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APPLICATION NOTE

Analysis of Commercial Pharmaceuticals Using PXRD (Powder X-ray Diffraction)

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OBJECTIVE

To demonstrate the use of X-ray diffraction (XRD) to investigate the crystal structure of Ibuprofen in products from two different vendors.

INTRODUCTION

The presence of polymorphs (different crystal structures) as well as solvates and hydrates of active pharmaceutical ingredients (APIs) can have a huge impact on the bioavailability and effectiveness of pharmaceuticals. For this reason, it is critical to identify the polymorph (or polymorphs) present in raw APIs as well as in pharmaceutical preparations. It is also essential to understand if and how those polymorphs change over time, or after exposure to different storage conditions. XRD, with its ability to identify different crystal structures, is uniquely positioned to identify the polymorphs present in pharmaceuticals. This application note will demonstrate how XRD is used to identify polymorphs in pharmaceuticals.

Ibuprofen is a well-known analgesic and nonsteroidal anti-inflammatory drug (NSAID) that is used to relieve pain from various conditions such as headache, dental pain, muscle aches or arthritis etc. There are two enantiomers of Ibuprofen (molecular formula = $C_{13}H_{18}O_2$): S(+)-ibuprofen (dexibuprofen) and R(-)-ibuprofen . These two enantiomers of ibuprofen are mirror images of each other and are not only different in crystal structure, but they also have differences in physical properties and chemical stabilities. Dexibuprofen, which is the pure S(+)-ibuprofen, has higher solubility, higher dissolution rates and a lower melting temperature compared to R(-)-ibuprofen. Racemic mixtures of ibuprofen contain both S(+)-ibuprofen and R(-)-ibuprofen.

In most of the commercially available over-the-counter formulations, Ibuprofen is present as a racemic mixture, and only the racemic compound (Ibuprofen-racemate) is in clinical use. In addition to the two enantiomers, there are two crystalline phases of racemic ibuprofen[2]: phase I (the conventional phase) is stable and phase II is metastable, based on different melting temperatures.

Historical powder x-ray diffraction patterns for Cu-Kα radiation for the pure S(+) enantiomer (dexibuprofen) and the racemic mixture are shown in Figure 1 and Figure 2, respectively. S(+)-Ibuprofen is monoclinic, with space group P21[4] while racemic ibuprofen also has a monoclinic structure, but with space group P21/c[4]. As you can see, the two patterns are quite different and should be easy to differentiate.

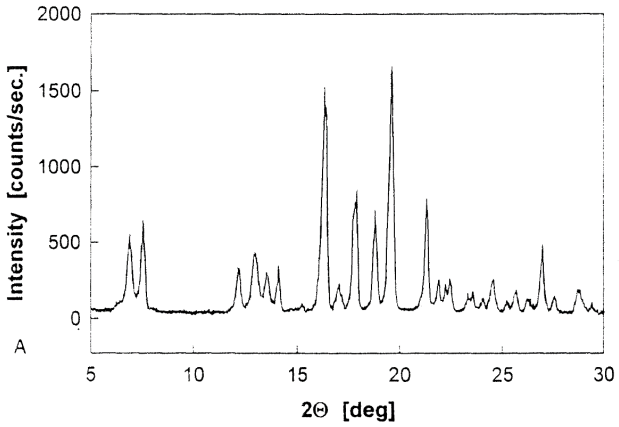

Figure 1: X-ray reference pattern of dexibuprofen (S(+)-ibuprofen)[1]

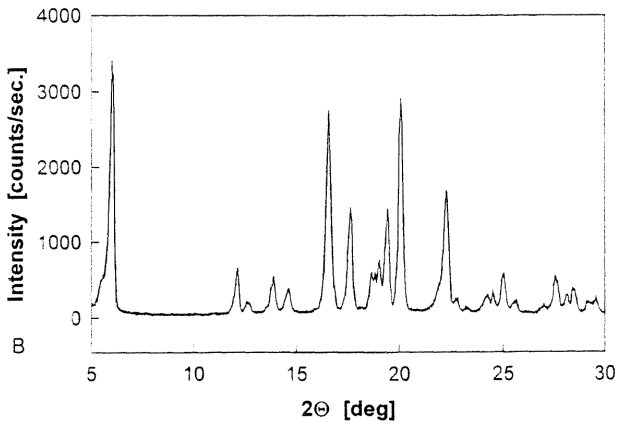

Figure 2: X-ray reference pattern of Racemic ibuprofen[1]

EXPERIMENTAL

Two commercial ibuprofen samples were purchased from a drugstore: (1) a white ibuprofen tablet from ZEE Medical Inc. and (2) a coated ibuprofen Advil® tablet manufactured by Pfizer. The coating of the Advil® was removed before analysis. Both tablets were broken into small pieces and ground in an agate mortar and pestle. The resulting powder from these tablets was dusted onto a zero-background sample holder, coated with a very thin layer of petroleum jelly, for analysis. The purpose of the petroleum jelly was to minimize any potential preferential orientation of the powder particles.

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The XRD patterns were acquired by coupled θ:2θ scans on a Rigaku Ultima III diffractometer equipped with a copper x-ray tube and Ni beta filter, parafocusing optics, computer-controlled slits, and a D/teX Ultra 1D strip detector. Data were acquired by coupled 2θ:θscan between 4.0° and 45.0° 2θ with a 0.02° step size.

RESULTS

Figure 3 compares the powder x-ray diffraction patterns from the two samples, displayed with a small vertical offset. In this figure, there are differences between these samples in overall peak intensities and also in the presence of few additional very weak peaks from the Advil, compared to the other sample.

Figure 4 and Figure 5 show the individual powder XRD patterns for the ZEE ibuprofen and Advil tablets, respectively. The racemic ibuprofen phase I from the International Centre for Diffraction Data (ICDD) Organic PDF-4 reference pattern (in green) is superimposed on the experimental data in both figures. The peak positions in both patterns agree with the diffraction pattern of the racemic form of Ibuprofen which has a crystal structure of monoclinic, P21/c[4]. Most of the Ibuprofen produced by pharmaceutical industries is the racemic form of Ibuprofen which includes the active (S)-(+)- and inactive (R)-(-) enantiomer. It has been found that there is no harm from the R-(-) enantiomer and that humans actually have an enzyme (isomerase) which can convert the inactive R- form to the active S- isomer form[3]. The weak peaks in the Advil sample match sucrose. The sucrose trace phase is probably due to the coating that was mostly removed by scraping (see the Experimental section). The broad peak near 18 degrees 2θ in both samples is likely due to a common amorphous additive such as starch.

CONCLUSION

This investigation shows how powder x-ray diffraction can be used to identify the crystalline polymorph of the active pharmaceutical ingredient present in pharmaceutical preparations. XRD analysis is a good technique not only in identifying the crystal structure of different polymorphs in the drug for some pharmaceutical development, but it also can determine the crystallinity in the drug and potential presence of other excipients in the formulation.

REFERENCES

1. G. Leising, R. Resel, F. Stelzer, S. Tasch, A. Lanziner, and G. Hantich: "Physical Aspects of Dexibuprofen and Racemic Ibuprofen". J Clin Pharmacol 1996; Vol 36: 3S-6S.
2. E. Dudognon, F. Danede, M. Descamps, and N.T. Correia: "Evidence for a New Crystalline Phase of Racemic Ibuprofen". Pharmaceutical Research, December 2008, Vol. 25, No. 12, p. 2853-2858.
3. J. V. McCullagh: Enantiomeric Separation/Resolution: "Analyzing the Experimental Results of the Resolution of the S- and R- stereoisomers of (+/-) ibuprofen, (2-(4'-isobutylphenyl)-propionic acid)". J. Chem. Educ. 2008, 85, 941.
4. ICDD Organic diffraction database (www.icdd.org).

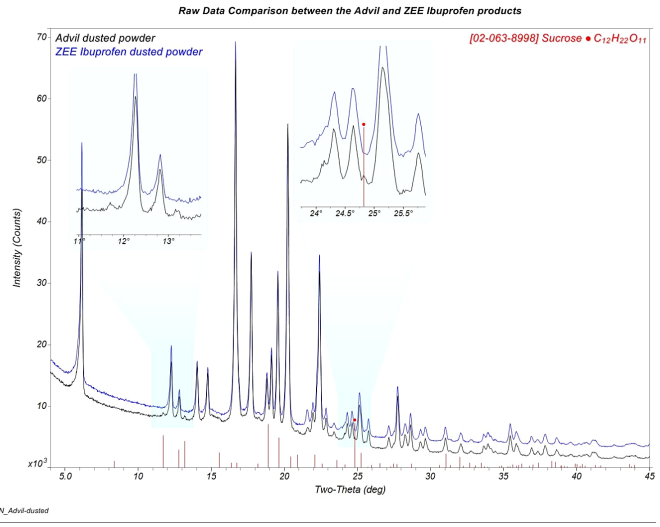

Figure 3: Comparison for the Ibuprofen products between two vendors

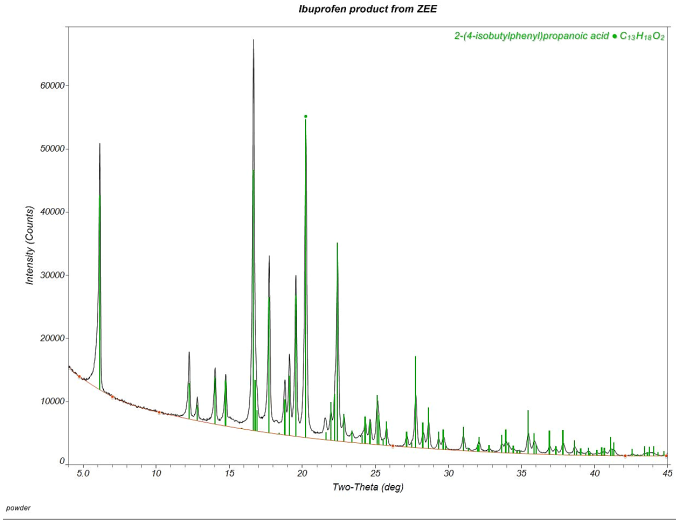

Figure 4: XRD pattern for the ZEE Ibuprofen tablet

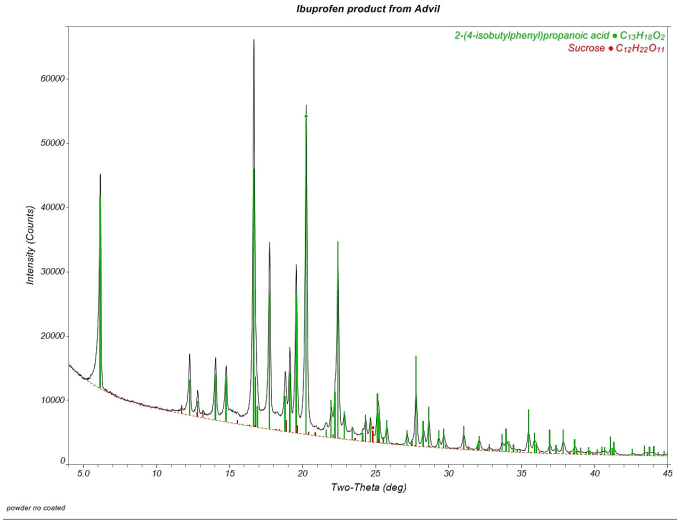

Figure 5: XRD pattern for the Advil® tablet