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Evaluation and study of mebendazole polymorphs present in raw materials and tablets available in the Brazilian pharmaceutical market

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ABSTRACT

The dissolution of a drug can be compromised by the presence of different polymorphs, which may have different solubilities. Importantly, the pharmacopoeiamonographs,usually not have tests for the characterization of these polymorphic forms of a drug. Was performed a study of polymorphic forms of mebendazole present in raw materials and also pills available in the Brazilian pharmaceutical market through the techniques of infrared (FTIR), differential scanning calorimetry (DSC), dissolution , solubility and X-ray diffraction pattern (XRPD). Through the analysis of FTIR and DSC curves showed that there are three main polymorphic forms of mebendazole present in raw materials and tablets that compound. The data obtained in the dissolution and solubility tests showed that Form A is less soluble than Form B which is less soluble than the C form, when using a dissolution medium without added surfactant. It has been found that in some tablets mebendazole there is a mixture of polymorphic forms, and that the raw materials present two major polymorphic forms. Then it is suggested the need of quality control regarding the type of polymorph used in the production of mebendazole tablets to ensure greater therapeutic efficacy.

INTRODUCTION

Many pharmaceutical solids exhibit polymorphism, which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the Crystal lattice (Grant, 1999). Polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, vapor pressure and density. These properties canhave a direct effect on ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, polymorphism can affect the quality, safety, and efficacy of the drug product (FDA, 2007). There are a number of methods that can be used to characterize polymorphs of a drug substance (Brittain, 1999). X-ray powder diffraction can also be used to provide unequivocal proof of polymorphism (Antonio *et al.*, 2008, Antonio *et al.*, 2009). Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry (DSC), thermal gravimetric analysis, and hot-stage microscopy), and spectroscopy (e.g., infrared (IR), Raman, solid-state nuclear magnetic resonance are helpful to characterize polymorphic forms (Brittain, 1999; FDA, 2007). Mebendazole (MBZ) presents three different polymorphic forms: A, B and C. The MBZ is a low water-soluble compound and has a slow rate of dissolution. The solubility of the three polymorphic forms in 0.1 M HCl follows the order: B> C> A. The MBZ has the biopharmaceutical classification II (low solubility and high permeability) and form C is more appropriate for handling drugs. The literature describes how C is more appropriate for handling pharmaceuticals (Liebenberg *et al.*, 1988, Costa *et al.*, 1991). The chemical structure of the compound MBZ is shown in Figure 1.

The three polymorphic forms of the MBZ have different physicochemical characteristics and can be differentiated from the solubility in 0.1 M HCl and a mixture of dioxane/water, IR

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spectrum, thermal properties, x-ray diffraction and partition coefficient in octanol: water (Costa *et al.*, 1991). The dissolution profile test, evaluating the use of surfactant, can discriminate polymorph in tablets produced with this drug.

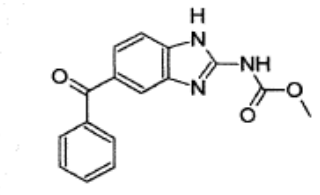

Fig. 1: Chemical structure of mebendazole.

Some studies to assess the MBZ polymorphs have been conducted. Himmelreich and colleagues evaluated the polymorphic forms of MBZ differential thermal analysis (DTA), IR +and solubility (Himmelreich *et al.*, 1977), identification of pathways MBZ present in raw materials and tablets in South Africa through thermal analysis of DSC analysis, IR, particle size, DRX and dissolution of the powder (Liebenberg *et al.*, 1988), assessment of toxicity and analytical aspects of the MBZ (Costa *et al.*, 1991), study of the solubility of the MBZ (Swanepoel *et al*., 2003a), rating of generic drugs containing MBZ by dissolution test (Swanepoel *et al.*, 2003b), X- ray variable-temperature powder diffraction analysis of the crystal transformation of the pharmaceutically preferred polymorph C of MBZ (De Villiers *et al.*, 2005), verified by IR spectroscopy and dissolution profile in samples of raw materials and drugs in Brazil (Froehlich and Gasparotto, 2005) analysis the purity of the crystal MBZ and stability suspension formulations using total Reflectance Spectroscopy Attenuated - Fourier Transform Infrared, FTIR-ATR, (Agatonovic-Küstrin *et al.*, 2008), Crystal structure determination of MBZ form a using high-resolution synchrotron X -ray powder diffraction data (Ferreira *et al.*, 2010), evaluating the effectiveness of solid dispersion with different proportions of hydroxypropylcellulose (Garcia-Rodriguez *et al.*, 2011) .

The World Health Organization estimates that one-quarter of the world population suffers from infestations of parasites and one of the most widely used drugs for these treatments is mebendazole, an anthelmintic drug acting on nematodes and some other worms. Some studies have been conducted to evaluate efficacy against various species of worms (Maki and Yanagisawa, 1988). Rodrigues-Caabeiro and colleagues conducted the study of the toxicity of the three forms of mebendazole and also the effectiveness against nematodes *Trichinella spiralis* (Rodrigues-Caabeiro *et al.*, 1987).

Mebendazole has been used for the treatment of trichuriasis (whipworm infection), enterobiasis (pinworm infection), ascariasis (roundworm infection), and hookworm infections caused by *Ancylostoma doudenale* or *Necator americanus*. The drug's broad spectrum of activity makes it useful in the treatment of mixed helminthic infections. Mebendazole has also activity against cestodiasis (tapeworm infection) caused by *Hymenolepis nana* (dwarf tapeworm), *Taenia saginata* (beef tapeworm), and *Taenia solium* (pork tapeworm); strongyloidiasis (threadworm infection), cutaneous larva migrans (creeping eruption), toxocariasis (visceral larva migrans), capillariasis, trichostrongylosis, and draculiasis (guinea worm disease). The drug has been effective in a limited number of patients for the treatment of hydatid cysts caused by *Echinococcus granulosus* (Mcevoy, 1988).

The drug appears to cause selective and irreversible inhibition of the uptake of glucose and other nutrients in susceptible helminths. The inhibition of glucose uptake results in the endogenous depletion of glycogen stores in the helminths. Mebendazole does not inhibit glucose uptake in mammals. Mebendazole appears to cause degenerative changes in the intestine of nematodes and in the absorptive cells of cestodes. The principal anthelmintic effect of the drug appears to be degeneration of cytoplasmic microtubules within these intestinal and absorptive cells (Mcevoy, 1988; Buys, 2003).

Regarding the studies of mebendazole medicine available in the Brazilian market there is not a more comprehensive verification of national manufacturers and also the comparison of techniques that facilitate the assessment of the MBZ polymorph. Thus, the present study aimed to evaluate the polymorphic form of MBZ in samples of raw materials and tablets purchased in the Brazilian pharmaceutical market in the Northeast, Midwest and Southeast covering obtain samples of the leading manufacturers of the drug in country. For the study to check the best dissolution medium for the tablet, review through the techniques of X-ray diffraction, differential scanning calorimetry, particle size and a study of sample preparation for FT-IR was performed.

MATERIALS AND METHODS

Samples

Three samples of raw materials from different manufacturers were acquired and were named A1, A2 and A3 and 23 medicines were purchased, containing 100 mg of MBZ in tablet dosage form, from different manufacturers, found in Brazil, named A4 to A26.

Reagents

Reagents potassium bromide, hydrochloric acid, acetic acid, formic acid, sodium acetate, sodium laurilsulphate (SLS) , monobasic potassium phosphate were obtained from Merck (Darmstadt, Germany). For the preparation of solutions deionized water obtained in (Bioscience Division) Millipore system was used. A placebo pill containing common excipients described in the inserts of each drug was manipulated. The excipients used were: starch, microcrystalline cellulose and magnesium stearate.

Determination of solubility of mebenzadolraw materials

The solubility and the dissolution profile were performed according to the method 2 described in USP 35 paddle. The tests were performed in a dissolutor, Ethiktechonology model 299/6TS (Brazil). The measured absorbances of the solutions were

measured on a Thermo spectrophotometer, model 201 Evotulion (USA). The solubility of MBZ raw material was evaluated in the following dissolution mediums: hydrochloric acid 0.1 $molL^{-1}$, hydrochloric acid 0.1 $molL^{-1}$with addition of 0.1, 0.5, 1.0, 1.5 and 2.0% SLS, deionized water, sodium acetate buffer, pH 4.5, potassium phosphate buffer pH 6.5 and pH 7.5. The buffers were prepared as described according to the American Pharmacopoeia.

In the preparation of samples were used approximately 250 mg in 250 mL of dissolution medium. The samples were shaken for 1 hour on shaker table, Tecnal, model TE-240(Brazil).After stirring the samples were centrifuged, Thermo Scientific, model MultifugeX3R (USA) at 5,000 rpm for 3 minutes and 1.0 mL of the supernatant was transferred to a 100 mL volumetric flask and diluted to the appropriate dissolution medium. MBZ The standard was prepared by initially dissolving in formic acid and dilution with methanol to obtain a 1.0 $mgmL^{-1}$ solution. From this solution a dilution was performed to obtain a 0.01 $mgmL^{-1}$ solution of the corresponding medium dissolution.

Dissolution profile of tablets MBZ

MBZ samples were evaluated in the form of tablets containing 100mg declared content acquired in national trade: Only samplesA22, A23, A24, A25 and A26 were chosen to carry out the test. The dissolution profile of the tablets was MBZ sample from the optimized conditions described in the U.S. Pharmacopoeia monograph USP 35: dissolution media 900 mL of HCl 0.1 $molL^{-1}$ containing 1.0% sodium lauryl sulfate, paddle apparatus, 75 rpm and rotation time of 120 minutes. To obtain an acceptable dissolution condition, Q > 75% , tests were conducted to evaluate the concentration of surfactant in the dissolution medium (0.1%, 0.50%, 1.0%, 1.5% and 2.0%), rotation (75 rpm) , dissolution media volume of 900 mL, collecting 5 mL and collection times of 5, 10, 15, 30, 45, 60, 90 and 120 minutes. To evaluate the actual dissolution of the polymorph present in the tablets and MBZ, discriminate the polymorphic forms was conducted using the dissolution profile of HCl as dissolution medium 0.1 $molL^{-1}$HCl and 0.1 $molL^{-1}$with 1 % surfactant, dissolution using the conditions above.

Particle Size

The particle size distribution and mean diameter of samples of raw MBZ were evaluated by spectrophotometry of scattering laser, MastersizerS, model S-MEM 5005, Malvern Instruments (Worcestershire, UK). Samples were suspended in water to perform the analyzes, with ultrasonic agitation for 2 minutes and read in triplicate.

X-ray diffraction

X-ray powder patterns (XRPD) were obtained on a system of X-ray diffraction, brand Philips model X'Pert, using voltage 15 kV, current of 5 mA, speed of 0.04 °/s and scan range 5-40 degrees.

Thermal Analysis - DSC (differential scanning calorimetry)

The DSC curves were obtained using a DSC, Mettler DSC822^{e}, software Star SW 8.10. Nitrogen was used as purge gas with a flow rate of 50 mL min^{-1}. The heating rate was 10 °C min^{-1} and a mass range of 3 mg to 5 mg used in alumina crucibles. Indium (melting point 156.6 ◦C) and tin (melting point 231.9 ◦C) were used for calibration of the DSC equipment.

Infrared spectroscopy

The IR spectra were obtained on a spectrophotometer PerkinElmer Spectrum Model 100 FT-IR Espectrometer using a range 4000-400 cm^{-1} resolution and 64 scans 4.0. We used an approximate amount of 1 % of drug dispersed in potassium bromide (KBr), this technique was used to identify different polymorphs present in the MBZ tablets that were found in the national market, no prior extraction of the sample was taken. The samples were analyzed using the diffuse reflectance device and the procedure in KBr tablet to check any polymorphic transition due to the pressure exerted on the usual procedure with potassium bromide pellets. Sample placebo tablet was also analyzed to assess possible interfering bands in characterizing the MBZ polymorph present in the tablet.

RESULTS AND DISCUSSION

Determination of solubility of stock solution of mebenzadole

In MBZ solubility test was observed that the compound is soluble in acidic media especially in the tested media hydrochloric acid 0.1 $molL^{-1}$ hydrochloric acid and 0.1 $molL^{-1}$ with the addition of SLS. In the other means a precipitate was observed after the final dilution in the preparation of standard solution.

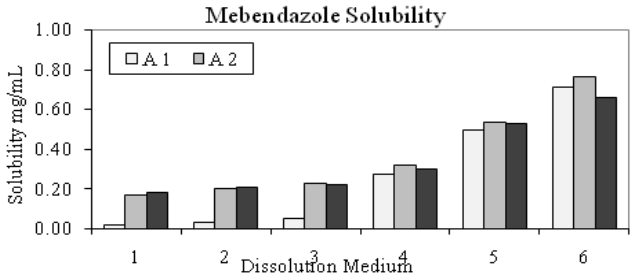

Fig. 2: MBZ solubility in different medium: (1-HCl0.1 M; 2-HCl 0.1 M + 0.1% SLS; 3-HCl0.1 M+ 0.5% SLS; 4-HCl 0.1M + 1.0% SLS; 5-HCl 0.1M +1.5% SLS; 6-HCl 0.1 M + 2.0% SLS).

The samples had a larger amount dissolved in the surfactant containing media compared to medium without SLS. The samples showed similar solubility when it was used as diluents through the means described in the monograph of the American Pharmacopeia, USP 35. Figure 2 shows a comparative graph of solubility MBZ samples of raw material means the more soluble is displayed. The data, lower solubility in medium without surfactant, indicating that the sample A1 should display in its constitution of MBZ polymorph A and polymorph C others

present in their composition, data confirmed by the results of DSC, IR and XRPD. To study the solubility of an analytical curve was obtained in the concentration range from 1.6 to 38.4 mgmL^{-1} using the medium Hydrochloric 0.1 molL^{-1}acid with 2% SLS wavelength of 312 nm , equation Y = 21.8526 + 0.0037 X , and linear regression coefficient of 0.9999 straight. Table I presents the results of a comparative study of linear correlation of MBZ drug with different concentrations of surfactant in the dissolution medium. The low relative standard deviation between the slopes of the equations of dissolution curves show that there was no interference of the concentration of surfactant in the quantification of dissolution (Hanashiro *et al.*, 2013).

Table 1: Data from the analytical curves in MBZ different dissolution medium.

Media	Linear Coefficient	Angular Coefficient	R^2
HCl 0.1molL^{-1}	0.0007	70.967	0.9995
HCl 0.1mol.L^{-1} + SDS 0.1%	0.0107	71.113	0.9949
HCl 0.1mol.L^{-1} + SDS 0.5%	-0.0037	73.156	0.9994
HCl 0.1mol.L^{-1} + SDS 1.0%	-0.0015	71.757	0.9988
HCl 0.1mol.L^{-1} + SDS 1.5%	0.0006	69.578	0.9928
HCl 0.1mol.L^{-1} + SDS 2.0%	-0.0072	72.739	0.9926
Average		71.552	0.9963
RSD		1.817	0.330

Determination and optimization of the dissolution profile of MBZ tablets

As the samples had different solubility behaviors of using the surfactant in the dissolution medium was proposed to verify the dissolution profile of different MBZ tablets using dissolution medium with and without surfactant. Before comparing the profiles proposed to perform an optimization of the dissolution test described in USP. A study of surfactant concentration was carried out while maintaining the stirring speed at 75 rpm and the dissolution medium volume of 900 mL.

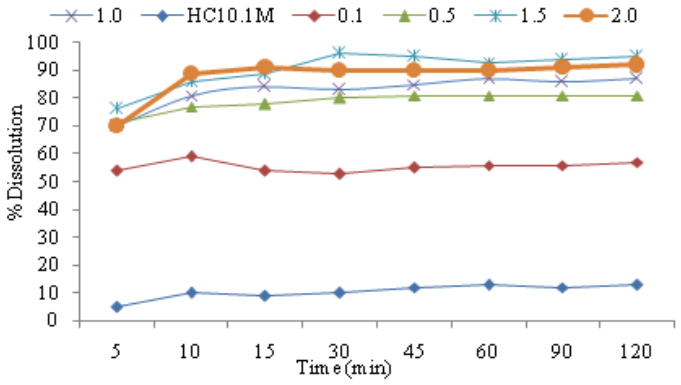

Fig. 3: Graph dissolving tablets MBZ in different media for sample A 24, (0.1 M HCl; 0.1 M HCl + 0.1% SLS; 0.1 MHCl + 0.5% SLS; 0.1M HCl + 1.0% SLS; 0.1M HCl + 1.5% SLS; HCl 0.1 M + 2.0% SLS.

Figure 3 shows the dissolution profile of 100 mg compressed MBZ in medium with 0.1 MHCl varying the concentration and SLS. The data show the increased dissolution rate for the MBZ in medium containing the surfactant, and the dissolution media with 1.5 and 2.0% SLS media with greater release of the MBZ. The value described in the Pharmacopoeia for dissolving the content of Q + 5, Q = 75 + 5 % at the time of 120 minutes (USP, 2013), was obtained only in media with 0.1 M HCl containing 1.0, 1.5 and 2.0% LSS. Figures 4 and 5 show the graph of the dissolution profile of five samples MBZ 100 mg tablet of the means of 0.1 M HCl and 0.1 M HCl with 1% SLS, respectively. Samples of tablets A24, A25 and A26 showed similar behavior, low dissolution rate, when the medium had not reported the surfactant. Sample A 23 showed the highest dissolution followed by the sample A22 with intermediate dissolution. With the use of surfactant in the dissolution medium was observed an increase of the dissolution rate for all samples, a greater increase was observed for the samples which showed reduced dissolution rate without the surfactant in the dissolution medium. These data demonstrate that the dissolution test containing the surfactant has little differentiation between samples with different polymorphs, additional tests required for evaluation of the MBZ polymorph samples compressed (Hanashiro *et al.*, 2013).

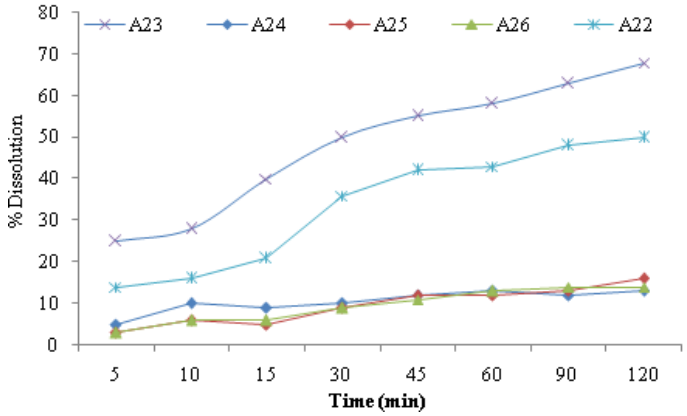

Fig. 4: Graph of dissolution profile the samples of tablets MBZ profile in the dissolution medium, 0.1M HCl.

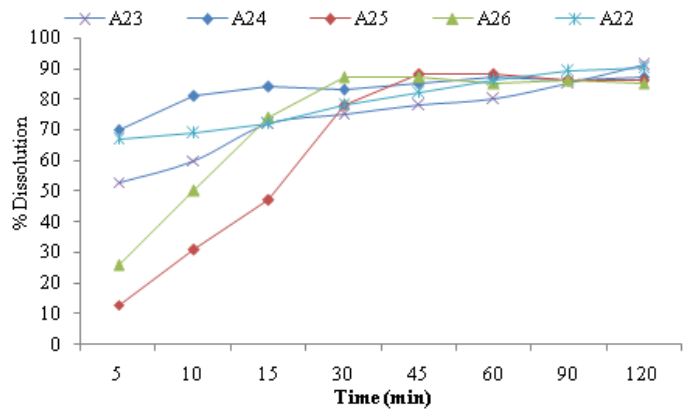

Fig. 5: Dissolution profile of the different samples of tablets MBZ in medium, 0.1M HCl + 1.0% SDS, USP conditions.

In the dissolution profiles is possible to see a major difference between the release rates of drug present in the tablet when compared to the profile obtained in the dissolution medium with and without addition of SLS. The tablet, identified with the polymorphic Form C of MBZ, has less variation and the sample of tablet, identified by IR as a mixture of polymorphic forms A and

C, has an intermediate difference. With the presence of the surfactant SLS, tablets of MBZ identified as form A by IR test, samples A 24, A25 and A26, showed similar profile dissolution, however, with reduced time to 30 minutes to release the samples A25 and A26, possibly due to the greater hardness of the tablets, 14kp to16 kp.

Particle Size

The average particle size of the samples did not differ, with the average size of 12 µm for sample A1, 10 µm for sample A2 and 13 µm for sample A3. Thus, by presenting a similar particle size did not influence this parameter in the solubility differences between the samples of raw material.

X-ray diffraction

The samples evaluated mebendazole raw materials A2 and A3 showed results consistent with the DRX polymorph C whereas the sample A1 presented data in accordance with the form A (Ferreira *et al.*, 2010, Antonio *et al*,. 2009, Rosa *et al.*, 2007, Rosa *et al.*, 2008,Swanepoel*et al.*, 2002, De Villiers *et al.*, 2005). Figure 6 shows the diffraction pattern for samples C and the polymorphic form A.

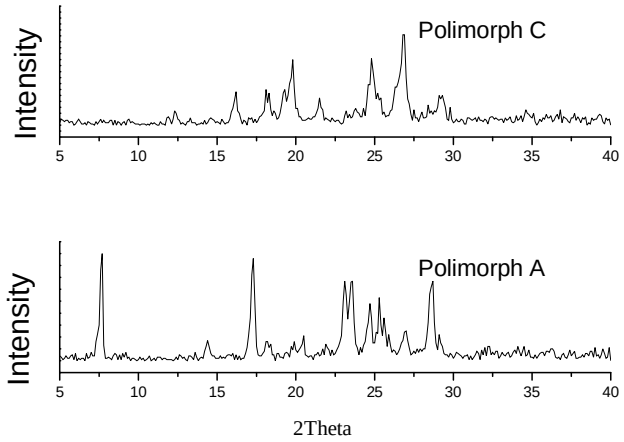

Fig. 6: Diffractogramof the sample MBZ polymorph C and A.

Infrared spectroscopy

Through analysis by infrared spectroscopy on samples from different manufacturers was possible to identify the two polymorphs A, and C and a mixture of polymorphs A and C. Table II shows the mean assignments for group –NH and – C=O of the MBZ.

Table 2: Absorption frequencies in the mid-infrared region for amino and carbonyl groups in the polymorphs of mebendazole (Liebenberg *et al*, 1998).

Sample	Assignments(cm^1)	
	Group –NH	Group–C=O
Polymorphs A	3365	1730
Polymorphs B	3350	1700
Polymorphs C	3405	1720

Figure 7 presents the spectra representing different polymorphs found in pure raw materials (A1 and A3) and mixture of both. IR data indicate that the samples A2 and A3 have the polymorph C therapeutically favorable, and the sample A1 to form A (Garbuio *et al*., 2013a; Garbuio *et al*. 2013b).

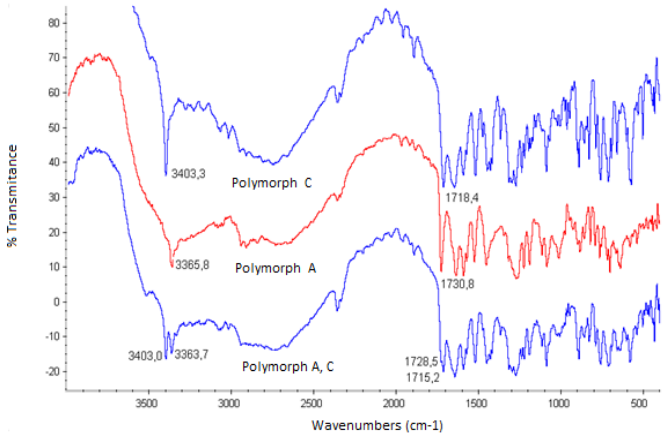

Fig. 7: Infrared spectrum for samples of MBZ form A and C.

In the evaluation of the analysis by infrared KBr and ATR procedure some differences between the results for samples 3 and 13 have been observedwith respect to the absorption band of the amino group. The data are presented in Table III.

Table 3: Results of polymorphs characterized mebendazole in various samples by spectrophotometry in the infrared range mode reading of the sample.

Polymorphism of Mebendazole - Infrared Method				
Sample	**Pellets**	**Assignments (cm^1) (-NH / -C=O)**	**ATR**	**Assignments (cm^1) (-NH / -C=O)**
A1	A	3368/ 1731	A	3369/1732
A2	C	3403/1717	C	3404/1717
A2	C	3403/1717	C	3404/1717
A3	A	3368/1731	A; C	3368/1731/ 3404/1717
A4	A	3368/1731	A	3368/1731
A5	A	3368/1731	A	3369/1732
A6	A	3369/1731	A	3368/1731
A7	A	3368/1731	A	3368/1732
A8	A	3368/1731	A; B	3369/1731 3352/1696
A9	A	3368/1731	A	3363/1730
A10	A	3369/1732	A	3370/1732
A11	A	3369/1731	A	3369/1730
A12	A	3368/1732	A	3363/1732
A13	A; C	3404/1731 3369/1732	A; C	3405/1717 3369/1733
A14	A	3368/1731	A; B	3370/1731 3351/1708
A15	A	3368/1732	A	3365/1732
A16	A	3368/1732	A	3370/1732
A17	A	3368/1731	A	3362/1731
A18	C	3403/1716	C	3404/1717
A19	A	3364/1728	A	3366/1731
A20	A	3368/1732	C	3369/1731
A21	C	3369/1732	A	3369/1732
A22	A; C	3404/3368 1731/1717	A; C	3405/1717 3369/1733
A23	C	3404 / 1717	C	3403 / 1717
A24	A	3366 / 1730	A	3365 / 1731
A25	A	3366 / 1730	A	3365 / 1730
A26	A	3366 / 1730	A	3366 / 1731

Thermal Properties

The DSC analysis was performed on samples of raw material and tablets MBZ to assess thermal events corresponding to the polymorphic forms. In Figure 8, the DSC curves for the samples of raw materials are presented.

The DSC thermogram of the samples shows some differences in the temperature range of 180 – 210◦C and in the range 240-280 ◦C. The DSC thermograms of the polymorph C exhibited three thermal events: a small endothermic / exothermic event (195 ◦C) and two sharply defined endotherms. The first is a sharply defined endotherm at 253 ◦C, which is followed by the second and the final melting endotherm at 330 ◦C. In the thermogram of form A there are two melting endotherms at 250-255 ◦C and the end of melting endotherm at 330 ◦C. Curves of samples of MBZ A2 and A3 DSC presented in accordance with the shape C, while the sample curve A1 consistent with Form A. The data to distinguish between forms A and C are in accordance with MBZ described in the literature (Swanepoel *et al.* 2002, De Villiers *et al.*, 2005).

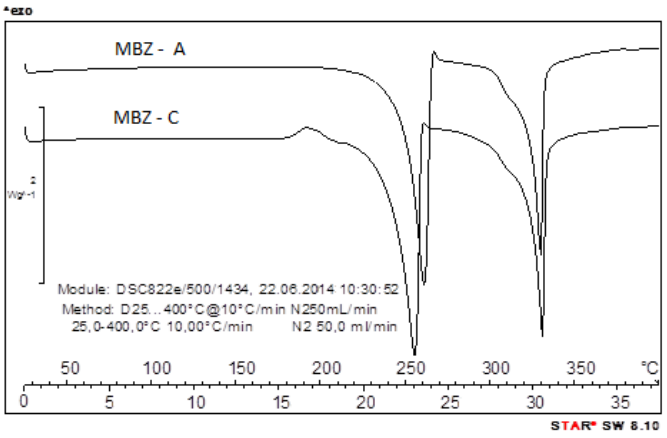

Fig. 8: DSC curves for samples of MBZ raw material A and polymorph C.

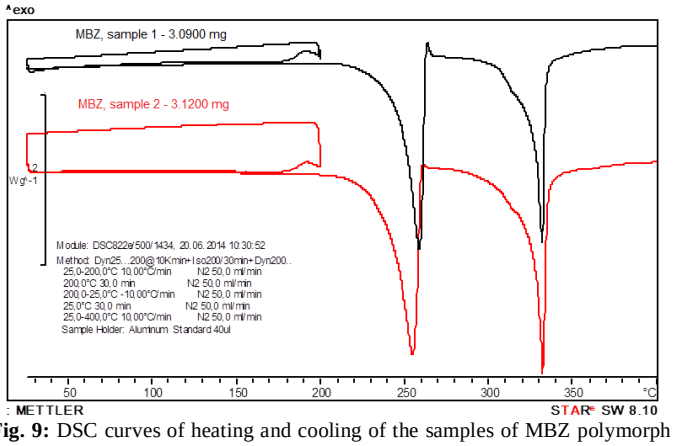

Fig. 9: DSC curves of heating and cooling of the samples of MBZ polymorph C.

To check possible migrations between the polymorphic forms, a study of thermal stability were evaluated. The literature describes the forms B and C are processed in the form when subjected to heat above 210 and 270 C, respectively (Himmerlreich, 1977; De Villiers *et al.*, 2005). The heating test followed sequentially heating and cooling was performed, it was found that in the second heating step endothermic event indicating that was absent after heating at 200 °C there is migration of the form C to form A. Figure 9 shows the DSC curves of heating and cooling of the samples of mebendazole raw material A2 proving the presence of form C with migration to form A.

Were evaluated by DSC samples MBZ tablets used in the study of dissolution, A22 to A26, was to verify that the polymorph present in the tablet, Figure 10.

For five samples of tablet MBZ used in the test of dissolution profile, were analyzed dy DSC to identify thepolymorphic form of MBZ. But not possible to distinguish by DSC method due to possible overlapping thermal events of the excipients in the formulation. Although the evaluation by DSC shows two exothermic events, at 167 °C and 220°C for three samples, the event next to 325°C was not observed. An important information that can be extract for DSC curves is about qualitative composition of tablets that shown different events mainly for two samples, indicating the use of different excipients in the formulations.

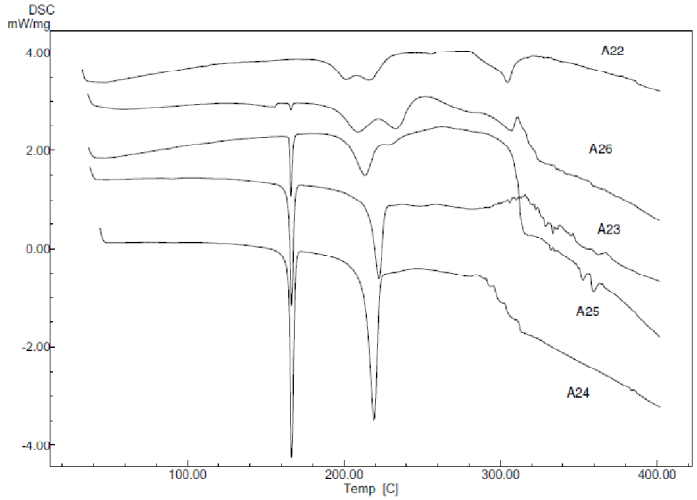

Fig. 10: DSC curves for samples of MBZtablet.

The dissolution test of tablets MBZ using dissolution media with and without addition of surfactant to the showed differentiation of the MBZ polymorphs. Between of the methods used to evaluate the polymorphic form of MBZ, the infrared method was the fastest and most selective, allowed detection of more than one hic polymorph from the characteristic bands of functional groups for each polymorphic form in both samples of the raw materials and tablets.

The test of X-ray diffraction was used only for analysis of the active pharmaceutical ingredient and allowed the differentiation of polymorphs of MBZ, however, was not used in the analysis of the drug.

The DSC test allowed to evaluate the polymorph of MBZ in pharmaceutical ingredient only in the analysis of the presence of tablet excipients hinders the visualization of thermal events.

CONCLUSION

The tests used for dissolution, IR, DRX and DSC have been useful in identifying the polymorphic form of the MBZ present in raw materials and tablets. For tablet MBZ technique IR showed more accurate and sensitive results when the presence of more than one polymorphic form, with a rapid and inexpensive assay occurs. The polymorphic form C that should be present in all tested medicines, was confirmed only in a few samples.

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