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Polymorphism incidence in commercial tablets of mebendazole: a vibrational spectroscopy investigation

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Mebendazole is a broad spectrum anthelminthic drug, which is widely used in large scale deworming programmes. This active pharmaceutical ingredient exhibits three crystal forms, namely, polymorphs A, B, and C. Therapeutic trials suggested that the most stable form, polymorph A, is inactive. However, the dissolution test normally used as a quality control tool is not able to discriminate among the polymorphs of mebendazole. In this work, the ability of the vibrational spectroscopic techniques (mid and nearinfrared absorption and Raman scattering) for the identification of the crystal form of this compound is evaluated. On the basis of these observations, this methodology is applied to determine the polymorphs of MBZ used in the formulation of the commercial tablets available in the Brazilian and German markets. Copyright © 2008 John Wiley & Sons, Ltd.

KEYWORDS: mebendazole; polymorphism; Raman scattering; infrared spectroscopy; near-infrared spectroscopy

INTRODUCTION

Mebendazole (MBZ) (methyl 5-benzoyl-1H-benzimidazol-2-yl carbamate, Fig. 1) is a synthetic broad spectrum benzimidazole carbamate anthelmintic drug used for more than 20 years in human and veterinarian medicine to treat a variety of parasitic infestations. MBZ is active against nematodes and cetodes,[1] being indicated in the treatment of single or mixed infestation by *Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenal* and *Necator americanus* (hookworms), *Strongyloides stercoralis* and *Taenia spp*. The importance of these infections is evidenced by recent estimates indicating that one quarter of the world's population is infected with one or more of these parasites,[2,3] giving rise to a combined disease burden that might be as great as those of malaria or tuberculosis.[4,5] The broad spectrum of activity, high efficacy, ease of administration and low costs generic versions exhibited by MBZ mean that it is now widely used in large scale deworming programmes, most of them focused to school-aged children in developing countries.[6–8]

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One factor that may contribute to the variability in the efficacy of a pharmaceutical formulation is the polymorphism of the active pharmaceutical ingredient (API). Polymorphism is the ability of a chemical compound to exist in more than one crystalline form.[9] The different structural arrangements of the drug are followed by changes in physicochemical properties, which can affect its bioavailability, manufacturability, purification, stability, and other performance characteristics of the API.[10] Considering the benzimidazole carbamates commonly applied in deworming programmes, MBZ and albendazole, just the former exhibit polymorphism. In the solid state, MBZ crystallizes in three polymorphic forms, namely polymorphs A, B, and C. Several authors pointed out possible differences in the bioavailability of the polymorphs of MBZ.[11,12] Even though some discrepancies are reported in the literature about the relative solubility of forms B and C, all the authors agree that form A is the least soluble one.[11,13,14] Thus form C is pharmaceutically preferred since its solubility is sufficient enough to ensure optimal bioavailability without exhibiting the toxicity associated to form B.[11,13–15] Furthermore, a therapeutic trial in 958 school-aged children in Thailand using a placebo and the MBZ polymorphs A and C suggested that form A has similar efficacy than the placebo in controlling hookworm and whipworm infections.[11] Other authors also reported on the polymorph dependence of the

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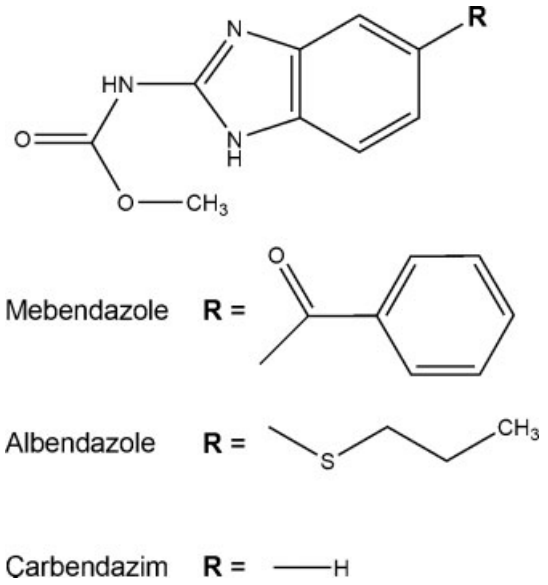

Figure 1. Schema of the mebendazole molecule and other benzimidazole carbamates.

anthelminthic efficacy of MBZ and proposed that at least 30% of the form A in the formulation is enough to suppress the desirable pharmacological activity.[12,16]

Owing to the very limited solubility of MBZ in water and organic solvents, which affects its absorption and behavior in the body, the Brazilian and United States pharmacopeias (USP) require the same dissolution test to ensure the quality of the tablets. Several authors verified that the prescribed dissolution test has no sensitivity to identify the polymorphs of MBZ.[12,15,17] Thus the necessity of modifying the USP dissolution test in order to adapt it to discriminate the MBZ polymorphs was repeatedly pointed out. Swanepoel *et al*.[15] investigated the influence of the dissolution medium in the effectiveness of the USP test showing that the dissolution properties of the three polymorphs are equal under these conditions. However, by using a slight modification of the dissolution medium, the polymorphs exhibited uneven profiles providing a method to discriminate between them. Nevertheless, since the solubility is directly determined by the crystal packing of the API molecules in the different polymorphs, experimental techniques sensitive to the crystal structure are advisable to perform this task.

Polymorphism in MBZ was usually investigated by X-ray diffraction.[18–21] This technique provides distinctive diffraction peaks that allow the identification of the MBZ polymorphs as pure or mixed forms. However, to the best of our knowledge no single crystal structure determinations have been performed in this compound depicting the nature of the crystal packing. Some insight on the intermolecular interactions was provided by the crystal structures of two MBZ salts (hydrogen bromide[22] and hydrogen chloride[23]) and a complex (propionic acid[24]). These structures show clearly the important role played by carbonyl and NH mediated hydrogen bonds in stabilizing the crystal lattice. The midinfrared absorption spectra exhibited characteristic signatures, mainly related to the carbonyl and NH stretching frequencies, used to fingerprint the crystalline forms.[18,20,25–27] These features were applied to quantify mixtures of the different crystalline forms by using internal reference and chemometric methods.[20,25,28]

Being considered a country where the helminthic infections represent a social problem and having a well-established generic-drugs program, the Brazilian market represents an interesting case of study.[29] The fact that several generic tablets of MBZ are available in this market combined with identification methods nonsensitive to the crystal structure could give raise to a wide distribution of solid forms. The aim of the present work is to investigate the distribution of polymorphic forms of MBZ in tablets available in the Brazilian market. Vibrational spectroscopy methods (mid and near infrared absorption and Raman scattering) were chosen to identity the crystalline form in tablets. Since, to the best of our knowledge, there are no reports on applications of Raman and near infrared techniques to the study of polymorphism in MBZ, we discuss first the main features of the Raman and near infrared spectra of the two polymorphs of MBZ usually found in pharmaceutical formulations (forms A and C). Following, this methodology was applied to commercial tablets, which were classified according to the corresponding crystalline forms.

Materials and methods

Polycrystalline samples of MBZ were kindly provided by Red Pharm and identified as form A and C using a Bruker AXS D8 Advance X-ray diffractometer. Representative tablets available in the Brazilian market were purchased directly from pharmacies. Several tablets containing 100 and 500 mg of MBZ and having API/excipients ranging from approximately 1 : 1 to 1 : 2, as well as an associated formulation of MBZ and thiabendazole (TBZ) (1 : 2 ratio) were investigated.

Mid infrared spectra were recorded on a Bruker IFS28 Fourier transform infrared (FT-IR) spectrometer with a spectral resolution of 4 cm^{-1}. KBr pellets of solid samples were prepared from mixtures of 200 mg KBr with 1 mg of sample in a laboratory press. FT-Raman spectra were recorded from the original samples on a Bruker IFS55 FTIR/FT-Raman spectrometer equipped with a Nd : YAG laser (1064 nm excitation line) and a liquid nitrogen-cooled Ge detector. FT-Raman spectra were acquired by accumulating 1024 scans at a spectral resolution of 4 cm^{-1}. Near infrared (FT-NIR) spectra were recorded from the original samples with a light fiber-coupled diffuse reflection probe on a Bruker Vector 22 spectrometer at a spectral resolution of 8 cm^{-1}.

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RESULTS AND DISCUSSION

As stated, infrared spectroscopy was widely used to identify the crystalline forms of MBZ. Raman spectroscopy is complementary to infrared allowing, due to differences in the selection rules, the observation of bands which could exhibit low intensity in the infrared spectroscopy. Figures 2 and 3 show the FT-IR and FT-Raman spectra of the two polymorphs of MBZ investigated in this work. Selected wavenumbers of the observed vibrational bands are listed in Table 1.

Let us first discuss briefly the vibrational spectra of MBZ based on the functional groups present in the molecule. Considering the Raman and infrared spectra of form C as a reference, it is interesting to compare our results with the vibrational spectra of benzimidazole,[30,31] carbendazim (methyl benzimidazol-2-ylcarbamate, Fig. 1)[32] and benzophenone.[33,34]

XH stretching modes

The IR spectrum of the ν(CH) and ν(NH) stretching modes region is characterized by a sharp and intense band around 3400 cm^{-1} corresponding to one ν(NH) stretching mode. By comparing these spectra with the ones of benzimidazole and carbendazim, it is possible to associate this band with the NH bond belonging to the carbamate moiety, since no intense IR bands of this character are observed in benzimidazole but a similar band is present in carbendazim. On the other hand, MBZ exhibits the broad infrared band around 2900 cm^{-1}

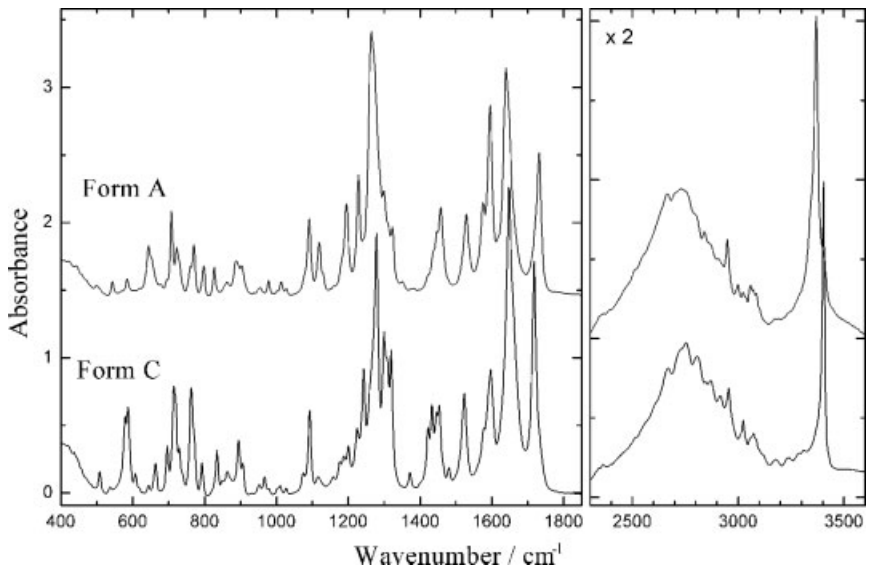

Figure 2. FT-IR spectra of the polymorphs A and C of mebendazole.

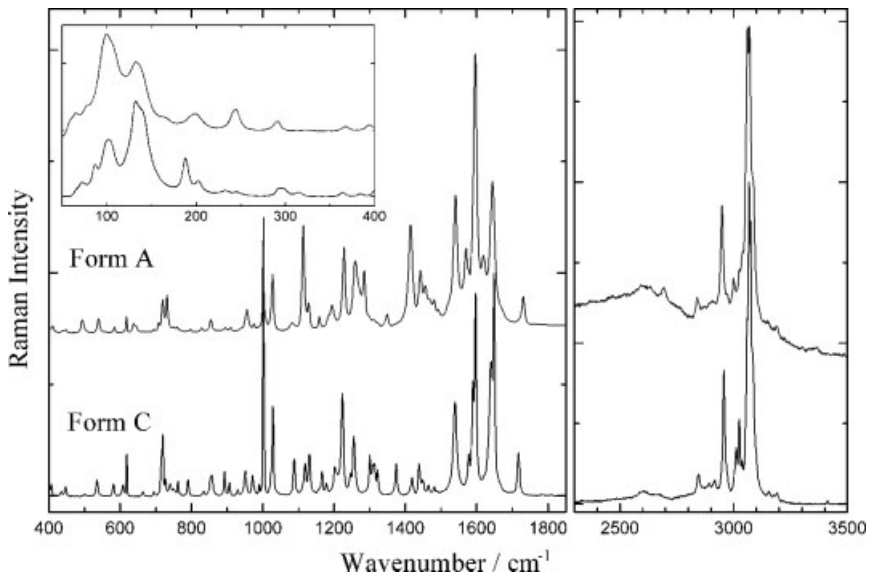

Figure 3. FT-Raman spectra of the polymorphs A and C of mebendazole.

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Table 1. Assignment of selected Raman, IR and NIR vibrational modes (wavenumbers in cm^{-1}) of the polymorphs C and A of mebendazole

Form C		Form A		
Raman	NIR/IR	Raman	NIR/IR	Assignment
	8 830	–	8 782	3 ν(CH)
	6 661	–	6 580	2 ν(NH)
	6 013	–	5 982	2 ν(CH)
	5 125	–	5 240	NH combination
	5 012	–	5 009	NH combination
	4 998	–	4 968	NH combination
	4 934	–	4 901	NH combination
	4 845	–	4 844	NH combination
	4 667	–	4 668	CH combinations
	4 563	–	4 537	CH combinations
	4 487	–	4 496	CH combinations
	4 443	–	4 446	CH combinations
	4 385	–	4 385	CH combinations
	4 358	–	4 344	CH combinations
	4 285	–	4 279	CH combinations
	4 259	–	4 260	CH combinations
	4 215	–	4 217	CH combinations
	4 170	–	4 190	CH combinations
	4 135	–	4135	CH combinations
	4 078	–	4 089	CH combinations
	4 065	–	4 057	CH combinations
3 412	3 403	3361	3 369	ν(NH)
3 084	3 087	3086	3 087	ν(CH)
3 068	3 071	3071	3 071	ν(CH)
3 025	3 023	3025	3 024	ν(CH)
3 012	3 010	3000	2 999	ν(CH)
2 957	2 955	2949	2 948	$\nu(CH_3)$
2 846	2 845	2841	2 840	$\nu(CH_3)$
1 717	1 718	1730	1 732	ν(C=O)
1 649	1 648	1644	1 647	ν(C=O)
1 639	–	1619	–	ν(C=N)
1 597	1 597	1596	1 595	ν(C=C)
1 589	1 590	1576	1 575	ν(C=C)
1 577	1 577	1570	–	δ(NH)
1 539	–	1540	–	δ(NH)
–	1 523	–	1 528	δ(NH)

characteristic of benzimidazole, whose origin was associated by Klots *et al*.[30] to tautomeric forms of this compound having also contributions of Fermi resonances. The Raman spectrum provides a better tool to investigate the ν(CH) vibrations. The wavenumber of the most intense bands are in good agreement with the ones of benzimidazole and can be assigned to this group. Below 3000 cm^{-1} the symmetric and antisymmetric ν(CH) modes of the methyl group are well resolved in the Raman spectrum.

Benzimidazole group modes

The vibrational modes of this moiety dominate the fingerprint region of the vibrational spectra. In general the observed wavenumbers agree very well with the ones reported by Morsy *et al*.[31]. These vibrations are also observed in carbendazim at similar wavenumbers. One of the most evident differences is associated to the *out of plane* modes of the phenyl ring (~750 cm^{-1}) which shift towards low energies due to the **R** substitution (Fig. 1).

Benzoyl group modes

The benzophenone molecule provides a very good reference to identify the contributions of the benzoyl group. The most intense infrared band of this compound corresponds to the carbonyl stretching and can be assigned to the band at 1648 cm^{-1}. Most of the characteristic modes of the six-membered ring of the benzoyl group are overlapped with the similar ring modes of the benzimidazole group, but, in the Raman spectra, it is possible to clearly identify its breathing mode at 1027 cm^{-1} as well as some *in plane* and *out of plane* deformation modes of the ring between 500 and 1100 cm^{-1}.

Methyl carbamate group modes

The most important contribution to the vibrational spectra of this group is the carbonyl stretching observed at 1730 cm^{-1}. This band is also present in carbendazim, as well as the *in plane* bending of the N–H carbamate bond around 1520 cm^{-1}.

Figure 4 shows the FT-NIR spectra of both crystalline forms, which are determined by overtones and combinations of the fundamental vibrational modes, some of these modes together their suggested assignment are listed in Table 1. The bands observed below 5000 cm^{-1} correspond to combination vibrations of the stretching ν(CH) and ν(NH) vibrations with deformation (δ(CH) and δ(NH)) and other stretching (ν(CC) and ν(CN)) vibrations. Even though an accurate assignment of these bands is not possible, the crystalline character of the compound gives rise to narrow bands which are potentially useful to discriminate the different crystalline forms. The overtones of the ν(CH) modes are observed around 6000 cm^{-1} (first overtones) and 8500–9000 cm^{-1} (second overtones). In the case of the ν(NH) stretching modes, the first overtone is characterized by an intense band at 6580 cm^{-1}.[35]

After identifying the main bands of the vibrational spectra of MBZ, we are able to compare the corresponding spectra of the two crystalline forms investigated in this work. By comparing the spectra of both polymorphs, one may notice that differences associated with changes in the relative intensities are more frequent than shifts in the wavenumber positions of the bands. That is not the case of the ν(NH) and ν(C=O) stretching modes which clearly fingerprint the crystalline forms.[18,20,27] Thus, the ν(NH) stretching modes of the polymorphs of MBZ provides a very sensitive tool to identify the respective crystalline

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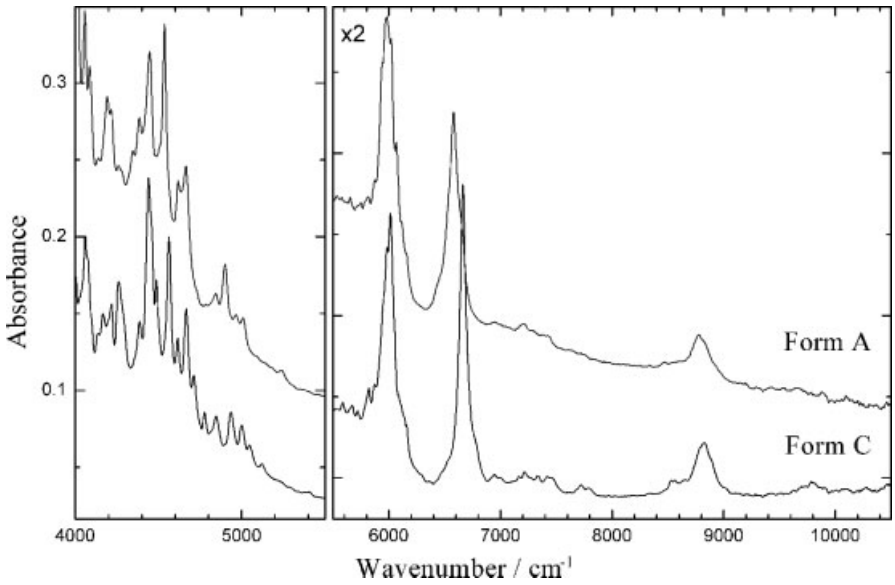

Figure 4. FT-NIR spectra of the polymorphs A and C of mebendazole.

form. As it was previously reported,[36] form C exhibits a very intense infrared band at 3403 cm^{-1}, whereas in form A this band is observed at 3361 cm^{-1}. Remembering that ν(NH) is expected at higher wavenumbers, the shift towards lower energies is an indication that the carbamate NH is participating in the hydrogen bond pattern. Generally, the higher the shift of the ν(NH) the strongest the hydrogen bond interaction. Thus the observed values suggest that form A is characterized by stronger intermolecular interactions becoming the most stable polymorph. More evidences in favor of this assumption can be found in the *in plane* deformation of the NH bond. This kind of interaction exhibits an opposite behavior to that of the stretching modes, since the δ(NH) absorption shifts towards higher energies as the hydrogen bond becomes stronger. The band associated with δ(NH) exhibits this effect being observed at 1522 and 1529 cm^{-1} in forms C and A, respectively. The differences between the hydrogen-bond strength in forms A and C is also observed in the NIR spectra not only due to the wavenumber of the first overtone of ν(NH) (6583 and 6659 cm^{-1} in forms A and C, respectively) but also in the corresponding linewidth. As a consequence of the hydrogen bond the vibrational mode becomes more harmonic exhibiting wider and less intense absorptions in the NIR spectra.[35–37] The ν(NH) infrared absorption band of the form C lying at higher wavenumbers as that of form A evidences, according to the *infrared rule* stated by Burger and Ramberger[38–40] that form C has a larger entropy and consequently, related to the free-energy curves, it is the less thermodynamic stable form at 0 K. This observation is consistent with the experimental reports of the monotropic transformation of form C into form A observed by thermal analysis and X-ray powder diffraction.[21]

The shift of the ν(C═O) stretching of the carbamate moiety may also be interpreted in terms of changes in hydrogen bonding. These bands were observed at 1730, 1717, and 1700 cm^{-1} in forms A, C, and B,[25] respectively. Notice that the relative ν(C═O) shift behavior in the two polymorphs is opposite to the one of ν(NH) suggesting the existence of an additional contribution which cannot be directly explained by inspecting the molecular structure of MBZ. An insight on this effect may be obtained by examining the crystal structure of MBZ complexes which exhibits two conformers. Both conformers are characterized by an intramolecular hydrogen bond involving a protonated nitrogen of the imidazole acting as a donor. In the hydrobromide salt and the propionic complex, the carbamete group is in a *trans* conformation leaving the carbonyl group in the acceptor role, whereas in the hydrochloride salt, the *cis* conformer of the carbamate moeitie gives rise to a hydrogen bond with the ether moiety. Thus the observed anomalous behavior could be tentatively explained as a competition between intra and intermolecular hydrogen bonds if the carbamate group is in the *trans* conformation. However, just the crystal structure determination of the MBZ polymorphs could confirm this hypothesis.

Notice that there are just subtle differences in the ν(CH) stretching modes between forms A and C of MBZ, as it may be verified from the fundamental modes (Raman and midinfrared) and the first overtone (NIR). Furthermore, other bands associated with the benzoyl group, such as the ring-breathing vibration (~1002 cm^{-1}) and the carbonyl stretching (~1660 cm^{-1}) are almost not sensitive to the crystalline form suggesting that this group does not play an important role in the crystal packing of MBZ. Several other shifts and intensity changes characterize the crystalline forms from the point of view of polymorph fingerprinting. Particularly, the region from 1300 to 1800 cm^{-1} possesses enough features

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to perform this task and will be used to investigate the commercial tablets.

The inset of Fig. 3 shows the low wavenumber bands of the Raman spectra. It is usually stated that in this spectral region lie the lattice vibrational modes which are directly related to the crystal packing and, as a consequence, to the polymorphism phenomenon. However, special care must be taken in defining what low wavenumbers mean. The comparison of experimental and calculated Raman spectra suggests that lattice vibrations are located below approximately 50 cm^{-1}, which is a region usually masked by the Notch filters commonly present in the spectrometers.[41] Nevertheless, the torsion of the molecular backbone characteristic observed below 400 cm^{-1} are very sensitive to small deformations induced by the intermolecular interaction and are also able to fingerprint the crystalline forms (inset of Fig. 3).

In the case of the NIR spectra, the spectral region below 5400 cm^{-1} exhibits several bands distinctive of each polymorph, since these combination bands have contributions of the ν(NH) and ν(C═O) stretching and δ(NH) deformation modes, which are the most sensitive fundamental vibrations. However, the most remarkable evidence of the crystalline form is the first overtone of the ν(NH), observed at 6579 and 6663 cm^{-1} in forms A and C, respectively. The stronger hydrogen bonding of form A is also evidenced in the NIR spectra, since this kind of interaction reduces the anharmonicity resulting in weaker and wider NIR bands.

As stated, vibrational spectroscopic techniques provide very useful features that allow the discrimination of the polymorphs of MBZ as raw materials. However, from the point of view of the quality control of formulated products it is also necessary to evaluate the capabilities of these techniques in the case of tablets. Thus several tablets containing MBZ, as single API or associated with TBZ (1 : 2), available in the Brazilian market were investigated using the methods described in this work. TBZ is also a benzimidazole derivative with broad-spectrum antihelmintic activity, but it is not based on a carbamate substitution. Thus the vibrational modes of TBZ do not overlap with the ν(C═O) and ν(NH) stretching modes of the carbamate group of MBZ and, as a consequence, the sensitivity of the discussed experimental method for polymorphs identifying is preserved.

Figures 5 and 6 show selected FT-Raman and FT-NIR spectra of the previously described tablets, including the spectra of the forms A and C as a reference. In general, it is remarkable that there are almost negligible contributions of the excipients in the vibrational spectra of the formulated products. In the case of the Raman spectra there is no important feature that can be assigned to the excipients, whereas the NIR spectra exhibit two medium intensity, wide bands around 5100 and 6800 cm^{-1} which are absent in the raw materials.

By comparing the APIs with the formulated tablets, three different scenarios were identified. Tablets labeled MBZ I and MBZ III are easily identified as containing forms A and C

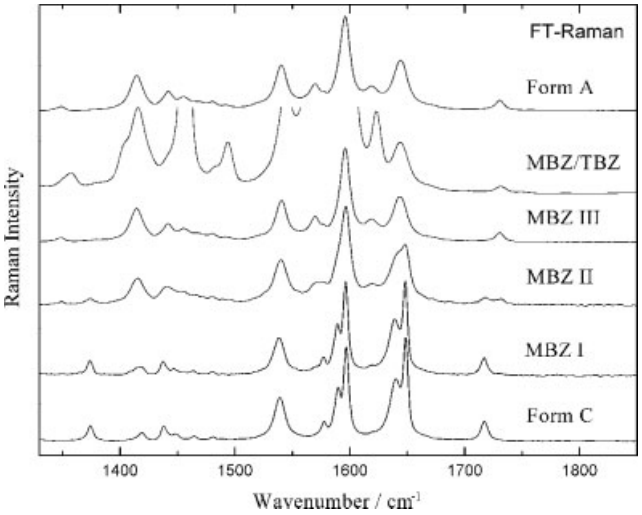

Figure 5. Comparison of the FT-Raman spectra of the mebendazole polymorphs of the pure active ingredient and commercial tablets. The Raman spectrum of the MBZ/TBZ sample was scaled to emphasize the contribution of mebendazole.

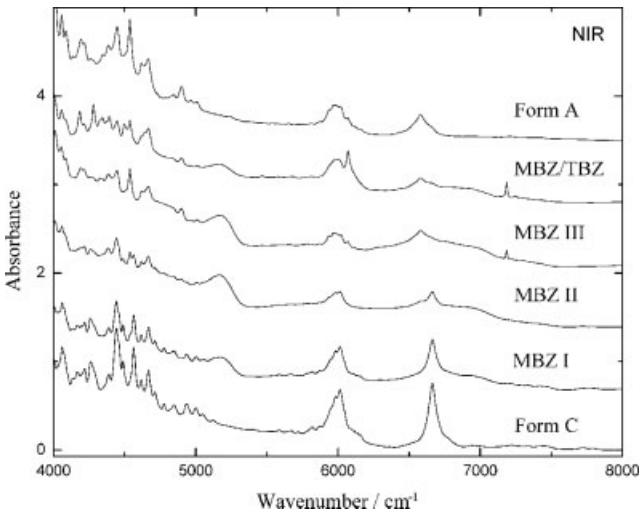

Figure 6. Comparison of the near Infrared spectra of the mebendazole polymorphs of the pure active ingredient and commercial tablets.

respectively. The characteristic Raman bands corresponding to the carbonyl group, and the splitting of the bands around 1640 and 1600 cm^{-1}, as well as the position of the first overtone of the ν(NH) stretching vibration (~6600 cm^{-1}) clearly support this conclusion. The third family of tablets is represented by the one corresponding to MBZ II. In this case, the signatures of both crystalline forms can be identified as, for example, two stretching modes of the carbonyl group (Raman) and two overtones of the ν(NH) absorption (NIR) showing that this kind of tablets is a mixture of both polymorphs (A and C). Finally, the carbonyl band observed

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in the MBZ/TBZ tablets allows to conclude undoubtedly that they are formulated using the form A of MBZ.

In order to extend our study to tablets from other markets, we also investigate some MBZ tablets available in the German market. In opposition to our results with the Brazilian samples, all the German tablets are formulated using form C. This observation is not surprising since the European Pharmacopeia requires the mid infrared spectrum as one of the quality control norms for the raw materials. Here it is important to emphasize that according to the European regulations, the midinfrared spectrum must be recorded *without recrystallization*. In the case of other pharmacopeias the recrystallization of the sample and the reference in the same solvent is required. This process completely erases the information of the original crystalline form since the crystal growing is ruled by the thermodynamic conditions of the crystallization medium.

As it was clearly proved, vibrational spectroscopy methods are highly sensitive to the crystalline form of MBZ. Several authors proposed modifications to the solubility test in order to improve its selectivity. The modified test could be an acceptable method for raw materials, but, in the case of tablets, the formulation process can introduce additional factors affecting directly the solubility (excipients, hardness, particle size, etc.). On the other hand, vibrational spectroscopy is directly probing the crystal structure being less dependent of the formulation process. The European Pharmacopeia is a very good example showing that including experimental techniques sensitive to the crystalline form in the pharmaceutical monographs provides a reliable methodology to guarantee the equivalence of the different formulations of the same API. It was also pointed out that several experimental techniques (X-ray diffraction, solid state NMR, FT-IR spectroscopy) could accomplish this task. Nevertheless our results showed that the FT-Raman and FT-NIR spectroscopies are especially valuable, since these methods not only discriminate easily among the polymorphs but also require almost no sample preparation being possible to measure through transparent packages.

CONCLUSIONS

In this work, Raman, mid infrared and near infrared spectroscopies were applied to the study of polymorphism in MBZ. These techniques offer a remarkable sensitivity to the crystalline form and, in addition to X-ray diffraction, can be applied as routine tools for the quality control of raw materials. Commercial tablets of MBZ available in the Brazilian market were also investigated with these methods. Thus the existence of different formulations containing pure form A or C, as well as mixtures of both polymorphs was verified. To the best of our knowledge, it is the first report showing the coexistence of commercial tablets containing forms A and/or C in a market. The regulations based on the USP solubility test favor the spreading of formulations which agree with the established quality control specification but that could exhibit differences in the bioavailability and bioequivalence. Our results clearly show the necessity of taking into consideration the crystalline form in the monographs of MBZ in order to guarantee the required interchangeability of the generic medicaments.

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