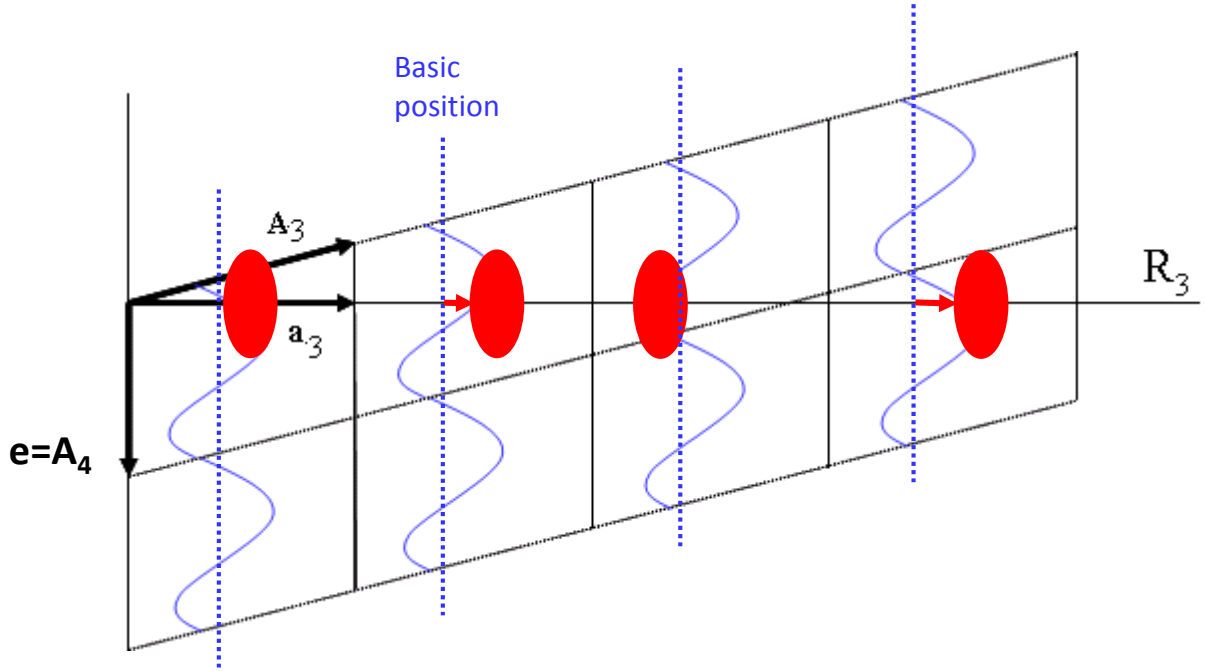
ICDD® International Centre for Diffraction Data

Acta Cryst. (2009). B65, 249–268

Harmonic modulation functions

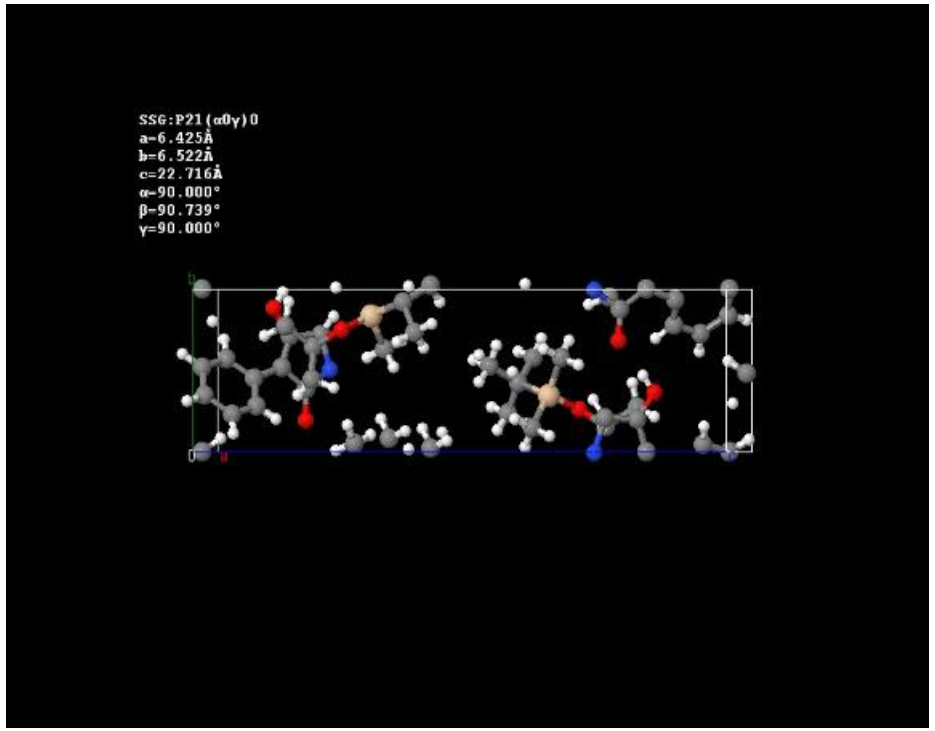
Any parameter describing structure i.e. atomic occupancies, coordinates or displacements can be modulated. The fact that modulation functions are periodic leads to possibility to express them as sum of harmonic functions:

$$p(x_4) = A_0 + \sum_n A_{s,n} \sin(2\pi n x_4) + \sum_n A_{c,n} \cos(2\pi n x_4)$$



Courtesy: V. Petricek, Institute of Physics, Praha, Czech Republic

Description of Modulation



SYS: Monoclinic

Superspace Group: P21(α0γ)0

Modulation Wave Vectors

q1 = (0.14216)a* + (0.38390)c*

C6 H5 ((C7 H6 N (O H) (O)) O (Si (C H3)2 (C (C H3)3))) - 05-001-0307

Positional Displacement Parameters (612)

Atom	Axis	WV ID	Cos	Sin
C02	x	1	0.06423(16)	0.01948(16)
C02	y	1	-0.02180(17)	0.00385(17)
C02	z	1	0.01805(5)	-0.03411(5)
C02	x	2	0.00373(16)	0.00023(16)
C02	y	2	0.00158(17)	-0.00333(17)
C02	z	2	-0.00018(5)	0.00416(5)
C02	x	3	-0.00050(18)	-0.00257(18)

Atomic Displacement Parameters (288)

Atom	WV ID	Tensor El.	Cos	Sin
C02	1	U11	0.0021(5)	0.0012(5)
C02	1	U12	-0.0007(4)	-0.0005(4)
C02	1	U13	0.0019(5)	0.0012(4)
C02	1	U22	0.0017(6)	-0.0014(6)
C02	1	U23	-0.0002(5)	0.0000(5)
C02	1	U33	-0.0010(7)	0.0024(6)
C02	2	U11	-0.0001(5)	-0.0002(5)

Occupation Modulation (0)

Special Functions

Occupational - Crenel (0)

Displacement - SawTooth (0)

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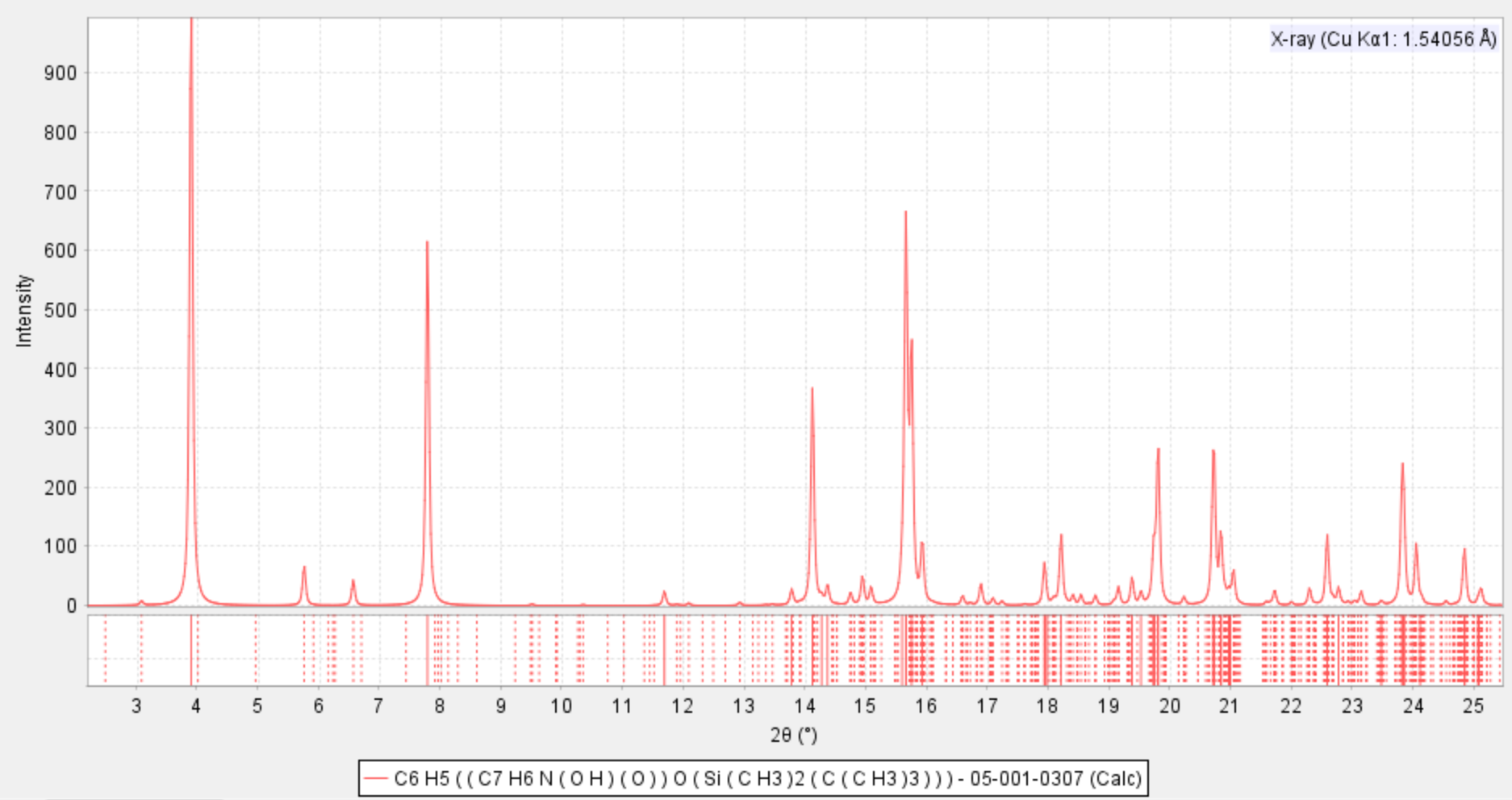
Powder Diffraction Pattern of a Modulated Structure



Dotted lines indicate satellite reflections

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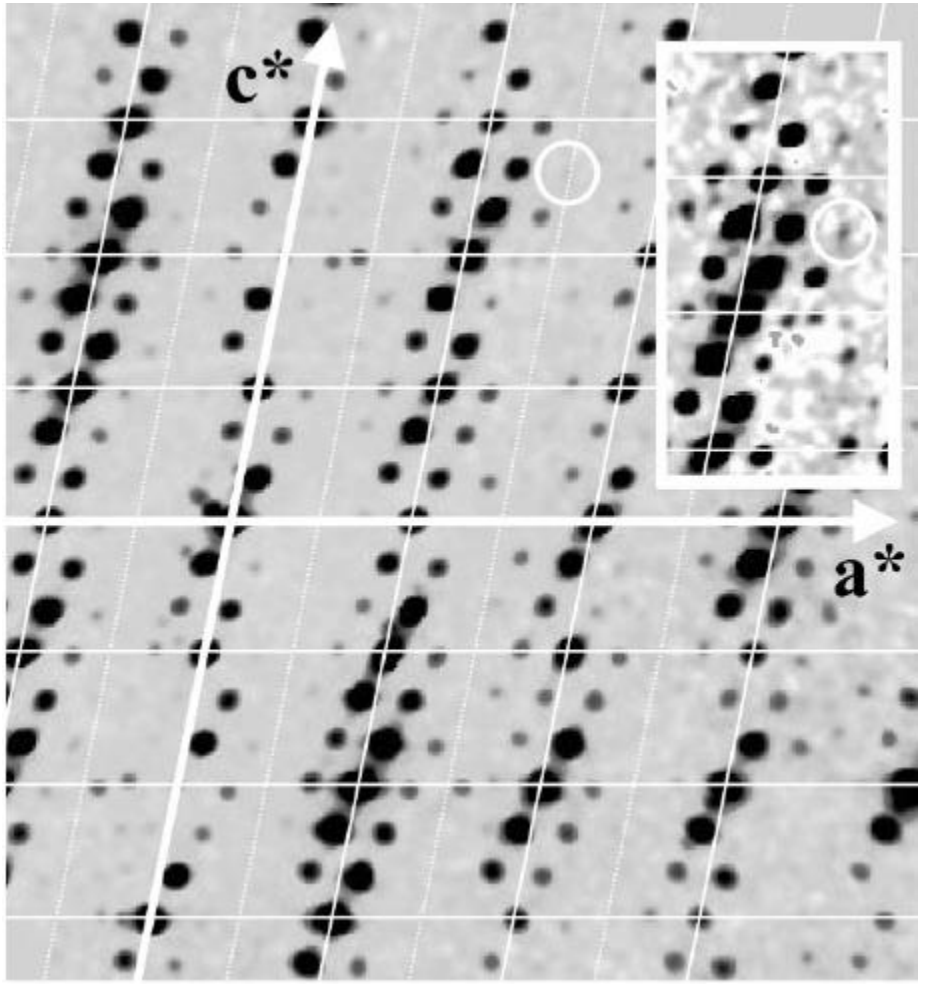
An Example of Modulated Structures in Excipients: Sodium Carbonate

At room temperature anhydrous sodium carbonate (γ phase) shows incommensurate modulation

First observed in 1964 with strong satellite reflections and solved in the harmonic approximation using one modulation wave and first order satellites

Structure was re-investigated in 2003 using fifth order satellites and additional modulation waves



Acta Cryst. (2003). B59, 337-352

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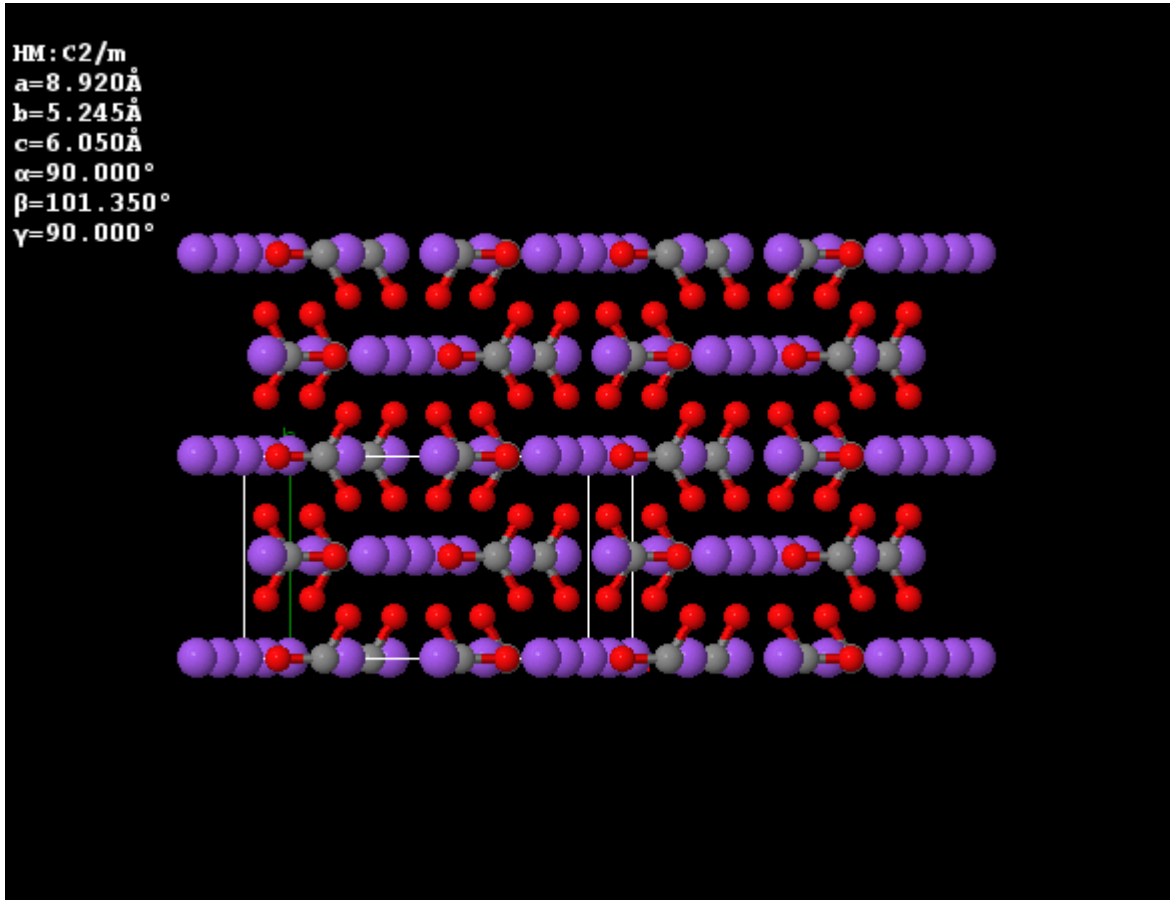
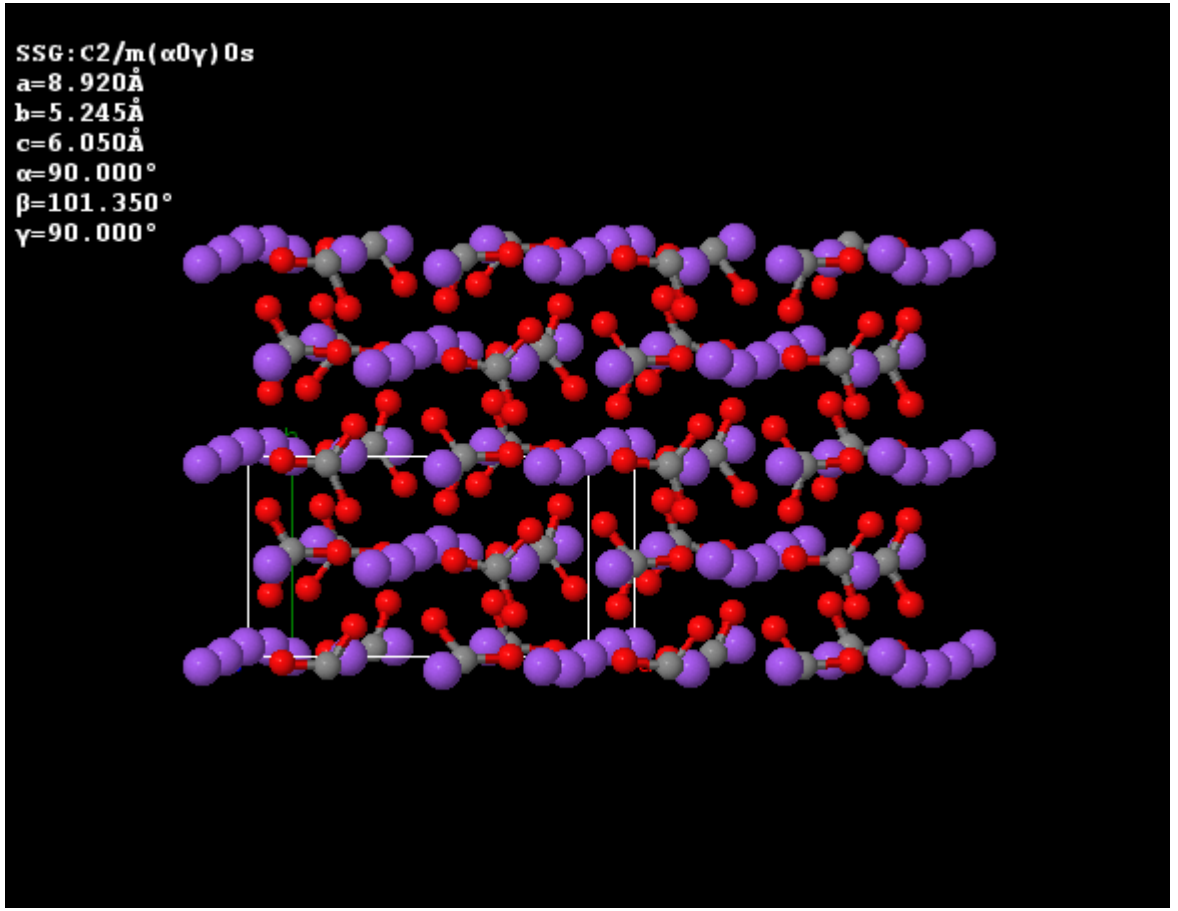
The Comparison



Average Structure



Incommensurately Modulated Structure

$$q_1 = (0.182)a^* + (0.322)c^*$$

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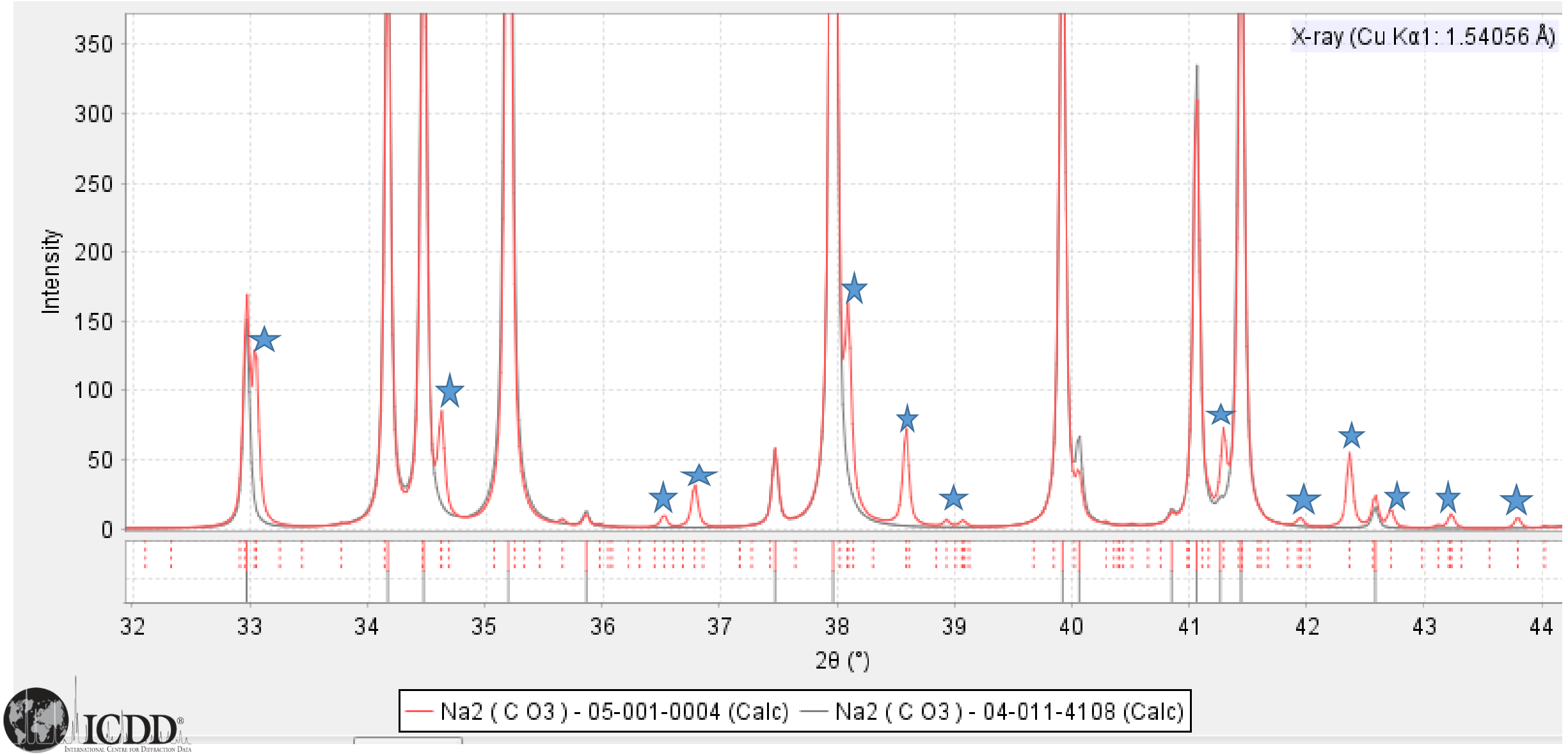
Comparison of Powder X-ray Diffraction Patterns



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Conclusions

- PDF-4/Organics was developed by targeting materials characterization of pharmaceutical and forensic samples using powder X-ray diffraction methods
- Targeted materials list is continuously reviewed to keep up-to-date with the developments in phase identification using PXRD
- More data is added to the existing card wherever available (example: atomic coordinates, property sheet, common & trade names, polymorphic designation, digital object identifiers)

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