

Rietveld Method in the Analysis of Polymorphism in Mebendazole Tablets Acquired in Brazil's Drugstores

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Mebendazole (MBZ) is an anthelmintic medicine known to exhibit the polymorphs A, B and C, where polymorph C is the one indicated for tablets. Mebendazole commercial tablets (references, generics and similars) were analyzed in this work using X-ray powder diffraction data and the Rietveld method (RM) aiming at characterizing and quantifying crystal phases. Form C was found in mixture with form A in formulations of 500 mg (reference and generic). One of the generics presented a batch with form B and another one with form C. All the other tablets presented form A.

Keywords: X-ray powder diffractometry, polymorphism, mebendazole, Rietveld method

Introduction

Mebendazole (MBZ), (5-benzoyl-1H-benzimidazol-2-yl)-carbamic acid methyl ester, is a synthetic broad-spectrum anthelmintic medicine widely indicated for the treatment of simple or mixed infestations.

According to the World Health Organization (WHO), more than 2 million people have some sort of worm or parasite in their bodies, and they do not know about it.¹ Schistosomiasis is a parasitic disease that is largely common and known to affect about 200 million people in the world.² Once the proper treatment fails to be done, the parasitic disease can cause a permanent damage in humans and in extreme cases it may even lead to death.

There are three classes of drugs in Brazil (reference, generic, and similar), which are designated by the law and defined by the Brazilian Regulatory Agency known as Agência Nacional de Vigilância Sanitária (ANVISA). Since 2003, all new similar or generic drugs must present the same bioequivalence of the reference drug to be approved by ANVISA to be distributed to the market.³ After 2014, all similar drugs sold in the Brazilian market shall present the same bioequivalence of the reference ones. The samples analyzed in this work were produced according to the old rules, where the similar, and only the similar, was not necessary to present the bioequivalence tests.

MBZ, a basic Biopharmaceutics Classification System (BCS) class II drug, is poorly BCS soluble. In addition, MBZ is known to exhibit polymorphism and according to the International Conference on Harmonisation (ICH) Q6A guideline,⁴ decision 4, the presence of polymorphs must be rigorously controlled in the case of drugs that are not highly BCS soluble in order to ensure that the drug bioavailability will not undergo any alteration. Polymorphism can be defined as the capacity of a molecule to crystallize in more than one crystal structure.⁵ The polymorphism in pharmaceutical solids can be related to the differences in bioavailability of the active pharmaceutical ingredient (API) since different polymorphs are known to exhibit distinct physicochemical characteristics, such as color, melting point, solubility, hygroscopicity, internal energy, enthalpy and entropy.⁶

MBZ exhibits three known polymorphic forms: A, B and C, which exhibit differences in terms of solubility, stability and therapeutic activity.⁷ The solubility of MBZ in acid environment is B > C > A.⁸ According to Rodriguez-Caabeiro *et al.*,⁹ after carrying out some tests in mice, the form C resulted as the most suitable one for use in anthelmintic treatments due to its lower toxicity in comparison to the form B, although both of them have presented similar anthelmintic effects. Among all polymorphic forms of mebendazole, form A is the one that presented the lowest effectiveness.⁹ In spite of this fact, mixtures of MBZ polymorphs are commonly found

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in solid formulations around the world and Brazil is not an exception.¹⁰ The presence of only polymorph A in tablets, or above 30% is known to have no therapeutic activity.¹¹ De Villiers *et al.*⁷ recommend the use of X-ray powder diffraction (XRPD) to investigate polymorphism in tablets of MBZ.

The crystal structure of the polymorph A was described by Ferreira *et al.*¹² and the crystal structure of the polymorph C by Martins *et al.*¹³

Polymorph B, on the other hand, has only its characteristic peaks reported by several authors without any description of its crystal structure: Rodrigues-Caabeiro *et al.*,⁹ Costa *et al.*,⁸ Swanepoel *et al.*,¹⁴ de Villiers *et al.*⁷ and Kachrinaniis *et al.*¹⁵ In the diffractograms reported by these authors, the following common peaks (d-spacings) can be observed: 9.36, 4.65, 4.11 and 3.62 Å. The diffractograms observed by Rodrigues-Caabeiro *et al.*,⁹ Costa *et al.*⁸ and de Villiers *et al.*⁷ are found to be very similar. The first most intense peak can be seen at 4.65 Å, while the second one is found at 9.36 Å as reported by all the authors except Kachrinaniis *et al.*,¹⁵ who reported the most intense peak at 14.62 Å.

There are several techniques used for characterizing polymorphs. These include spectroscopy [infrared (IR), Raman, nuclear magnetic resonance (NMR)],¹⁶⁻¹⁸ thermal analysis [thermogravimetry (TG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC)], microscopy [scanning electron microscopes (SEM), transmission electron microscope (TEM), field emission gun (FEG)], which can provide information concerning the existence of polymorphism, its stability, hydration, besides indicating material crystallinity.^{16,19,20} For the purpose of investigating the crystal structures in tablets,

the Rietveld method (RM)²¹ with X-ray powder diffraction data is the most suitable tool. It allows the identification and quantification²² of crystalline phases, and where the amorphous content is likely to be determined, the addition of an internal standard is used.²³ For the use of the RM is mandatory the knowledge of the crystal structure models of all crystalline phases present in the sample.

In this work, commercial tablets of MBZ available on the Brazilian market were analyzed by the RM using XRPD data. Also, it was possible to determine the relative amount of polymorphic forms A and C of MBZ. As aforementioned, the lack of a description of the crystal structure of form B⁸ only allowed us its identification in tablets.

Experimental

Samples

13 batches of MBZ tablets were purchased from drugstores in the city of Araraquara, SP, Brazil, between July/2009 to October/2010. The tablets included two reference formulations, five generic formulations and two similar³ formulations. The identification of all drugs analyzed are shown in Table 1.

X-ray powder diffraction

Prior the measurements, the tablets had their coatings removed and subsequently were milled in agate mortar and sieved through a mesh 200. The obtained powders were softly pressed in a 20-mm diameter and 0.2 mm depth sample holder.

Table 1. Nomenclature system for the mebendazole tablets analyzed, with manufacture and expiration dates, and presentation, as declared by the manufacturer prescribing information

Drug class	Sample code	Date of manufacture	Date of expiration	Presentation / mg
Reference	R-01	11/2008	11/2013	500
Reference	R-02	7/2008	7/2011	100
Generic	G-01	10/2009	10/2012	100
Generic	G-02 batch L1	5/2009	5/2011	100
Generic	G-02 batch L2	2/2010	2/2012	100
Generic	G-02 batch L3	5/2010	5/2012	100
Generic	G-03	11/2007	11/2010	500
Generic	G-04	8/2008	8/2010	100
Generic	G-05	10/2009	10/2012	100
Similar	S-01 batch M1	6/2009	6/2011	100
Similar	S-01 batch M2	8/2009	8/2011	100
Similar	S-01 batch M3	12/2009	12/2011	100
Similar	S-02	7/2008	7/2011	100

Table 2. Unit cell dimension and space group of the forms A, B and C of the MBZ and excipients α -lactose-monohydrate, β -D-mannitol and talc used in refinements

Unit cell parameter	Form A ¹²	Form C ¹³	Lactose ^{a 29}	β -D-Mannitol ³⁰	Talc
a	5.5044(2) Å	5.1480(9) Å	7.982(2) Å	8.672(8) Å	5.293(3) Å
b	11.2872(2) Å	7.8779(15) Å	21.562(3) Å	16.875(1) Å	9.179(3) Å
c	12.5276(5) Å	17.907(3) Å	4.824(1) Å	5.560(5) Å	9.469(3) Å
α	66.694(2)°	82.425(6)°	90°	90°	90°
β	82.959(2)°	82.743(7)°	109.57(3)°	90°	90°
γ	78.444(2)°	71.091(13)°	90°	90°	90°
Z	2	–	2	4	2
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1$	$P2_12_12_1$	$C\bar{1}$

^a α -Lactose monohydrate.

The XRPD data of all tablets were obtained in the range of 2 to 30° (2 θ) with $\Delta\theta = 0.02^\circ$ using a Rigaku RINT2000 copper (CuK α) rotating anode diffractometer operating at 42 kV and 120 mA. A receiving slit of 0.3 mm, divergence slit of 0.25 mm, 2.5° divergence Soller slit and a curved graphite monochromator in the diffracted beam were used.

Rietveld refinement

The refinements were performed using the Topas Academic v.4.2 software.²⁴ The fundamental parameters model²⁵ implemented in the program was used to adjust the peak broadening. The crystallite size was refined considering an anisotropic form, having independent lorentzian and gaussian components for the family of planes (h00), (0k0), (00l), (hk0), (h0l), (0kl) and (hkl).²⁶ The background was adjusted using a Chebyshev polynomial.²⁷

The unit cell parameters were refined together with the parameters for the correction of the preferred orientations artifacts using the spherical harmonics model (four terms).²⁸ The atomic coordinates of the crystal structures were kept fixed at the published values.^{12,13}

The crystallographic data for forms A and C are shown in Table 2. The crystal structure model of form B has not yet been reported, and in this work, the information about the interplanar distance d x intensity available were obtained from Costa *et al.*,⁸ Table 3, were used to identify this polymorph in the tablets.

The crystal structures of the excipients α -lactose-monohydrate, β -D-mannitol and talc were used in some refinements and their unit cell dimensions and space groups are also listed in Table 2.

Results

The polymorphs of MBZ show intense and characteristic peaks in the region between 4 and 10° (2 θ), which are

Table 3. Position and intensity (I100) of the form B

Form B ⁸	
Diameter / Å	Intensity (I100) / %
14.62	60
9.36	83
7.26	42
7.08	47
4.65	100
4.55	42
4.21	46
4.11	63
3.92	46
3.62	67
3.52	50
3.11	40
3.09	43

useful in aiding the visual differentiation among the three polymorphs A,¹² B⁸ and C,¹³ as can be observed in the simulated patterns shown in Figure 1. The Topas Academic v.4.2 software was used to simulate the powder patterns from the crystallographic information framework (cif)

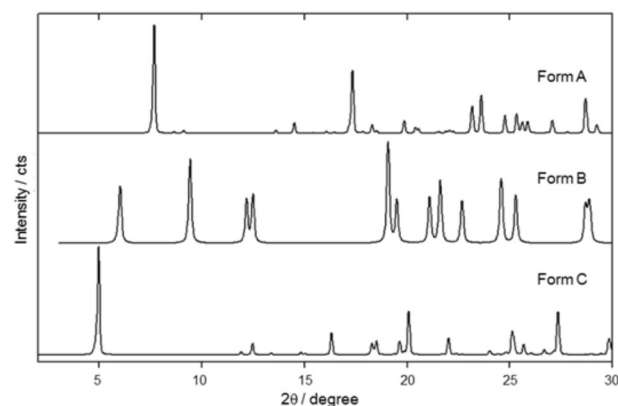


Figure 1. Simulated patterns of forms A, B and C using the Topas Academic v.4.2 software. Powder patterns of forms A and C were simulated from the reference crystal structures,^{12,13} while form B was simulated on the basis of the reference characteristics peaks.⁸ The region ranging from 2 to 10° (2 θ) is related to the characteristic intense peaks of the three polymorphic forms of MBZ, which can be used for phase identification.

files for form A and C, and data reported in the literature were provided in Table 2 for form B. All simulations were done considering an average crystallite size of 100 nm. The intense peaks presented by forms A, B and C were found at 7.68°, 6.02° and 4.98°, respectively.

The excipients used in the tablets and those informed in the package insert of each medicament can be found in the Supplementary Information (SI) section. The crystal structures of the excipients lactose (α -lactose monohydrate),²⁹ mannitol (β -D-mannitol)³⁰ and talc (100682-ICSD) were used in the analyses.

The typical Rietveld plot showed in Figure 2 (sample R-01) is represented by the observed diffracted pattern (●), the calculated one (continuous line), and the difference between them as well as the Bragg peaks positions (|) of each crystalline phase present in the sample. The amorphous phase (excipients and possible fractions of the API) does not present Bragg peaks and its contribution to the diffractogram is in the background. The results from quantitative phase analysis (QPA) and the refinement agreement indexes³¹ of all samples (references, generics and similar) are listed in Table 4.

Reference medicaments

R-01

The Rietveld plot of sample R-01 is shown in Figure 2. This tablet presents 95.5(3) wt.% of form C and 4.5(3) wt.% of form A. The most intense peak of form A is indicated by the arrow.

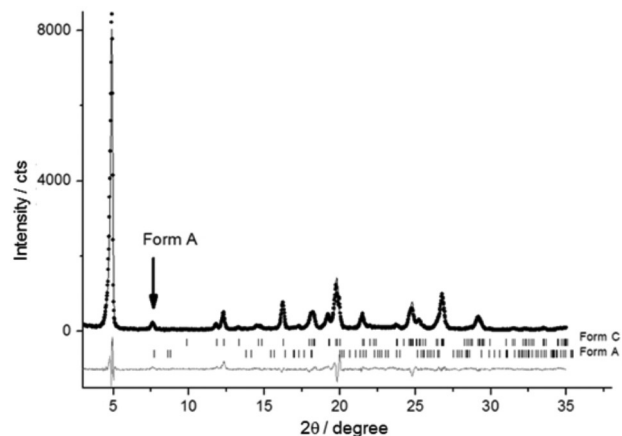


Figure 2. Rietveld plot of sample R-01. The arrow indicates the most intense peak of form A of mebendazole.

R-02

This other reference tablet, R-02, contains only the form A of MBZ, and the crystalline excipients β -D-mannitol and talc (Figure 3).

Generic medicaments

G-01

The generic G-01 exhibited the form A of the API as well as the excipients β -D-mannitol and talc in crystalline form.

G-02 (batch L1)

In the case of the G-02-L1, form B peaks reported by Costa *et al.*⁸ were observed at d-spacings = 14.62, 9.36,

Table 4. Rietveld refinement agreement factors (R_{wp} and χ^2) of the reference, generic and similar tablets. QPA obtained in method Rietveld and relative percentage (RP) on API in the tablets to mebendazole forms

	R_{wp} / %	χ^2	Form A [RP] ^a / %	Form C [RP] ^a / %	Mannitol / %	Talc / %	Lactose / %	Mg St ^b / %
R-01	10.84	1.56	4.5(3) [4.5]	95.5(3) [95.5]	—	—	—	—
R-02	15.52	3.75	50 (3) [100]	—	43.79(3)	5.8(6)	—	—
G-01	12.04	2.02	65.6(7) [100]	—	28.8(6)	5.6(2)	—	N.Q. ^c
G-02-L1	12.69	2.69	3.9(3) [42.4]	5.3(3) [57.6]	90.72(5)	—	—	—
G-02-L2	9.67	4.36	—	66.2(3) [100]	33.8(3)	—	—	—
G-02-L3	11.17	3.71	—	68.7(6) [100]	31.3(5)	—	—	—
G-03	11.68	2.91	4.5(3) [5]	84.4(7) [95]	—	2.1(2)	8.9(6)	—
G-04	9.84	1.37	94.1(4) [100]	—	—	5.9(4)	—	—
G-05	12.00	2.46	100 [100]	—	N.Q. ^c	—	—	N.Q. ^c
S-01-M1	9.38	3.86	90.7(3) [100]	—	—	—	9.3(3)	—
S-01-M2	6.75	1.56	85(1) [100]	—	—	2(1)	13(1)	—
S-01-M3	11.47	2.75	100 [100]	—	—	—	—	—
S-02	10.30	1.46	93.7(4) [100]	—	6.3(4)	—	—	—

^aThe relative percentage of API in the tablets can be found in square brackets: [RP]; ^bMg St: magnesium stearate; ^cN.Q.: identified, but not quantified. Between brackets are the standard deviations obtained at the end of the refinement: (standard deviation). R_{wp} and χ^2 : Rietveld refinement agreement factors.

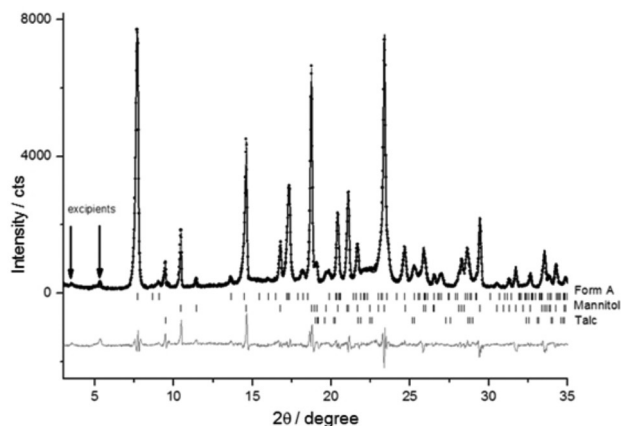


Figure 3. Rietveld plot of sample R-02. The arrows indicate the peaks of the excipient magnesium stearate that were not adjusted in the refinement owing to the fact that its crystal structure has not been reported.

7.26, 7.08, 4.65, 4.55, 4.21, 4.11, 3.92, 3.62, 3.52, 3.11 and 3.09 Å. The Rietveld plot of G-02-L1, depicted in Figure 4, shows the peaks of form B (indicated by solid vertical lines). The low intense peak in $2(\theta) = 4.43^\circ$ ($d = 19.9$ Å) corresponds to sodium lauryl sulfate, a crystalline excipient. Besides form B, this figure also shows two peaks of forms A and C and some peaks related to unidentified compounds, in $2(\theta) = 6.35^\circ$ and 11.64° ($d = 14.3$ and 7.6 Å). Eight other batches of this same product were analyzed and only polymorphic form C of MBZ was identified.

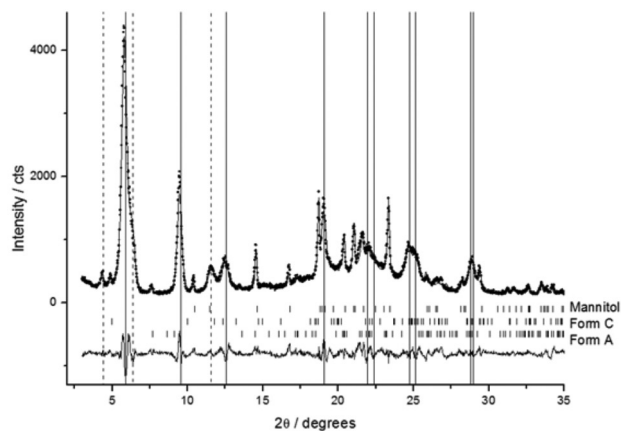


Figure 4. Rietveld plot of sample G-02-L1. Vertical solid lines indicate the peak positions of form B while the vertical dashed lines are the excipients peaks after refinements.

G-02 (batches L2 and L3)

G-02-L2 was produced nine months after batch L1, and the following batch L3 was produced twelve months after batch L1. The latter ones (L2 and L3) showed the same results. The Rietveld plot obtained for batch L2 is shown in Figure 5 and forms B and A are not present in the sample. Only peaks of form C of

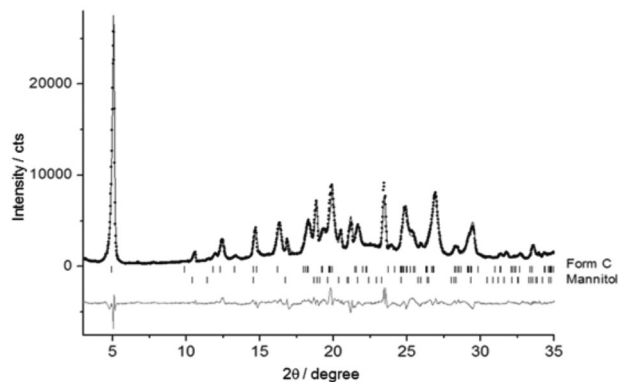


Figure 5. Rietveld plot of sample G-02-L2.

MBZ and the excipient β -D-mannitol were identified in the refinement.

G-03

The Rietveld plot of the generic sample G-03 of 500 mg (Figure 6) shows the peaks of form A, form C, the crystalline excipient α -lactose-monohydrate and one peak at 9.5° (2θ) that was attributed to the most intense peak of the excipient talc, although it is not listed in the prescribing information. This peak at 9.5° is found to be the most intense one for this excipient and it appears without overlapping with other peaks. The second most intense peak of talc appears at 28.6° , overlapping with form A peaks of MBZ as can be seen in the inset of Figure 6.

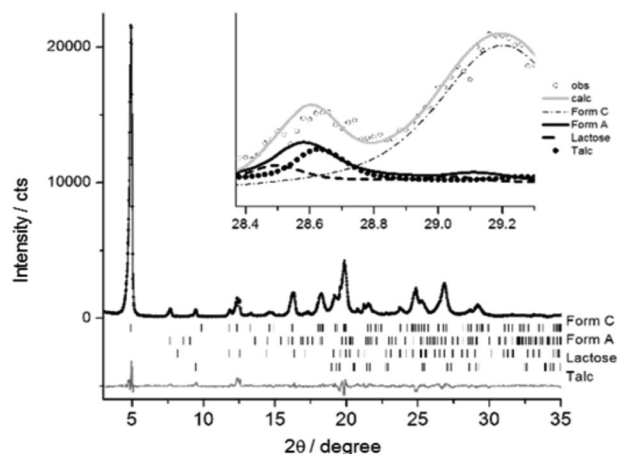


Figure 6. Rietveld plot of a sample G-03.

G-04

The Rietveld plot of sample G-04 (Figure 7) shows the peaks of the form A of MBZ and of the crystalline excipient talc.

G-05

The Rietveld plot of the G-05 sample (Figure 8) shows only the peaks of form A of mebendazole.

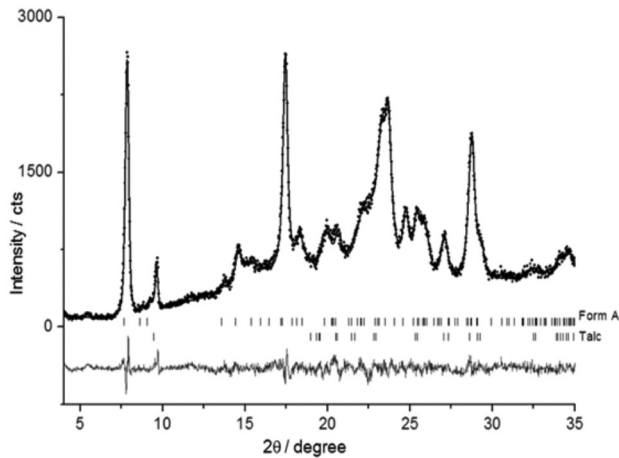


Figure 7. Rietveld plot of sample G-04.

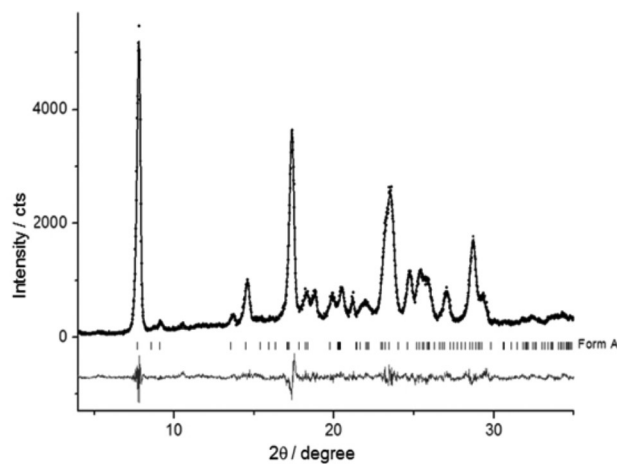


Figure 8. Rietveld plot of G-05 sample.

Similar medicaments

S-01 (batch M1)

Figure 9 shows the Rietveld plot of sample S-01-M1 where we could identify the peaks of form A of MBZ as well as of the excipient α -lactose-monohydrate present in the medicament.

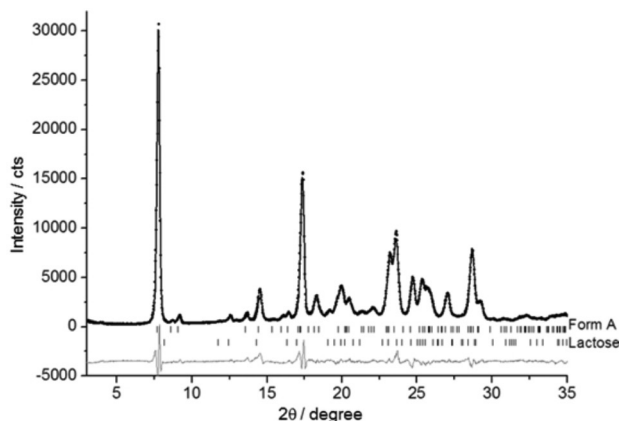


Figure 9. Rietveld plot of sample S-01-M1.

S-01 (batch M2)

Batch M2 was produced two months after batch M1. Its Rietveld plot is shown in Figure 10 with the peaks of form A of MBZ and the excipients α -lactose-monohydrate and talc.

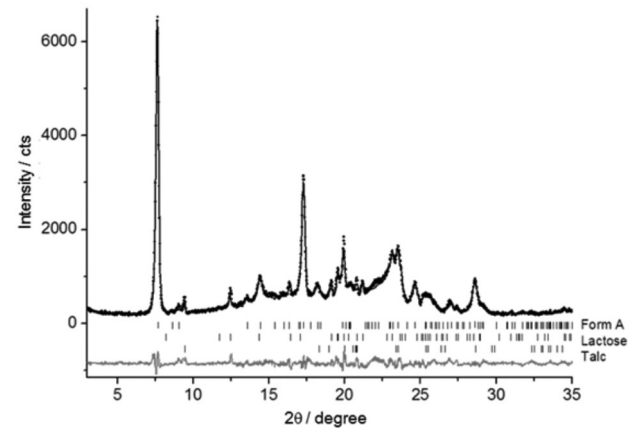


Figure 10. Rietveld plot of sample S-01-M2.

S-01 (batch M3)

Batch M3 was produced six months following the manufacture of batch M2. The Rietveld plot of batch M3 (Figure 11) shows only the peaks of form A of MBZ.

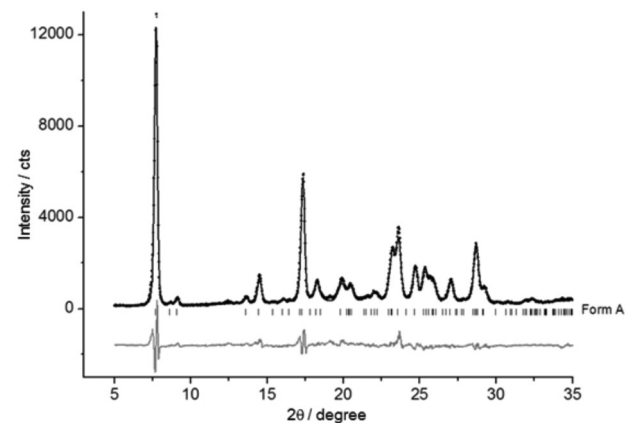


Figure 11. Rietveld plot of sample S-01-M3.

S-02

The Rietveld plot of sample S-02 (Figure 12) shows only the peaks of the form A and of the excipients β -D-mannitol. There are no unidentified peaks in this sample.

Discussion

The batches (with respective dates of manufacturing), presentation of formulation, code of sample and percentages found for each polymorph in the tablets can be seen in the SI section. Most of the tablets exhibits the polymorphic form A. Four tablets exhibited form C, being two of them of 500 mg and the other two of 100 mg. The 500 mg

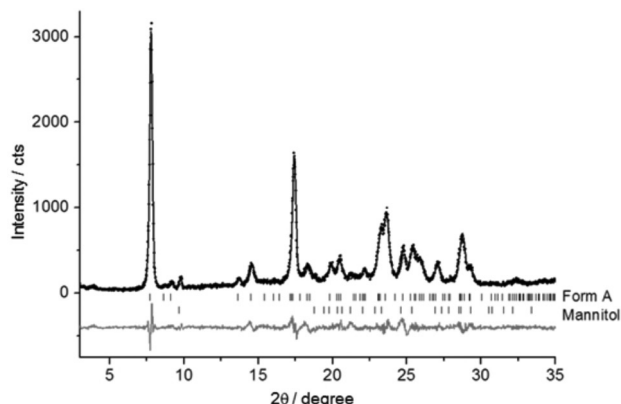


Figure 12. Rietveld plot of sample S-02 displaying the presence of only form A of MBZ and β -D-mannitol.

generic medicament (G03) mostly presented the same polymorph of the 500 mg reference (R01) one. Surprisingly, the 100 mg reference presented the polymorph A, which is the less efficient one among all polymorphs of mebendazole according to Rodriguez-Caabeiro *et al.*⁹ All other medicaments, except G-02, displayed the same polymorph A. G-02-L1 contains mostly the not recommended form B, and G-02-L2 and G-02-L3 present the form C, which is the most appropriate form according to Rodriguez-Caabeiro *et al.*⁹ Unfortunately, the solubility tests of the medicaments could not be performed to look for a correlation with the polymorphs found in the tablets.

Reference medicaments

In the reference tablet R-01 (Figure 2), all peaks in the powder pattern were adjusted during refinement, indicating that all the crystalline phases present in the tablet have been identified. No excipients peaks were observed. In this case, they can be present in amorphous form or perhaps their amount were so small that their peaks could not be observed. In the Rietveld plot for the sample R-02 (Figure 3), two peaks (located at 3.6° and 5.33°) were not adjusted during refinement, though they were attributed to the excipient magnesium stearate owing to the fact that the peak positions of the most intense reflections of this excipients are in the same 2θ positions as those in the sample.

Generic medicaments

Sample G-01 exhibits the form A of the MBZ as well as the excipients β -D-mannitol and talc in crystalline forms. The crystal structures of the two excipients are largely known and they could be employed in the Rietveld refinement. One low intense peak (5.31°) does not correspond to polymorphs of MBZ and neither to β -D-mannitol nor talc. This unknown peak in fact corresponds to the most intense peak of the

excipient magnesium stearate and could be identified by comparing it with the powder diffraction of this excipient.

The powder pattern of form B from the work of Costa *et al.*,⁸ was compared to the powder diffraction of G-02-L1, indicating the presence of this polymorphic form in the tablet. The peaks related to the form B from the work published by Costa *et al.*⁸ were included in the refinement, confirming the presence of this form in sample G-02. In the diffractogram, shown in Figure 4, the characteristic peaks of form B are more intense than the peaks of forms A and C, indicating that its presence in the tablet is larger than the other two. In the following batches of this medicament, G-02-L2 and L3, we could not verify the presence of form B. This can be associated with batch-to-batch reproducibility and/or different polymorphic forms of the active pharmaceutical ingredient, though the β -D-mannitol remains crystalline in all the batches analyzed for this medicament.

Sample G-03 exhibits the polymorphic form C of MBZ in a larger amount than form A. In the package insert of this medicament the talc is not declared, though the two most intense peaks of this excipient were identified in the refinement (Figure 6). It was possible to confirm its presence in the tablet by the Rietveld refinement.

This other sample, G-04, exhibits form A of MBZ and the increase observed in the baseline background indicates an amorphous content, which can be caused by amorphous excipient, cellulose microcrystalline for example.

The manufacturer of this sample is the same one responsible for the production of G-05 and S-02. In the generic medicament, all the excipients are found to be amorphous while in the similar one β -D-mannitol is seen to be present in crystalline form. The two tablets of this manufacturer exhibit form A of MBZ.

Similar medicaments

All the peaks have been identified in the S-01 batch M1 as well as the other excipients, with the exception of α -lactose monohydrate, which is presented in amorphous form. The M2 batch was manufactured two months following batch M1. There is a difference between the excipient talc of the latter two batches; it is found to be crystalline in batch M2 while it is amorphous in batch M1. A third batch of medicament S-01 was purchased, batch M3, which was manufactured six months following batch M1. However, there are no unidentified peaks for this sample. The results obtained indicate the crystallinity of the excipients may vary batch by batch. In the first batch there was only one excipient in crystalline form. In the batch manufactured two months following the first one there were

two excipients in crystalline form (α -lactose-monohydrate and talc). In the last batch, manufactured six months following the first one, all excipients were amorphous.

Conclusions

The four tablets analyzed: R-01, G-02 batches L2 and L3 and G-03, showed mostly form C; eight tablets (R-02, G-01, G-04, G-05, S-01 batches M1, M2 and M3; and S-02) showed form A and one (G-02 batch L1) showed mostly form B. One batch of medicament G-02 exhibited two peaks at 6° and 9.44°, which can be related to form B of MBZ. Other tablets showed the characteristic peak of form A, including the reference ones.

Medicaments available in the national market exhibit differing range of polymorphs in their composition.

It is worth noting that by means of XRPD and the RM it was possible to identify forms A, B and C besides quantifying forms A and C in the tablets, given the presence of mixtures of polymorphs.

Regarding excipients used in the manufacturing of tablets, a significant lack of quality control in the raw material has been observed. Some excipients that usually exhibit crystalline form in tablets showed an amorphous form, which undoubtedly raises questions as to the nature of the excipient in the formulation.

The methodology employed in this work, using XRPD and the overlapping of powder patterns obtained in the literature is remarkably interesting to regulatory agencies for the evaluation of polymorphism in commercial tablets and to the pharmaceutical industry in the production line for quality control purposes.

Supplementary Information

Supplementary information, including excipients on the package insert of each medicament, batches, presentation of formulation, code of sample and percentages found of each polymorph in the tablets, as well as simulation of forms B of the mebendazole described in the literature, are available free of charge at <http://jbcs.s bq.org.br> as PDF file.

Acknowledgments

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