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Título del estudio:
Polymorph analysis of an agrochemical compound

Palabras clave:
Difracción de polvo cristalino (XRD), Difracción de Monocristales (SXRD), Cambridge Structure Database (CSD) Searching, Agrochemical Compound...

Test realizado por:
Unidad de RayosX

1. INTRODUCTION: FROM DIFFRACTION TO POLYMORPHISM

X-ray diffraction is based on constructive interference of monochromatic X-rays and a crystalline sample. These X-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. The interaction of the incident rays with the sample produces constructive interference (and a diffracted ray) when conditions satisfy Bragg's Law ($n\lambda=2d \sin \theta$). This law relates the wavelength of electromagnetic radiation to the diffraction angle and the lattice spacing in a crystalline sample. These diffracted X-rays are then detected, processed and counted. By scanning the sample through a range of 2θangles, all possible diffraction directions of the lattice should be attained due to the random orientation of the powdered material. Conversion of the diffraction peaks to d-spacings allows identification of the mineral because each mineral has a set of unique d-spacings. Typically, this is achieved by comparison of d-spacings with standard reference patterns.

A crystal form is defined by the arrangement of the molecules in the solid state. The unit cell and space-group symmetry determines many aspects of the arrangement of the diffraction pattern. This unit cell is the repeating unit of the crystal structure. Polymorphs are a specific type of crystal form system characterized by the ability of a compound to exist in different arrangements and/or conformations of the crystal lattice, but having the same molecular formula.

Polymorphism has important consequences in the development of drugs. The existence of multiple crystal forms with differences in the solid-state properties can translate into significant effects on the bioavailability of the active drug substance, the shelf life of the drug, and manufacturability of drug substance and drug product. Powder X-ray Diffraction (PXRD) and Single Crystal Diffraction (SXRD) are powerful tools in identifying different crystalline phases by their unique diffraction patterns. The most recent USP has included the criteria in the general chapter on using X-ray powder diffraction for phase identification and for the equivalence of two powder patterns. High-resolution PXRD patterns provide good data to determine the phase composition of crystalline samples, yet morphology and particle shape/size can induce severe preferential orientation that can degrade the utility of XRD powder data. Small changes in the X-ray powder patterns due to the appearance of new peak(s), additional shoulders or shifts in the peak position can imply the presence of a new polymorph[1,2,3,4].

2. OBJECTIVE

The objective of this study is to determine the purity of one sample basing on the comparison of their diffraction pattern with other of already reported structure. Based on the appearance and/or positioning of the peaks, we can infer if the analyzed sample is only incorporated or not, by the reported compound. Will it seek, if you find more than one crystalline pattern in the retrieved pattern, determine the nature of the crystalline phase that coexists with the reported pattern.

The X-Ray Unit develops its activity based on a Quality Management System certified by the ISO 9001: 2015 Standard regarding the reception, management of samples and analysis by the techniques of Single Crystal, Crystalline Powder and RX Fluorescence.

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1 Pharmaceutical Research, Vol. 20, No. 4, April 2003 Scientific Considerations of Pharmaceutical Solid Polymorphism in Abbreviated New Drug Applications (Lawrence X. Yu, et al.).

2 Chem. Mater. 1994, 6, 1148-1158, Solid-state Pharmaceutical Chemistry (S. R. Byrn et al.)

3 J. AM. CHEM. SOC. 2005, 127, 5512-5517 Crystalline Polymorph Selection and Discovery with Polymer Heteronuclei (Christopher P. Price et al.)

4 http://en.wikipedia.org/wiki/Polymorphism_(materials_science)

3. MATERIALS AND METHODS

3.1. Test Item

Identity:	**********
Active ingredient:	**********
Source:	Supplied by Sponsor
Batch Number:	**********
Appearance:	Colorless small crystals, suitable for single crystal analysis.
Storage conditions:	Room temperature
Safety precautions:	Normal handling procedure for chemical products, according with the Material Safety Data Sheet supplied by sponsor.

3.2. Method

The powdered samples were measured on Philips type powder diffractometer fitted with Philips "PW1710" control unit, Vertical Philips "PW1820/00" gonniometer and FR590 Enraf Nonius generator. The instrument was equipped with a graphite diffracted beam monochromator and copper radiation source ($\lambda(K_{\alpha 1})$=1.5406Å), operating at 40 kV and 30mA. The X-Ray powder diffraction pattern (XRPD) has been collected by measuring the scintillation response to Cu Kα radiation versus the 2Θ value over a 2Θ range of 3-60, with a step size of 0.02° and counting time of 3 s per step.

The single crystal data collection was performed with BRUKER APPEX-II CCD diffractometer fitted by fine-focus sealed tube, Mo Kα radiation, λ = 0.7107 Å.

4. RESULTS

4.1. Database search

Structures of crystalline material are typically determined from X-ray or neutron single-crystal diffraction data and stored in crystal structure databases. Once the structure is solved, information about the structure is saved in a file and deposited in the Cambridge Structure Database (CSD)[5]. Other scientists can search and retrieve structures from the database. Scientists can use the CSD to compare existing data with that they obtain. Crystals are routinely identified by comparing reflection intensities and lattice spacing from X-ray powder diffraction data with entries in powder-diffraction fingerprinting databases (some structure details were hidden...)

[5] http://www.ccdc.cam.ac.uk/products/csd/

HANFOS

Reference:

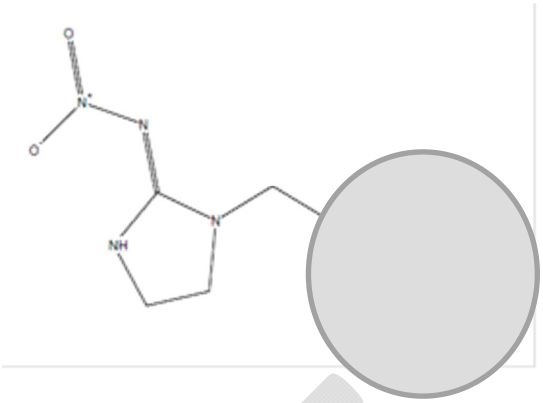
Formula:

Compound Name:

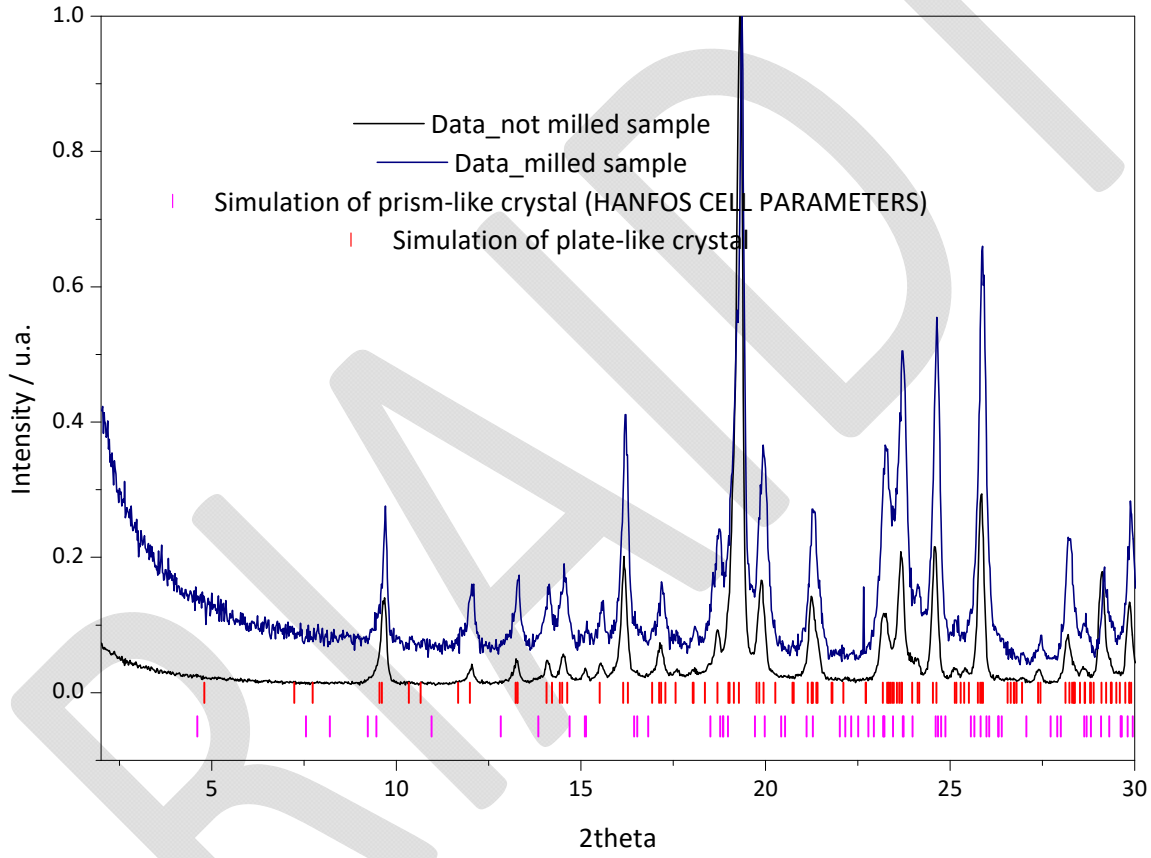
Synonym:

Space Group:
Space Group No.:

R-Factor (%): 5.84 *Temperature(K):* 293 *Density(g/cm^3):* 1.564



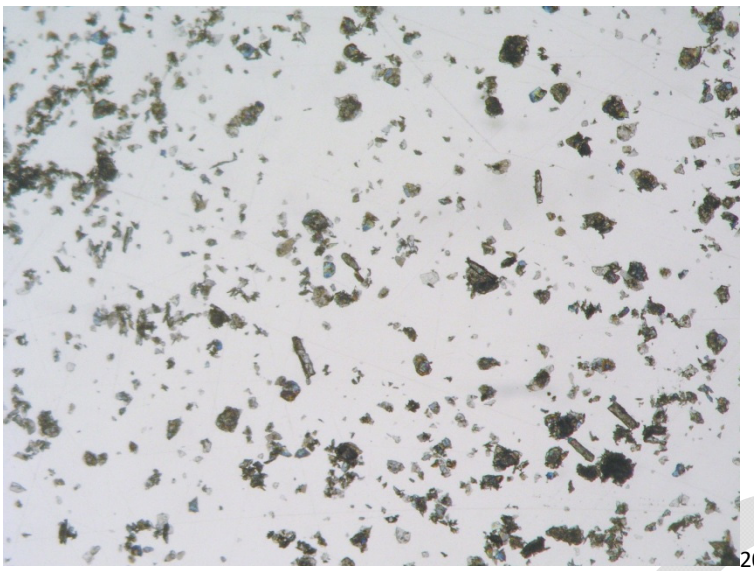
4.2. Powder diffraction measurements and simulations



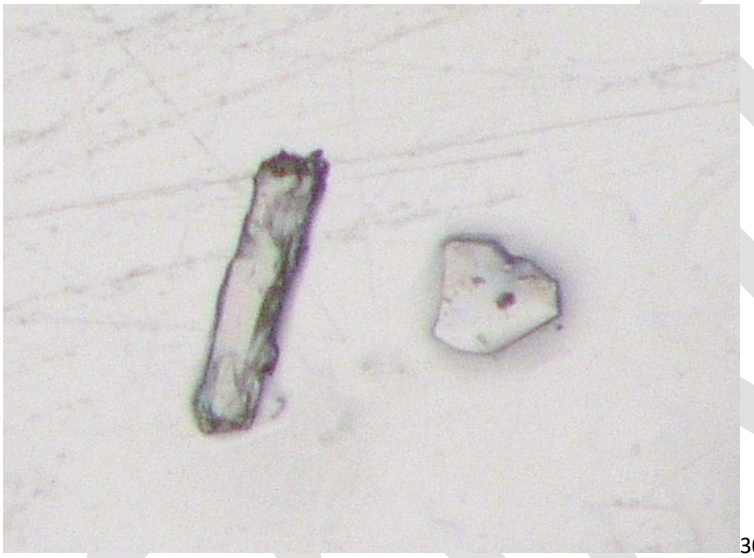
From the graph obtained in the powder diffraction measurements, it can be observed that based on the peak position predictions from the reported HANFOS structure, (see magenta predictions) the predominant crystal structure in the measured sample, is not the same as the reported pattern.

4.3. Sample visualizations & deep inside crystal morphology

4.3.1. Microscope photos



20X zoomed photo taken from as received sample



30X zoomed photo showing the two crystals mounted on the single-crystal diffractometer.

It can be observed that there are two types of crystals, both of them suitable for single-crystal analysis: prism-like and plate-like (see below for crystal characterizations).

4.3.2. Cell and symmetry for two kind of crystals from single-crystal analysis

Single crystal analysis was performed in order to obtain the cell parameters and symmetry, for each kind of crystals morphology.

Crystal data: (details for crystal parameters were sent to the sponsor)

Plate-like crystal:	Prism-like crystal:
Monoclinic, P21/n	Monoclinic, P21/n
Hall symbol: -P 2yn	Hall symbol: -P 2yn
Cell parameters from 143 reflections	Cell parameters from 110 reflections
a = *** (10) Å	a = *** (29) Å
b = **** (8) Å	b = ****(9) Å

c = **** (13) Å	c = **** (37) Å
β = 102.928 (2)0	β = 99.179 (44)0
V = 2171.4 (3) Å3	V = 1109.71(8) Å3
Theta range for the measured reflections (Θmin-Θmax) = 2.8–19.90	Theta range for the measured reflections (Θmin- Θmax) = 2.8–17.650
T = 298 K	T = 298 K
Plate, colorless	**Prism, colorless**
Crystal dimensions (min*mid*max) 0.1 * 0.1 * 0.02 mm	Crystal dimensions (min*mid*max) 0.07* 0.06 * 0.27 mm

More detailed molecular packing was sent to the sponsor.

5. CONCLUSIONS

It can be concluded from the different analyses that the sample is formed by two polymorphs (two packing arrangements) of the analyzed compound, one of them not yet reported on CSD.

Moreover, we can confirm that the whole sample has been well defined if we take into account the two types of structures and we plot either peak predictions or simulations of these two polymorphs into the powder diffraction pattern in 4.2.

6. STATEMENT OF OWNERSHIP

This report contains a study conducted by Unidade de Raios X at Universidade Santiago de Compostela on behalf of *********

All records remain the property of the sponsor. Under no circumstances will any data be discarded without the sponsor's knowledge. No samples are retained.