Total Pattern Analysis Using the New Organic Powder Diffraction File: PDF-4/Organics

Fangling Needham, Ph.D. and John Faber, Ph.D.
The International Centre for Diffraction Data (ICDD)

Abstract

The International Centre for Diffraction Data (ICDD) Powder Diffraction File (PDF) has been used as an indispensable tool in phase identification and identification of unknowns. A new relational database structure for the PDF-4/Organics enables total pattern analyses. Peak shape analyses provide information on particle size and strain distributions in the specimen. Bragg intensities give us information about possible preferred orientation and texture effects in powder specimens. Taken together, these complement the typical quantification processes (qualitative and quantitative phase identification). This enhanced information content arises as a direct result of 122,000 calculated pattern entries populated in the PDF-4/Organics database. Examples that focus on total pattern analyses of pharmaceutical hydrates will be presented.

Introduction

X-Ray powder diffraction techniques have been used for a variety of scientific applications, including semi-quantitative small particle size determination, residual stress determination and very sophisticated solid state structure determination. Particle size effects are seen in the Bragg peak shapes: large particles produce sharp Bragg lines, whereas small particles produce broad Bragg lines. In the area of particle size determination, one can simply match the unknown sample diffraction pattern with that of the substance with known ASTM-grain-size-number. Alternatively, for powders with particle size < 0.1 μm, a mixture of unknown and a standard with particle size > 1000 Å can be used to determine the particle size of the unknown. The difference in breadth "B" derived from the broad line of the unknown and the sharp line of the standard can then be used for equation (1).

$$t = (0.9\,\lambda)/(B\cos\theta) \qquad (1)$$

Where λ is the incident beam wavelength, B is net Bragg line full-width-at-half-maximum after correction for instrumental resolution, and θ is the Bragg angle. "t" is the particle size. Other applications include information for the crystal strain, depth of penetration, and crystal orientation. One of the most widely used applications is the crystal structure determination. Simple structures such as those of NaCl can be solved in a few minutes. However, complex structures such as those of proteins are more time consuming to solve. The Bragg lines' positions give information about the size/shape of the unit cell; as seen above, the profile shapes can give information about particle size; the integrated intensities give information about the unit cell content. The signature of all of these effects is available in the full digitized diffraction scan and can be easily observed in the ICDD powder diffraction (PDF-4) databases.

ICDD PDF-4/Organics 2003

The ICDD PDF-4/Organics database consists primarily of organic compounds. The released 2003 PDF-4/Organics database consists of 147,201 entries and the 2004 release will have 60,000 additional entries. PDF-4/Organics database was subdivided into subfiles according to the nature of the compounds and their industrial/pharmaceutical application. The statistical distributions of subfiles and other relevant properties in the PDF-4/Organics database are listed in Table 1. The 2003 release also contains 106,000 unique empirical formulas, 3,079 common names, 139,204 unique compound names, 709 distinct journals, 206 organic functional groups, and 3,740 Pearson symbol codes. The 2004 release of the PDF-4/Organics database, with 60,000 additional patterns, will cause the aforementioned statistical numbers to increase by 10-50% depending on the properties in question.

By comparing data within the same sub-file classification, a detailed correlation among the chemical, physical, and crystallographic data can easily be deduced. Pharmaceutical polymorphs and hydrates are such examples for consideration in this paper.

Table 1. Statistical Information For PDF-4/Organics 2003 [1]

Subfile or Relevant Properties	Number of Entries
Total Number of Compounds	147201
Drug Activity Compounds	4508
Pharmaceutical and Polymorphs	1192
Excipient and Polymorphs	184
Polymers	615
Forensic	2015
Inorganic	1776
Merck	1554
Ambient Condition	146917
With Reported Melting Point	147201
Author's Reported Density	112050
Calculated Density	129238
Literature Citations	84674

Thermodynamics of Polymorphs and Hydrates

The thermodynamic equilibrium of two polymorphs lies at the difference in their Gibbs free energy (equation 2).

$$\Delta G = \Delta H - T\Delta S \qquad (2)$$

Here the ΔH and the ΔS are the enthalpy and entropy differences between the two polymorphs. The difference in enthalpy is proportional to the difference in the intermolecular energy (ΔE) and in volume (ΔV) at a constant pressure (equation 3). The difference in entropy represents the different degree of disorder between the two polymorphs.

$$\Delta H = \Delta E + P\Delta V \qquad (3)$$

It has been observed that during crystallization, the less stable polymorph is formed first, followed by the transformation into a more stable polymorph. At a given temperature, the difference in Gibbs free energy is proportional to the logarithm of the thermodynamic activity ratio of two phases and hence approximately proportional to their solubility ratio (S_2/S_1) (equation 4).

$$\Delta G \sim RT \ln(S_2/S_1) \qquad (4)$$

When crystallization occurs in an aqueous solution, water can be incorporated into the crystals; hence, the hydrated compounds are formed. Pharmaceutical hydrated and polymorphic groups have very closely related chemical and physical behavior patterns. A hydrated group with the same anhydrous moiety (or the drug molecule) with different numbers of water molecules can have different crystalline structures which translate into different physical and chemical properties. One important common behavior for both polymorphs and hydrates is hydrogen bonding. Different polymorphs often exhibit different or present/absent intermolecular hydrogen bonding properties which will produce varied molecular stacking arrangements. The water moiety in a hydrated molecule has the ability to bond (hydrogen bonding) to the functional group of the drug substance or the water moiety of other molecules. Therefore, hydrogen bonding in the pharmaceutical hydrates is also a major contributor to their solid state crystal structures.

Analysis of Example Hydrates in the PDF-4/Organics 2003

There are 12,500 hydrates in the PDF-4/Organics 2003 database. Hydration of a pharmaceutical substance can occur during the production process or during the storage period. The water molecules can be incorporated into the final product during the crystallization from the aqueous solution or can be absorbed from the atmosphere. Also, an anhydride often has different hydration states associated with it. For example, Colchicine [Figure 1] by Merck is a suppressant for gout. In the PDF-4/Organics 2003 database, there are patterns of anhydrous Colchicine [2] (C22H25NO6), Colchicine monohydrate [3] (C22H25NO6.H2O), and Colchicine dihydrate [4] (C22H25NO6.2H2O). Among these three forms, the structures of monohydrate and dihydrate are well characterized [Table 2].

The Colchicine monohydrate was crystallized from aqueous ethanol and the Colchicine dihydrate was from water. The Colchicine monohydrate crystal structure has one water molecule bonded to three different alkaloid molecules, and each Colchicine molecule is hydrogen bonded to three water molecules. Therefore, the water and the alkaloid molecules in the Colchicine monohydrate are evenly distributed. On the other hand, the Colchicine dihydrate crystal structure shows that there are four water molecules hydrogen bonded to two Colchicine molecules. Also, there are two conformational polymorphs per hydrogen bonding unit for the Colchicine dihydrate. Since these two hydrogen bonded molecules have different intramolecular dihedral angles among rings A, B, and C [see Figure 1], one conformational polymorph is expected to have higher Gibbs free energy than the other. The fact that both polymorphs coexist in the same Colchicine dihydrate molecules is likely attributed to the compensation from the hydrogen bonding energy. Colchicine has been reported to have high water solubility. The fact that the aqueous ethanol produces only the monohydrate indicates that the more acidic, higher vapor pressure of ethanol and the less availability of water influences the degree of hydration. Figure 2 shows the comparison of the powder diffraction patterns of anhydrous and hydrated Colchicine (pseudo-polymorph) in the PDF-4/Organics 2003 database. The intermolecular hydrogen bondings for both hydrates played an important role in the pseudo polymorphism among the three structures. Hence, the very different corresponding powder patterns are observed in the PDF-4/Organics 2003 database. The somewhat uniform distribution of intensities among a wide range of d-spacings for the anhydrous Colchicine indicates that the atoms are evenly packed in the crystal lattice. However, the hydrated Colchicines have most of their intensities distributed at low angle regions. With less water influence, the Colchicine Monohydrate is more symmetrically packed to form rhombohedra crystals. On the other hand, the Colchicine dihydrate, with two water molecules per molecule, is less symmetrically packed as monoclinic crystals. It can also be seen that less symmetrically

Figure 1. Colchicine A-Aromatic Ring, B-Seven-Membered Saturated Ring, C-Troponoid Ring

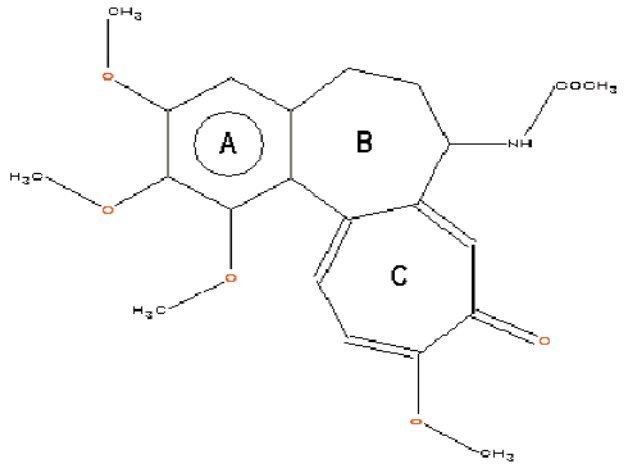
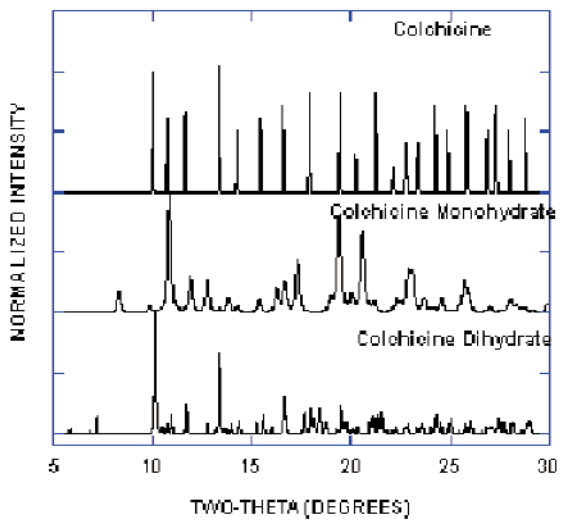


Table 2. Physical Properties And Cell Parameters For Two Colchicine Hydrates [1]

	Monohydrate	Dihydrate
Crystal System	Orthorhombic	Monoclinic
Space Group	P2121(19)	P21(4)
a - Angstrom	9.145(2)	17.08(1)
b - Angstrom	13.2(3)	10.7(7)
c - Angstrom	17.942(4)	13.88(1)
α - degree	90	90
β - degree	90	117.9(1)
γ - degree	90	90
Z	4	4
Volume	2165.85	2234.4

Figure 2. X-Ray Powder Patterns for Colchicine, Colchicine Monohydrate, and Colchicine Dihydrate [1]



packed and with one extra water molecule, Colchicine has larger molecular volume [see Table 2].

Summary

The pharmaceutical polymorphs and hydrates affect their bio-availabilities and their diagnostic or therapeutic effectiveness. Because of these correlations, FDA has strict requirements for all drugs to be free of their polymorphic forms unless they are identified and proven to be as effective or not interfering with the main active ingredient. Pharmaceutical databases such as PDF-4/Organics provide a large number of polymorphs and hydrates as reference patterns. Data in the database for related polymorphs and hydrates can provide insight for their chemical, physical, and structural information.

References

1. *ICDD PDF-4/Organics 2003 database was released in November 2002.*
2. *ICDD Grant-in-Aid, Institute of Physics, University College, Cardiff, Wales. Sample from British Drug Houses, Poole, England, UK. PDF# 000080713.*
3. *L. Yu Izotova, K. M. Beketov. B. T. Ibrgmov, M. K. Yus upov, J. Inclusion Phenomena 28, 33 (1997) PDF# 020708455.*
4. *Lessinger, L. Margulis, T. N. Acta Crystallogr., Sec. B 34, 578 (1978); PDF# 020613381.*

Dr. Needham is a Senior Scientist at ICDD and holds a Ph.D. in Organic Chemistry from Northeastern University, Boston, Massachusetts. As a graduate student, Dr. Needham did research on breast anti-tumor agents as an American Cancer Society Research Fellow. Later research work was carried out on PET diagnostic agents at Massachusetts General Hospital.

Dr. John Faber, a past contributor to American Pharmaceutical Review, holds the position of Principal Scientist at the International Centre for Diffraction Data (ICDD) and has previously spent 3 years as the Assistant Director for Research at the University of Illinois at Chicago, 7 years in corporate R&D at Amoco Corporation and 17 years at Argonne National Laboratory. Phone: (610) 325-9814; E-mail: faber@icdd.com