# FORMULATION ANALYSES OF OFF-THE-SHELF PHARMACEUTICALS

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**INTRODUCTION**

Several common high sales volume pharmaceutical tablets were examined for phase identification by X-ray powder diffraction. The purpose of the analysis was to see whether common, yet complex multi-ingredient formulations, could be easily analyzed using a new database, PDF-4/Organics, and associated software designed for pharmaceutical analysis.

The PDF-4/Organics database is an ongoing annually updated collaboration between the International Centre for Diffraction Data (ICDD) and the Cambridge Crystallographic Data Centre (CCDC). This database combines data taken from both powder diffraction experiments and data collected from single crystal crystallographic determinations that can be calculated into a reference powder pattern. The database also contains bibliographic references for sample preparation, data collection, and associated physical property measurements. In total, the database contains 218,194 entry sets with 416,554 references citations from 931 journals. Data from all sources are standardized, statistically analyzed, and extensively reviewed and edited prior to publication. In the 2004 release, several inorganic salts and excipients were also added to the database to aid those doing formulation analysis in law enforcement and pharmaceutical analyses. The inorganic additions included data from collaborations between the ICDD, FIZ-Karlsruhe, and the National Institute of Standards and Technology (NIST). Therefore the database represents select data from multiple sources all combined for the purpose of unknown identification.

The conversion of the data from multiple global sources into a common relational database, PDF-4/Organics, was a multi-year development effort by the ICDD. The analyses described in this paper are one of the first large scale tests to see if the database and associated software performed for its intended use in organic and organometallic material identification.

**SAMPLE PREPARATION**

Samples were chosen from contributions by the authors and coworkers. The selection was haphazard with the exception that all samples received were analyzed and the study focused on as-received tablets taken directly from commercial packaging. The following formulated tablets were investigated.

| Tablet | Manufacturer |
|---|---|
| Alka-Selzer Plus® | Bayer |
| Tums® EX (Extra Strength) | GlaxoSmithKline |
| Pepcid® AC | Johnson&Johnson-Merck & Co. |
| Promethazine Hydrochloride | Paddock Laboratories, Inc. |
| Benadryl® | Warner – Lambert Company |
| Kroger Decongestant | The Kroger Company CVS |
| Decongestant Antihistamine | CVS/Pharmacy® |
| Alavert™ | Wyeth Consumer Healthcare |
| Robitussin® Cough Drops | A. H. Robbins |
| Claritin® | Schering-Plough |
| Celebrex™ Capsules | G. D. Searle & Co |
| Donnatal | Wyeth Pharmacueticals |
| Effexor® | Wyeth Consumer Healthcare |

Table 1. *Tablets and manufacturers or commercial sources.*

Samples were analyzed on two different powder diffractometers. The authors are grateful to Bernie Squires of Rigaku-MSC, Inc., who ran several samples on a desktop X-ray diffractometer, during instructional classes at the annual ICDD X-ray Diffraction Clinic. A second set of samples were run on a diffractometer during an evaluation trial at Oak Ridge National Laboratory. In both cases, the authors had unique but temporary access to the equipment, therefore each sample was analyzed a single time.

Tablets were ground in a mortar and pestle and then one of two sample preparation methods were used depending on the instrument available for analysis. Both diffractometers used a Seeman-Bohlin focusing reflection geometry.

Method A – Cavity mounts were backfilled with powdered tablets. The samples were then run using Cu radiation and variable slits, a 0.05 step size with scans from 5 to 65 degrees two theta. Total data collection time was approximately 2 hours using a scintillation counter.

Method B – Samples from powdered tablets were lightly dusted onto a Vaseline® coated zero background holder. Ni filtered Cu radiation was used with a 15 minute total data collection time. A fast data collection time with good counting statistics was made possible by using PANalytical's X'Celerator detector. The area from 3 to 75 degrees two theta was scanned using a 0.017 degree step size.

**DATA REDUCTION AND ANALYSIS**

In both cases, the data was received in electronic format. Once received, data was displayed using the program POWDERX [1], the background was then stripped using the Sonneveld algorithm and a 2nd derivative peak finding program was used to generate a text file of d-spacing and peak intensities. The authors intentionally avoided using sophisticated integrated software packages that are available with most modern diffractometers in order to more fully test the capabilities of the database.

As mentioned above, the data in the PDF-4 database comes from multiple sources that is reviewed by editors for accuracy and self consistency. A complex series of indexes are prepared that allow the database with interface to automated data collection processes and rapid search and identification algorithms [2,3]. In Release 2004, a prototype version of the program SIeve+ was used for searching. SIeve+ (Search, Index, SIeve+) is a new program [4] developed by the ICDD to replace the historical PCSIWIN program and the functional operation of paper products such as the Hanawalt Search Manual, Alphabetic and Organic Indexes. In this way, the database can be used to identify materials through conventional Hanawalt, Alphabetical and

Fink searches. SIeve+ offers the advantage over paper products in that these searches are rapidly performed and, by using a 32-bit code, can handle the large size and entry populations of modern databases. The PDF-4/Organics database is housed in a 7 CD-ROM set. SIeve+ introduces a new text importer that can automatically read a wide variety of input files containing d-spacings and intensity information. The program also includes Fink and Long 8 search algorithms [5]. The former uses the strongest and longest eight d-spacings and the latter uses the 8 longest d-spacings. These searches have historical precedent and have demonstrated success in identifying low symmetry complex compounds which have larger unit cells and characteristic d-spacings in the high d, low angle region of the diffraction pattern. These searches have lost favor in the last 20 years since the permutation of the 8 lines for an active index resulted in enormous size, which slowed computer searches or made a paper index too cumbersome (multiple volume) whenever one searched a large entry population. Fast processors and large storage in modern PC's enable these search techniques.

In the analyses, text files produced during data reduction were imported into SIeve+ using the file importer. All three search algorithms, Hanawalt, Fink, and Long 8, were used to identify phases. A goodness of fit between the observed d-spacing and the reference d-spacing is calculated for each of the top 8 d-spacings and a cumulative score is used to rank the candidates [5]. The program is integrated with the database so that the database subfiles can be examined and many parameters can be interactively changed in the search programs.

**RESULTS**

Different tablet formulations were analyzed by the methods described above. The major crystalline phase was identified in each tablet for all formulations. Common excipients such as sucrose, mannitol, cellulose, and alpha lactose monohydrate were frequently identified in the tablet formulations. In fact, cellulose was a major ingredient in five formulations and alpha lactose monohydrate in four formulations. The importance of adding excipients to the database is demonstrated in the analysis of Pepcid® AC, and Celebrex™ Capsules shown in Figures 1 and 2, respectively. Pepcid® AC contains an organic excipient, microcrystalline cellulose. The PDF-4/Organics database has the ability to simulate digitized patterns. The pattern for cellulose, shown in Figure 1, was simulated from PDF 00-050-2241, a sample of bleached Egyptian cotton, by applying a pseudo-Voight peak shape and optimizing the peak width to the sample. Using this method, all five tablets containing micronized cellulose could be identified with a simulated pattern analysis. Inorganic excipients were frequently found in the various tablets. These included titanium dioxide, silicon dioxide, iron oxides used as colorants and fillers, calcium carbonate and sodium bicarbonate used in antacids, and talc used as a processing aid.

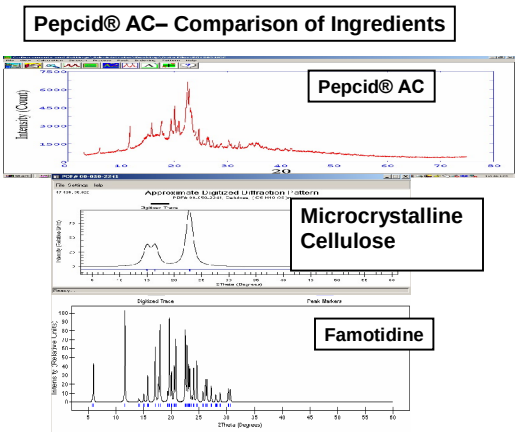


Figure 1. *Comparison of the raw X-ray diffraction data for a tablet of* Pepcid® AC *compared to the digitized reference patterns of microcrystalline cellulose, and famotidine (active ingredient).*

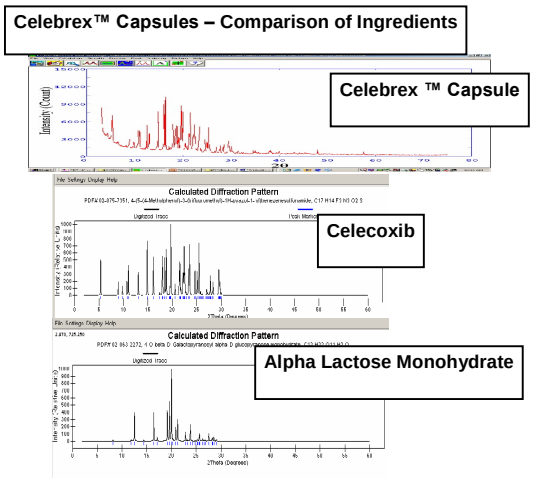



Figure 2. *Comparison of the raw X-ray diffraction data for a* Celebrex™ Capsule *compared to the digitized reference patterns of alpha lactose monohydrate, and Celecoxib (active ingredient).*

The program SIeve+, after identification of the major crystalline excipients, eliminates peaks due to the phase match and then searches and matches the residual pattern. Using this procedure, additional phases and active ingredients were identified. In the 13 tablets, there were 15 active ingredients, 13 of which were identified. Alka-Selzer Plus® had two active ingredients, the antacid sodium bicarbonate and aspirin. In the Promethazine hydrochloride tablet analysis two polymorphs of promethazine hydrochloride were identified. The active ingredient not identified in this analysis was loratidine. Loratidine is the active ingredient in both Alavert™ and Claritin®. Two excipient phases were identified in each of these tablets and, as one would expect, the unidentified residuals closely resemble each other. The structure of loratidine has been elucidated, published, and is contained in the Cambridge Structural Database (CSD). However, the structure is significantly disordered which prevented the calculation of a high quality reference pattern for inclusion in the Powder Diffraction File™. This drug will be targeted for analysis by ICDD's grant-in-aid process, where materials of industrial importance are targeted for characterization by qualified laboratories for inclusion in the Powder Diffraction File™. The grant program has characterized hundreds of commercial drugs. Overall, the analyses identified 87% of the actives by number and 92% by chemistry.

The identification process accounted for 48 phases in the 13 tablets. Besides the aforementioned difficulty in analyzing loratidine, there was also large residuals in the analyses of Pepcid® AC, CVS decongestant and the Robitussen® cough drop. Three phases or more were identified in each of these latter samples, but several unidentified peaks remained. Several difficulties arise in analyzing the residual patterns that includes issues with both experimental measurements and the data reduction algorithms. The data reduction process did not correct for specimen orientation and did not correct for close overlapping peaks in the residual analysis. The latter reduces the effectiveness of the match process as the number of phases and peaks are identified. There were also many low intensity peaks (<5) that may have been easier to resolve and identify by using longer count times, smaller step sizes, and better counting statistics. The authors did not pursue this study since this was not the intent of this analysis, but anticipate that several additional phases could be identified by taking the steps outlined above.

The course of the investigation yielded several unanticipated results. For example, four formulations contained alpha lactose monohydrate but they matched three different PDF® reference files. The PDF® files include a stereo specific lactose whose pattern was calculated from a single crystal analysis and two unindexed experimental powder patterns. We hypothesize that the three files may represent three degrees of molecular orientation since the patterns differ primarily in relative intensity. The fourth sample, Effexor®, was so severely oriented that automated phase identification was unable to find a solution. However, given a clue from the prior analyses, it was noticed that the typically weak (040) and (080) peaks were the strongest two peaks in the pattern. These peaks' intensities were manually corrected which resulted in rapid identification. Overall, the thin film sample preparation technique (Method B) resulted in highly accurate d-spacings, but some specimen orientation. In most cases, Effexor® being the exception, the d-spacing accuracy facilitated the identification due to high goodness of merit (GOM) fits used to sort and list candidate identification.

Through trial and error, we found that using a mixed search strategy was more effective than using any of the search algorithms independently. The results are interpreted as follows. In most tablets, the strongest phase was an excipient that was readily identified using a Hanawalt Search. Once this phase was removed, we frequently tried to identify low symmetry organic compounds using Fink or Long 8 searches. In the PDF-4/Organics database, patterns calculated from crystallographic analyses are only calculated out to 30 degrees two theta (Cu radiation). This was a practical tradeoff between content and size of the database since each 5 degrees two theta would effectively double the database size. However, as a consequence, residual patterns may have artificially large peaks above 30 degrees which can interfere with a Hanawalt search that is based on the strongest lines. An alternative approach would be to record experimental data to 30 degrees. We do not recommend this approach with pharmaceutical tablets since many of the high symmetry excipients need the wider angular range to experimentally measure enough d-spacings to achieve a high GOM match. The mixed algorithm search strategy was effective in identifying phases where experimental data collection encompassed a broad two theta range. Finally, we should note that many formulations contained micronized, microcrystalline or amorphous content. This includes materials such as cellulose, cellulose derivatives, lactose and starch. This can present a challenge to many data reduction programs resulting in false peak assignments or poor intensities if these materials are not adequately separated from the background.

**CONCLUSION**

Several common high sales volume pharmaceutical tablets were examined for phase identification by X-ray powder diffraction. Using the PDF-4/Organics database and associated search software, the major crystalline phase was identified in each of the 13 tablet formulations tested. An average of 3.5 phases were analyzed per tablet and the active ingredient, usually a minor phase, was identified in 87% of the formulations. All analyses were performed on ground tablets without any physical or chemical treatments to separate or concentrate the phases.

The results emphasized the effectiveness of using a combined source database, such as PDF-4/Organics, for analyzing pharmaceutical formulations. Active ingredients were identified by reference to both single crystal derived powder patterns and experimental powder patterns. In this particular series of experiments, significantly more phases were

identified by comparison to the experimental powder diffraction data than by the reference patterns calculated from single crystal studies despite the 7/1 ratio of calculated to experimental patterns in the database. We attribute this result to the multi year focus on obtaining experimental patterns on commercially relevant materials in the ICDD's grant program and the prevalence of inorganic excipients in the samples.

**REFERENCES**

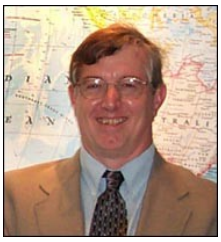

(1) POWDERX is a program written by Dr. Cheng Dong, (Institute of Physics, Chinese Academy of Sciences, P.O. Box 603, Beijing 100080, P.R. China. E-mail: chengdon@aphy.iphy.ac.cn) POWDERX is a Graphical Powder Diffraction Analysis program which includes: specimen displacement, aberration correction, background stripping, alpha-2 stripping, smoothing, peak offset determination, peak find. It is available upon request for non-commercial use.

(2) S. N. Kabbekodu, J. Faber, T. G. Fawcett, "New Powder Diffraction File, PDF-4 in a relational database format: advantages and data mining capabilities", Acta Cryst, (2002) B58, 333-337.

(3) J. Faber and F. L. Needham, "The New Organic Powder Diffraction File: Applications for Polymorphism and Search Indexing, American Pharmaceutical Review, (2002), 5, Issue 2, 70-75.

(4) SIeve+ is a new program designed to work as an interactive plug-in with PDF-4/Organics. This program is an upgrade of the program PCSIWIN and has additional features tailored for pharmaceutical analysis. More details can be found at www.icdd.com.

(5) J. Faber, C. A. Weth and J. Bridge, " A plug-in program to perform Hanawalt or Fink search-indexing using organics entries in the ICDD PDF-4/Organics 2003 database", Powder Diffraction, 19 (1), March 2004.

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