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The use of the software JST-XRD for identification of crystalline phases in pharmaceutical raw materials and tablets

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ABSTRACT

Study of polymorphism is of great importance for the pharmaceutical industry once polymorphs may display different physicochemical properties, which, in turn, may result in stability differences that can bring problems for the manufacturing stages and the quality of final products. Although research on organic polymorphs has greatly increased in the last decades, it still does not cover all needs for the pharmaceutical market. Techniques such as spectroscopy in the infrared region, nuclear magnetic resonance, thermal analysis, X-ray diffraction, etc., can be used to identify polymorphism. The polymorphism is a property of the crystalline solid state, and can be evaluated by X-ray diffraction once each polymorph exhibits one specific X-ray diffraction pattern. The JST-XRD program is a tool designed to help the identification of crystalline phases (including polymorphs) present in pharmaceutical ingredients and tablets by using X-ray diffraction data obtained from scientific articles and patents. This paper presents new implementations for the JST-XRD and describes its use in the analysis of active pharmaceutical ingredient and marketed tablets of norfloxacin, mebendazole and atorvastatin calcium. By the means of comparison, JST-XRD allowed identifying the crystalline phases in the diffraction patterns of the analyzed drugs, showing the program suitability for polymorphism research, pre-formulation and quality control in pharmaceutical industries. JST-XRD can also be used for educational purposes in undergraduate and graduate programs in order to show the potentiality of X-ray powder diffraction in polymorphism analysis.

Keywords: X-Ray Diffraction. Crystalline Polymorphs, Pharmaceutical Ingredients, Qualitative Phase Analysis, Lazarus, Software.

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INTRODUCTION

Active pharmaceutical ingredient (API) and excipients: the importance of characterization

Pharmaceutical drugs are formulated by using active pharmaceutical ingredients and excipients. API and excipients raw materials are marketed in powder form, which can be crystalline or amorphous. Crystalline powder displays a highly organized structure with a periodic arrangement, while amorphous materials are characterized by not having long-range order or periodic arrangement.

Polymorphism consists of several crystalline forms or various crystalline structures for the same formula (Bernstein, 2002).

X-ray diffraction (XRD) is an important characterization technique for pharmaceutical ingredients in crystalline form. This technique makes possible to determine crystalline structures and unravel detailed information about the molecular conformation and packing, intra and intermolecular bonds, which can be correlated to the physicochemical properties of the material.

Considering the fact that the XRD pattern is characteristic of a crystal structure, it can be used for identification of polymorphs in raw materials and tablets of crystalline pharmaceuticals.

X-ray powder diffraction (XRPD) databases of organic compounds are available, including the APIs and excipients, such as PDF-4 Organics provided by ICDD (International Centre for Diffraction Data) (ICDD, 2016) with 501,964 records, of which, 431,359 are based on data from the Cambridge Structural Database (CSD) (Allen, 2002). The CSD is a database of crystal structures (Allen, 2002) containing organic and organometallic molecules with more than 800,000 cataloged structures (CSD, 2016). However, several information on polymorphs are still only found in patents or scientific papers. This information is presented as XRPD pattern or tables containing, sometimes, only the positions and relative intensities (2θ, I100) or (d, I100) for the most intense Bragg peaks. Some of these XRD powder patterns are of low quality (with high

noise, and it is not rare they are poor copies of the original diffractogram), which makes the compound identification difficult. Fortunately, characteristic peaks provided in patents tables can be used to generate diffractograms, which can be compared to the XRPD pattern of raw material or solid pharmaceuticals for phase identification.

The development of tools for pharmaceutical ingredients analysis is of great importance for the pharmaceutical industry, for educational purposes, in regard of teaching about polymorphism in the pharmaceutical field, as well as for personnel training in the analysis field. These are the main objectives of the JST-XRD program (Tanaka, 2015), which uses X-ray diffraction data to identify phases (eg. polymorphs) in crystalline materials, which includes pharmaceutical ingredients and final products.

The continuously improved JST-XRD software makes use of the (2θ, I100) or (d, I100) data from patents, paper or even self-laboratory data, to generate X-ray powder diffraction patterns and compare them with the observed diffractogram of the material under analysis. This software allows now overlaying one observed XRPD pattern with up to ten generated diffraction patterns and, by visual comparison, identifies the crystalline forms present without having to rely on commercial databases.

The JST-XRD user can create their own database with the crystalline forms, which usually uses.

Application cases: norfloxacin, mebendazole and atorvastatin calcium

Norfloxacin is a broad spectrum antibiotic being used to treat various infections. It has the anhydrous Forms A, B and C and various hydrates forms (Barbas et al., 2006; Roy et al., 2008; Puigjaner et al., 2010). The hydrates forms are more soluble than the anhydrous (Hu et al., 2002). Although the anhydrous Form A is the commercial form (Purohit & Venugopalan, 2009), the sesquihydrate form is occasionally found mixed with Form A in tablets marketed at drugstores.

The forms with known crystal structure are the anhydrous A (Barbas et al., 2007) and the hydrated forms sesquihydrate (Ravindra, 2009), dehydrate (Roy et al., 2008), 1,25 hydrated (Roy et al., 2008) and 1,125 hydrated (Roy et al., 2008). Forms B and C have unknown crystal structure, and only interplanar distances and relative intensities are known. Sustar (Sustar et al., 1993) published a table with positions and relative intensities of Forms A and B in 1993. Barbas (2006, 2007) published XRPD patterns of Forms A, B and C. Structure for Form A is known, so it can be used to identify this form in the raw materials and products. As the Forms B and C have unknown structures, the diffraction data available in the literature may be used to identify these forms. However, data published by these two authors are not consistent. The XRPD patterns of Form B published by Barbas in 2006 and 2007 are not similar. The powder pattern of 2006 presents some peaks in equivalent positions and intensity of the patterns presented by the author in 2007 and other peaks at different positions.

Mebendazole and norfloxacin are examples of API, which present polymorphism, although not all polymorphic forms have known crystal structures.

Mebendazole is an antihelminthic indicated for the treatment of parasitic worms. It has three anhydrous polymorphic forms reported in the literature: A, B and C, and only the Forms A and C have known crystal structure described by Ferreira, et al. (2010) and Martins, et al. (2009) respectively. Tables of interplanar distances versus relative intensities are available for Form B, as published by Kachrimanis et al. (2010), Swanepoel et al. (2003), Rodriguez-Caabeiro et al. (1987) and de Villiers et al. (2005). Brusau et al. (2008), Swanepoel et al. (2003) and Brits et al. (2010) published only XRPD patterns. Himmelreich et al. (1977) and Aboul-Enein et al. (2002) mention the existence of Form B, but without providing information regarding X-ray powder diffraction. Polymorphs of mebendazole display significant differences in solubility. For example, according to Swanepoel et al. (2003) and de Villiers et al. (2005), the drugs that contains more than 30% of Form A have a reduced efficiency. The reduced toxicity and bioavailability make the form C preferred clinically (Brits et al., 2010).

Atorvastatin belongs to the statin class. Statin drugs are often prescribed for cholesterol (LDL - low density lipoprotein) management. The patent of the reference drug Lipitor® was described by Briggs (Briggs et al., 1999) for Pfizer, which presents the Form I of the atorvastatin calcium. Atorvastatin presents at least 19 crystalline forms described in the patents: Briggs (1999) for Forms I, II and IV; McKenzie (2000) for Form III; Byrn (2003) for Form V to Form XIX. The Form I was indexed and the complete data (2θ, d, I) was given by Antonio et al. (2008).

MATERIAL AND METHODS

The JST-XRD software was developed using the IDE (Integrated Development Environment) Lazarus (Lazarus, 2016), which is a free and open source development tool that allows visual and object-oriented programming. Lazarus provides a code editor, a visual form creation environment, Lazarus Component Library (LCL), debugger and the GUI (Graphical User Interface) integrated with the compiler Free Pascal.

Here we describe the latest version of JST-XRD software that incorporated several features since the previous version (Tanaka et al., 2015).

The JST-XRD software imports data from a file with the information (2θ, I100) or (d, I100), obtained from publications in patents or scientific journals. When peak position is given in 2θ it is converted into interplanar distance using Bragg's law:

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

where: d is the interplanar distance, λ is the X-ray wavelength and θ is the angle of incidence of the X-ray beam (Bragg angle).

Thus, imported data are stored in a specific folder in the format (d, I100) and the compound name is entered in the list as available for use. It was decided to store data in the form (d, I) considering that d does not depend on the wavelength used in the measurement.

In order to plot the XRPD pattern, user can choose among (2θ, I), (d, I) and (Q, I) where Q=2θ/d. The user can also vary the peak width, plot step size, line color, line width and the initial and final 2θ, d or Q or simply accept the default values (Fig. 1). To plot in (2θ, I), one should choose the wavelength of the incident radiation: Cu, Cr, Fe, Co, Mo. If the wavelength is not in the list, it can be provided in "Other".

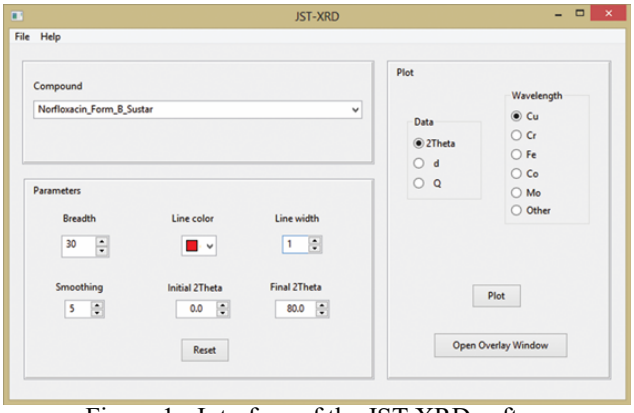

Figure 1 - Interface of the JST-XRD software.

Once the XRPD pattern is plotted, user can change any of the parameters in the interface and replot it as often as desired. The user can also save the image of the pattern under visualization.

The peak profile is Gaussian (Eq. 1) with breadth controlled by the user.

$$y(x) = I \cdot e^{-\frac{(x-x_0)^2}{2w^2}} \qquad (1)$$

where I is the relative peak intensity, x0 is the Bragg peak position (2θ, d or Q) and w is the full width at half maximum of the Gaussian.

At the points where peak profiles overlaps, the resulting intensity y(x) is the sum of the contribution of the profiles at that point x, according to Eq. 2.

$$y(x) = \sum_j I_j \cdot e^{-\frac{(x-x_{0j})^2}{2w_j^2}} \qquad (2)$$

Menu "File" in the "Diffractogram" window of the JST-XRD software allows user saving the diffractogram image as well as the XY data corresponding to the generated point-to-point intensity.

"Overlay-XRD" window (Fig 2a) allows selecting up to 10 patterns generated by JST-XRD. For any of the calculated patterns, user can change line color, maximum intensity, apply peaks shift related to sample displacement S and apply a Y (y-axis) displacement. Any compound added in the list "Patterns" can be replaced any time.

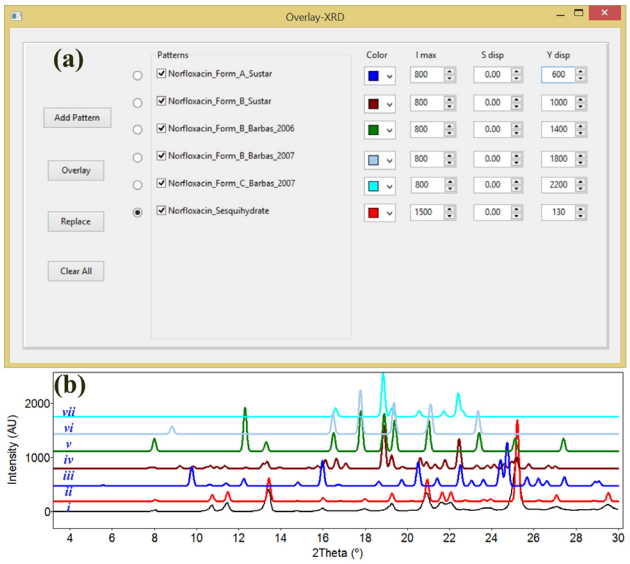

Figure 2 - (a) Selecting patterns to overlay. (b) part of the "Diffractogram" window with superimposed XRPD patterns (i) imported observed XY data, (ii) sesquihydrate, (iii) Form A Sustar, (iv) Form B Sustar, (v) Form B Barbas 2006, (vi) Form B Barbas 2007 and (vii) Form C Barbas.

An observed data can be plotted for comparison (Fig. 2b) through overlays with any or all the listed pattern presented in the "Overlay-XRD" window. The observed pattern can be corrected for 2θ0 and moved vertically.

The software JST-XRD is available at the site http://labcacc.iq.unesp.br/jst-xrd with all the data used in this paper and news about the software and laboratory notes.

RESULTS AND DISCUSSION

Case 1: Norfloxacin API raw material

The first example is the analysis of an active pharmaceutical ingredient of norfloxacin sesquihydrate using the JST-XRD.

Primarily, (d,I) or (2θ,I) data for norfloxacin were imported to the JST-XRD list of compounds: Form A and B described by Sustar (1993); Form B and C described by Barbas (2006, 2007) and Form sesquihydrate described by Ravindra (2009). Form A Sustar (1993), Form B Sustar (1993), Form B Barbas (2006), Form B Barbas (2007) and Form C Barbas (2007) are represented in Figure 2b. The sesquihydrate data was obtained by pattern decomposition of the observed powder pattern of a pure sesquihydrate sample using the Topas Academic v5 (Coelho, 2012). It can be seen that the two Forms B described by Barbas in different years (2006, 2007) display different peak sets (overlapping and non-overlapping peaks). By comparing of Form C described by Barbas (2007) with Form B described by Sustar (1993), it is observed that every peak of Barbas Form C is present in the pattern of Sustar Form B. Based in these data, the user cannot be able to decide among one of these Forms.

Table 1 - 2Theta (2θ) versus relative intensity (I) for the Forms A, B, C and sesquihydrate of norfloxacin

Form A (Sustar)		Form B (Sustar)		Form B (Barbas 2006)		Form B (Barbas 2007)		Form C (Barbas)		Form sesquihydrate (Ravindra)	
2θ	I	2θ	I	2θ	I	2θ	I	2θ	I	2θ	I
5.55	1	7.77	2	8.0	28.6	8.84	16.81	16.59	19.31	8.04	1.77
9.76	44	7.96	3	12.3	100	16.47	44.46	18.86	100	9.39	0.05
10.62	3	9.20	6	13.3	21.4	17.77	100	19.24	19.58	10.74	7.66
11.39	6	9.83	5	16.5	42.8	19.36	71.41	20.54	13.30	11.47	11.60
12.23	16	10.45	3	17.8	92.8	20.98	16.73	21.71	11.99	13.42	28.46
14.80	8	10.65	6	18.9	85.7	21.11	63.63	22.43	53.36	14.78	0.29
15.95	58	10.95	4	19.4	71.4	23.35	52.46	22.60	12.05	15.98	3.96
16.71	3	11.33	6	21.0	71.4					16.81	0.33
18.62	10	12.33	2	23.4	42.8					17.98	2.99
19.71	14	13.14	11	25.1	28.6					19.24	9.61
20.49	55	13.34	15	27.4	28.6					20.21	0.40
21.39	17	13.93	3							20.93	26.96
22.49	48	15.32	2							21.60	10.94
23.02	12	15.73	6							22.04	11.11
23.58	14	16.10	20							22.72	1.48
24.36	38	16.62	23							23.58	1.81
24.71	100	17.07	12							23.90	2.62
24.43	27	18.86	100							25.21	100
25.65	20	19.24	30							26.19	1.30
26.19	17	19.75	4							27.08	7.40
26.58	11	20.59	24							28.87	0.53
27.42	20	20.88	15							29.45	10.67
28.87	9	21.29	9								
29.06	10	21.76	20								
		22.43	68								
		23.26	7								
		23.77	7								
		24.10	9								
		24.57	11								
		24.92	16								
		25.13	24								
		25.72	10								
		26.66	7								
		26.99	5								

In the Figure 2b the observed data (black line) is plotted together with all the Forms selected in Figure 2a. In this figure it is observed that the sesquihydrate form seems to be the one present in the raw material.

All data shown in Table 1 is standardized in (2θ, I) with λ =1.5404, but originally some data were presented in (d, I).

Case 2: Norfloxacin marketed tablet

The first tablet selected for comparison was from one norfloxacin product acquired in one drugstore in the city of Araraquara - Brazil. Its diffractogram is represented by the black line in the Figure 3, which is the saved image from JST-XRD. Also plotted in the Figure is the powder patterns of the Forms A and B of the Sustar (1993), sesquihydrate Form (Ravindra et al., 2009) and excipient magnesium stearate (private data from one sample of the laboratory authors). The powder diffraction pattern of Form B and magnesium stearate were rescaled to fit the observed intensities. In the Figure 3, it can be seen that all the peaks have been identified, even those of low intensity. Thus, it is concluded that the analyzed tablet has the mixture of forms A and B described by Sustar (1993).

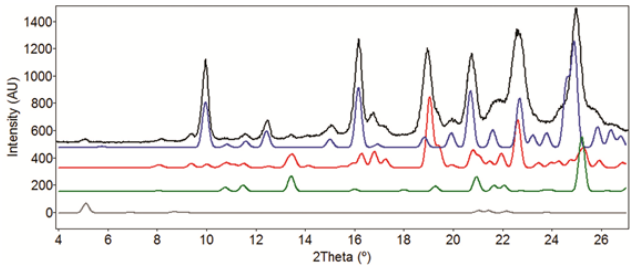

Figure 3 - Overlay of reference norfloxacin tablet (black), Form A of Sustar (blue), Form B of Sustar (red), sesquihydrate Form (green) and magnesium stearate (pink). All patterns were shifted vertically to improve the visualization

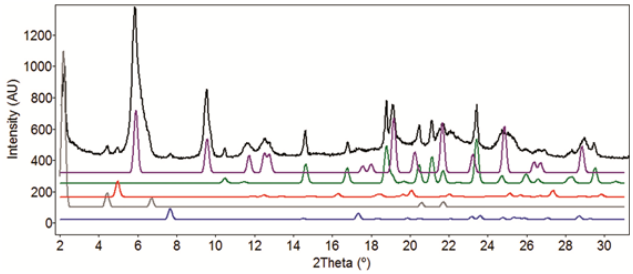

Figure 4 - Observed data of a mebendazole (black) and diffraction pattern of Forms A (blue), B (wine), C (red) and excipients beta D-mannitol (green) and sodium lauryl sulfate (gray). All patterns were shifted vertically to improve the visualization.

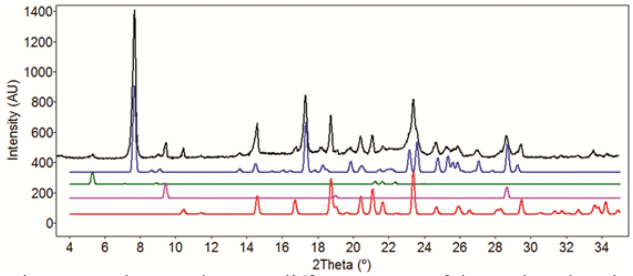

Figure 5. Observed X-ray diffractogram of the mebendazole (black). In blue is the XRPD pattern of mebendazole Form A. The excipients identified in the sample are Mg stearate (green), talc (pink) and beta D-mannitol (red). All patterns were shifted vertically to improve the visualization.

Case 3: Mebendazole marketed tablet

The mebendazole tablet selected for comparison was from one product acquired in one drugstore in the city of Araraquara - Brazil.

The Figure 4 shows the observed diffractogram in black and the identified API: Form A, B, C of mebendazole and the excipients beta D-mannitol and sodium lauryl sulfate. Powder patterns of Forms A, B, C and of the excipient beta D-mannitol were rescaled to fit their intensity in the observed diffractogram. Sample displacement was applied for the sodium lauryl sulfate, beta D-mannitol, mebendazole Form B and C to fit the peak position.

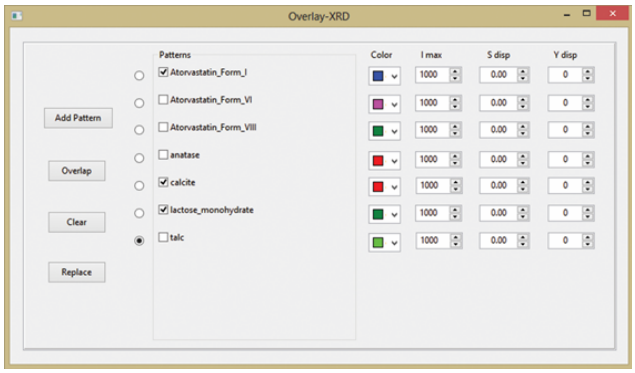

Figure 6 - Overlay-XRD window showing all three forms of atorvastatin and the excipients commonly used in atorvastatin tablets.

The third tablet example is for another mebendazole, which was commercially acquired in Araraquara city - Brazil.

Figure 5 shows a saved JST-XRD image of the observed diffractogram of mebendazole tablet. The XRPD patterns of mebendazole Form A is present. The excipients identified in the sample are Mg stearate, talc and beta D-mannitol. It is possible to note the good agreement for all the crystalline phases identified in the sample through the X-ray powder diffraction patterns and the software JST-XRD.

Case 4: Atorvastatin Calcium tablet

The forth case is for the atorvastatin calcium tablet, also acquired at the city of Araraquara - Brazil.

The Figure 6 is an image of the "Overlay-XRD" window of JST-XRD, with the Form I, VI and VIII of atorvastatin calcium together with some excipients normally observed in tablets of this API. In this figure one can note that only the atorvastatin Form I and the excipients calcite and lactose monohydrate are checked and these are the compound identified in the tablet and shown in Figure 7.

In the Figure 7b and 7c are magnifications where one can observe in details the Bragg peaks for the compounds identified.

In the examples, crystalline phases of API and excipients could be adequately identified using the facilities of peak shift due to sample displacement and/or 2θ0, vertical pattern displacement, pattern scaling and peak broadening. The software also proved to be a good tool to help in the identification of polymorphic mixtures in tablets and raw materials, for the case when the crystal structures are unknown.

The JST-XRD is suitable for XRPD phase identification. Besides its potential of practical use in R&D, it has also the potential for use as teaching tool in experimental and/or theoretical classes about the use of X-ray powder diffraction for phase identification. Concerning the educational application, the authors are

providing, as supplementary material, a short theoretical note and laboratories guides for two experiments.

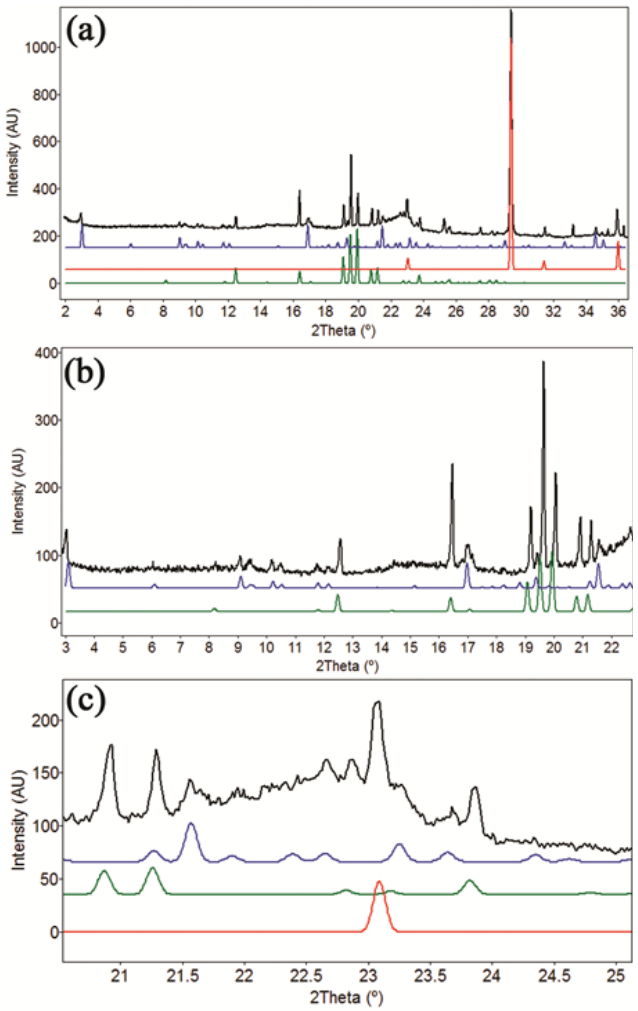

Figure 7 - (a) Full observed pattern of the atorvastatin calcium tablet (black) with the XRPD pattern of atorvastatin Form I (blue), and the excipients lactose monohydrate (green) and calcite (red), with vertical shift of the patterns to improve the visualization. (b) Magnification between 3° and 22°(2θ) with vertical shift of the patterns. (c) Magnification between 20.8° and 25.2°(2θ) with vertical shift of the patterns.

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RESUMO

Uso do software JST-XRD para identificação de fases cristalinas em insumos farmacêuticos e medicamentos

O estudo do polimorfismo é de grande importância na indústria farmacêutica porque os polimorfos podem apresentar diferentes propriedades físico-químicas, podendo resultar em diferenças na estabilidade e desse modo causar problemas nas etapas de manufatura e no produto final. Embora a pesquisa de moléculas orgânicas que apresentam polimorfismo tenha aumentado bastante nas últimas décadas, ainda não contempla todas as necessidades do mercado farmacêutico. Para a identificação de polimorfismo podem ser utilizadas técnicas como espectroscopia na região do infravermelho, ressonância nuclear magnética, análise térmica (DSC), difração de raios X, etc. O polimorfismo, por ser uma propriedade do estado sólido e cristalino, pode ser avaliado através da difração de raios X, já que cada polimorfo apresenta um padrão de difração de raios X único. O programa JST-XRD é uma ferramenta projetada para auxiliar a identificação de fases cristalinas, incluindo polimorfos, presentes em insumos farmacêuticos e comprimidos, usando dados de difração de raios X obtidos em artigos científicos e patentes. Esse trabalho apresenta novas implementações no JST-XRD e descreve seu uso na análise de amostras de princípio ativo e comprimidos comerciais de norfloxacino, mebendazol e atorvastatina cálcica. Através das comparações realizadas, JST-XRD permitiu identificar todas as fases cristalinas dos difratogramas dos fármacos analisados, mostrando que o programa é adequado para pesquisa em polimorfismo; na pré-formulação e controle de qualidade em indústrias farmacêuticas, assim como para uso didático em cursos de graduação e pós-graduação a fim de mostrar as potencialidades da difração de raios X na análise de polimorfismo.

Palavras-chave: Difração de Raios X. Polimorfos Cristalinos. Insumos Farmacêuticos. Análise de Fase Qualitativa. Lazarus. Software.

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