JST-DRX: A Software to Generate X-Ray Powder Patterns from Patents Data

Julia Sawaki Tanaka 1;
Carlos de Oliveira Paiva Santos 1;
Selma Gutierrez Antonio 1

1 Department of Physical Chemistry, Institute of Chemistry, UNESP – Univ Estadual Paulista, Araraquara, SP, Brazil
e-mail:julia@iq.unesp.br

***Abstract*—The software JST-DRX was developed to generate X-ray powder diffractograms based on information 2θ x I (Bragg angle x Intensity) of pharmaceutical ingredients, obtained from patents and articles. This software is used to generate diffractograms for identification of polymorphs of raw materials of active ingredients and solid drugs, when the crystal structure is unknown.**

***Index Terms*—Crystal structure; X-ray powder diffraction; polymorph; pharmaceutical**

I. INTRODUCTION

A substance can crystallize in several different crystal structures, despite having the same chemical structure. This property is called polymorphism. Polymorphs have different physicochemical properties such as solubility, dissolution rate, chemical stability, melting point, etc.

The most common form of drug administration is orally in solid form. The therapeutic effectiveness of the drug is, in many cases, directly related to the crystalline structure (polymorphism) of the active pharmaceutical ingredient present in the raw materials.

The drugs in the solid state deserve special attention because its dissolution may be affected significantly by the inherent characteristics of the drug itself, the presence of excipients that favor or hinder the dissolution and by the chosen manufacturing techniques [1]. Therefore the solid forms for oral use, either for immediate or for modified release are those which might present problems regarding the bioavailability and bioequivalence [2].

During the production stages (e.g. drying, compacting, grinding) the transformation between crystalline forms may occur with a consequent change in its formulation. This phase change can affect product stability and in some cases, the bioavailability of the drug, thus, it is highly relevant to study the possible crystal forms of the drugs (polymorphs) both in the raw material and in the finished medicines [3].

In this context, the application of various techniques such as thermal analysis [4] [5], chromatography [6], X-ray powder diffraction [4], [6], [7], [8], [9], [10], [11] among others are of a great importance for the control of raw materials used in the manufacture of medicines and for the control of finished drugs as well.

At the Institute of Chemistry, UNESP, Araraquara, the Polycrystal Crystallography Group works in the development of qualitative and quantitative analysis of polycrystalline materials using X-ray powder diffraction (XRPD) and the methods of Rietveld [12] and PONKCS [13] among others.

The XRPD is a powerful technique for qualitative and quantitative analysis of the crystalline solid mixtures [14]. The XRPD has proven to be feasible for drug analysis thanks to technological advances, which have greatly enhanced the X-rays generating devices (rotating anode, synchrotron light, focusing mirrors, etc.), X-rays detection (solid state detectors position sensitive detectors, multiple detectors, etc.) and improvement of the data resolution (synchrotron light, sagittal monochromators, focusing mirrors, etc.). All those advances resulted in a greater sophistication in the characterization of pharmaceuticals, allowing the obtaining of a larger amount of information of the diffraction pattern [3].

The Rietveld method [12] for crystal structure refinement has a great potential in terms of identification and quantification of organic compounds, mainly due to the advances mentioned above regarding generation and detection of X-rays as well as advances of computational resources. With the Rietveld method it is possible to unambiguously identify the polymorphs and quantify each of them. However, the method is limited to cases where the crystal structure is known. Moreover, the PONKCS (Partial Or No Known Crystal Structures) method [13] allows the quantification of phases without the knowledge of the crystalline structure, although it requires the diffraction data of the pure material. Very often there is no information available on the crystal structure and there is no pure material to be measured by XRPD. In such situations it is necessary generate diffraction patterns based on information obtained from patents and articles. For this purpose the software JST-DRX was implemented.

II. DEVELOPMENT

For the implementation of JST-DRX it was used the Integrated Development Environment (IDE) Lazarus, which is

free and open source software that allows visual and object-oriented programming and is based on the Free Pascal compiler.

The JST-DRX software reads data from a file containing the information 2θ x I or d x I obtained from references such as patents or publications in scientific journals. Table 1 shows the data (d x I) extracted from patent WO 2001 / 47933 A1 [15] and the converted values 2θ for each peak.

Table 1.
Data extracted from the patent WO 2001/47933 A1 of Olanzapine

Form I			Form II		
d	***2θ***	***I100***	***d***	***2θ***	***I100***
9.946	8.882	100	10.269	8.603	100
8.558	10.327	15.18	8.577	10.304	7.96
8.245	10.721	1.96	7.472	11.833	1.41
6.886	12.844	14.73	7.125	12.411	6.50
6.379	13.870	4.25	6.146	14.398	3.12
6.244	14.171	5.21	6.071	14.577	5.12
5.590	15.840	1.10	5.485	16.145	0.52
5.306	16.694	0.95	5.218	16.976	6.86
4.982	17.789	6.14	5.125	17.286	2.47
4.833	18.339	68.37	4.987	17.767	7.41
4.726	18.761	21.88	4.767	18.598	4.03
4.629	19.157	3.82	4.716	18.800	6.80
4.533	19.565	17.83	4.479	19.805	14.72
4.462	19.878	5.02	4.331	20.489	1.48
4.952	20.678	9.19	4.229	20.985	23.19
4.235	20.959	18.88	4.141	21.438	11.28
4.086	21.733	17.29	3.987	22.275	9.01
3.825	23.230	6.49	3.721	23.894	14.04
3.749	23.711	10.64	3.565	24.957	2.27
3.698	24.041	14.65	3.537	25.157	4.85
3.582	24.835	3.04	3.383	26.321	3.47
3.506	25.378	9.23	3.252	27.404	1.25
3.339	26.671	4.67	3.134	28.453	0.81
3.281	27.157	1.96	3.085	28.917	0.45
3.214	27.732	2.52	3.064	29.119	1.34
3.112	28.660	4.81	3.011	29.640	3.51
3.051	29.247	1.96	2.874	31.090	0.79
2.948	30.290	2.40	2.810	31.814	1.47
2.817	31.732	2.89	2.722	32.877	0.20
2.759	32.421	2.27	2.643	33.882	1.26
2.660	33.666	1.86	2.601	34.453	0.77
2.634	34.010	1.10			
2.596	34.523	1.73			

In the patent WO 2001 / 47933 A1 [15] the peaks positions are given in interplanar distances d (Å) versus relative intensity $I100$, which is usually a percentage of the most intense diffraction pattern. Therefore, $I100$ must be $\leq$ 100. The interplanar distances are converted to 2θ using Bragg's Law ($\lambda = 2d$ senθ), i.e., the peak position is given by:

$$2\theta = 2*\text{arcsen}(\lambda/2d),$$

where: θ is the angle of incidence or reflection of the beam of X-rays, λ is the wavelength of X-rays and d the interplanar distance.

The input data for the JST-DRX software (Fig. 2) can be 2θ x I or d x I. The XRPD pattern is built from these data, where the ordinate represents the point to point intensity y_i for each value of $2\theta_i$ represented on the abscissa. Which means, for each point (2θ, I) on the table it is positioned a normalized Gaussian function so that the intensity I is distributed within a full width at half maximum (FWHM). For the points between the two peaks, where the overlap of two Gaussian functions can occur, the sum of the values of functions is taken in consideration.

In the JST-DRX software, the user can set the FWHM of the peaks, the color and the line width of the XRPD pattern, the maximum intensity and the region ($2\theta_{initial}$ and $2\theta_{final}$) in which the diffraction pattern must be plotted. The smoothing factor can be changed so that the software runs smoother curves when the range 2θ is expanded.

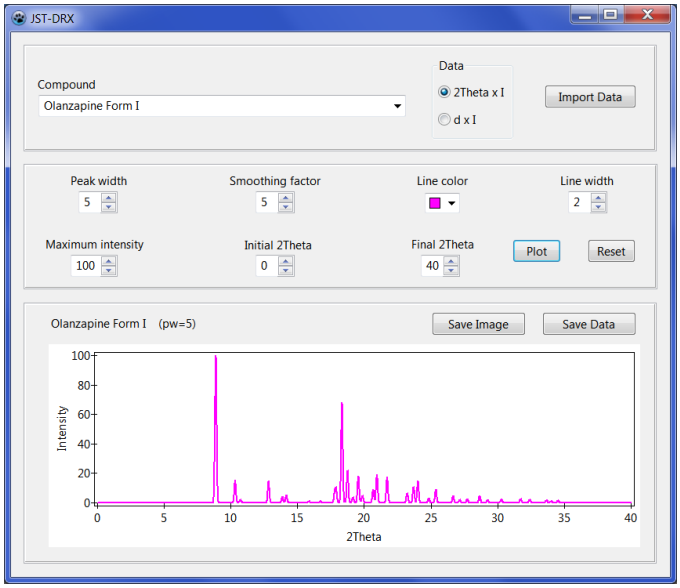

Fig. 1. JST-DRX software interface.

With this information, the software generates and plots the XRPD pattern in a window, allowing the user to view it and change the parameters as needed. Finally, the software allows you to save the image of the generated diffraction pattern as well as the (x, y) values of its points.

III. APPLICATION

Following is presented an example of the use of diffraction patterns generated by the JST-DRX in the analysis of pharmaceuticals.

Based on the X-ray diffractions data of Forms I and II of Olanzapine antipsychotic [15] shown in Table 1, the XRPD patterns of Figures 2 and 3 were generated for Forms I and II, respectively, using the JST-DRX software.

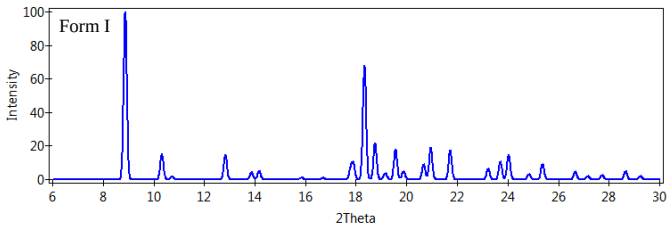

Fig. 2. Diffractogram of Form I, generated by JST-DRX software based on the information of patent WO0147933A1 in Table 1.

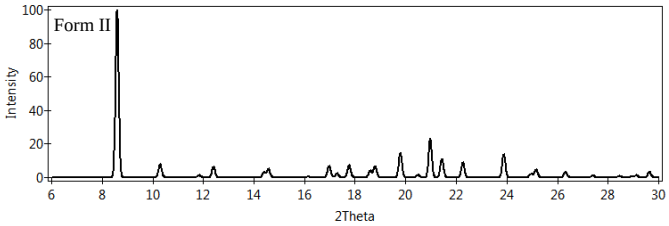

Fig. 3. Diffractogram of Form II, generated by JST-DRX software based on the information of patent WO0147933A1 in Table 1.

Figures 4 and 5 show XRPD patterns observed for two batches (A and B) of the raw material of Olanzapine, where the purpose is to identify which polymorph is present.

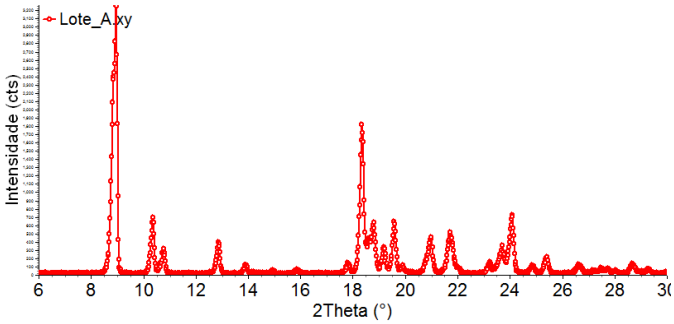

Fig. 4. Experimental XRPD pattern of Olanzapine Batch A.

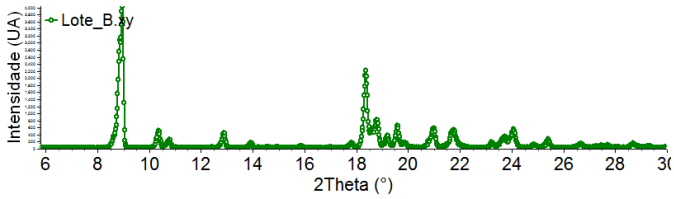

Fig. 5. Experimental XRPD pattern of Olanzapine Batch B.

In Figures 6 and 7 are presented comparison of the XRPD pattern of the batch B with the generated diffraction patterns of Forms I and II.

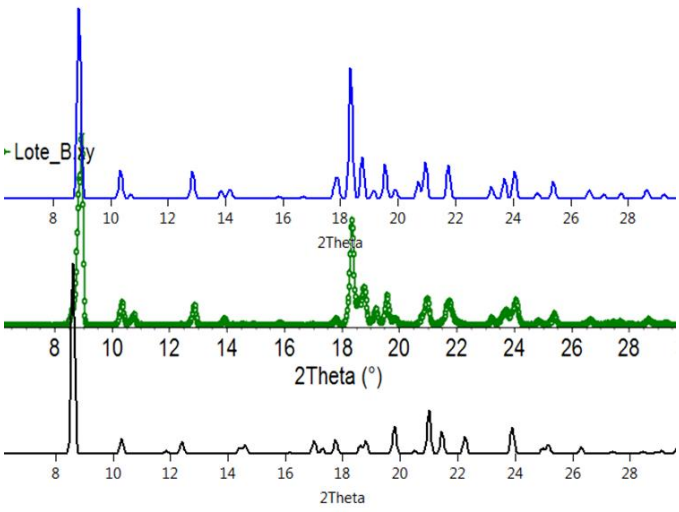

Fig. 6. Comparison of XRPD pattern of the Olanzapine Batch B (green) with the diffraction patterns generated of Form I (blue) and Form II (black).

In Figure 6, a visual analysis without a detailed observation of the diffraction patterns, one has the impression that only Form I is present. Due to a high overlapping of the peaks a slower measurement was performed in the region around 2θ = 17°, where a characteristic peak of Olanzapine Form II occurs. The comparison is shown in Figure 7.

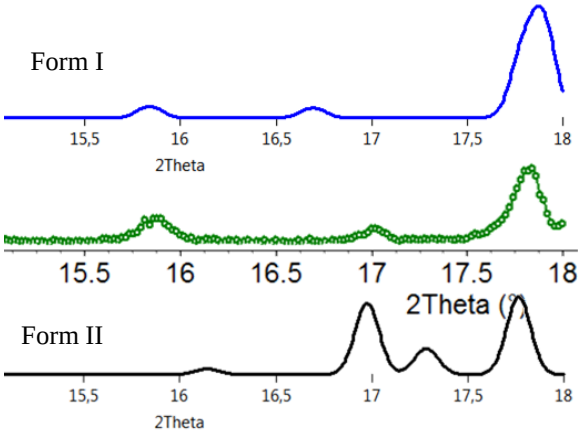

Fig. 7. Magnification comparing the XRPD pattern of Olanzapine Batch B (green) with the diffraction patterns generated for Form I (blue) and Form II (black).

In the Figure 7, it is noted that the peak of Form II at about 2θ = 17° is also observed in the XRPD pattern of Batch B.

Based on these analyses, it is concluded that the Batch B also presents the Olanzapine Form II.

In Figures 8 and 9 are shown comparison of the XRPD pattern of Batch A with XRPD patterns of Forms I and II generated by the JST-DRX software.

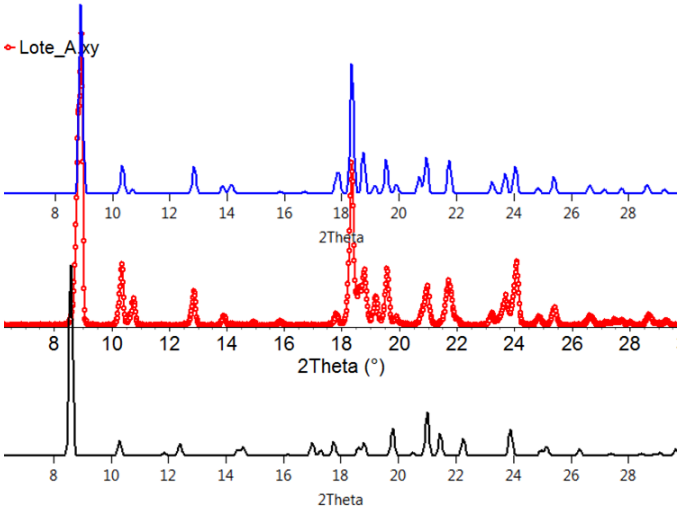

Fig. 8. Comparison of XRPD pattern of Olanzapine Batch A (red) with the diffraction patterns generated for Form I (blue) and Form II (black).

In Figure 8, in Batch A only the peaks of Form I are observed.

In the expansion of Figure 9, note also that only the peaks of Form I are observed. The characteristic peak of Form II (black) around 2θ = 17° is not observed.

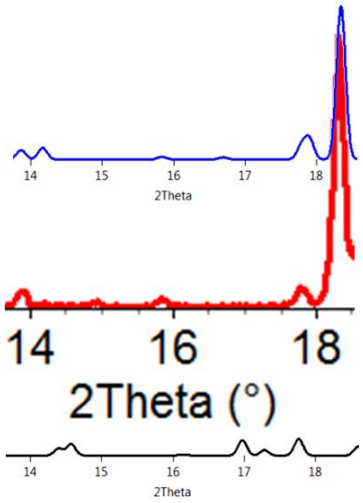

Fig. 9. Magnification comparing the XRPD pattern of Olanzapine Batch A (red) with the diffraction patterns generated for Form I (blue) and Form II (black).

This same type of analysis can be performed to check if a polymorph present in a raw material or marketed tablet is the one expected to be active for the desired treatment. This type of analysis is only possible if the diffractogram of each polymorph is available.

IV. Conclusion

The JST-DRX software is able to generate X-ray powder diffraction patterns from 2θ x I (Bragg angle x intensity) or *d* x I data of pharmaceutical ingredients, obtained from patents and articles. The XRPD patterns generated by the software can be used to identify polymorphs of active principles in raw materials and solid drugs, when the crystalline structure is unknown.

The diffraction patterns generated by the JST-DRX software will be used by undergraduate, master's and doctoral students of the Polycrystal Crystallography Group of the Institute of Chemistry - UNESP, in the analysis of drugs of the RENAME (National List of Essential Medicines) and the Brazilian Program of Public Pharmacy. Initially, the diffraction patterns will be used in the characterization of drugs distributed by the Local Health Center of Araraquara, based on the agreement, which the group has with the city Health Department. Subsequently, the diffraction patterns generated will be included in a database of X-ray powder diffraction data of drugs to be available on the internet.

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