Drug Development and Industrial Pharmacy, 24(5), 485–488 (1998)

COMMUNICATION

Identification of the Mebendazole Polymorphic Form Present in Raw Materials and Tablets Available in South Africa

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ABSTRACT

A preformulation study of four different raw materials of mebendazole showed that three samples were polymorph C and the other polymorph A, or a mixture of form A and B. X-ray powder diffractometry and infrared spectroscopy indicated that this powder could be form B, but powder dissolution, for which a much slower dissolution was obtained, suggests polymorph A. Literature prescribes the use of polymorph C pharmaceutically, but generic manufacturers should be aware that forms other than C are still available on the market. The four mebendazole tablets currently available in South Africa were also tested and it was found that all of them contained polymorph C.

INTRODUCTION

Three polymorphic forms of mebendazole, identified as A, B, and C, can be formed through controlled crystallization procedures. Mebendazole is poorly water soluble and has a slow dissolution rate. Significant therapeutic differences have been observed between the different polymorphic forms, which supports the fact that the low solubility and poor rate of solution of the drug are important factors limiting its use in the treatment of several diseases (1).

The solubility of the three polymorphs in both water and 0.03 M hydrochloric acid is in the order B > C > A. The polymorphs differ with respect to their infrared (IR) spectra, x-ray powder diffractograms (XRD), and differential scanning calorimetry (DSC) thermograms (1,2). Polymorph C is apparently pharmaceutically favored.

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During this generic preformulation study, four raw material samples were studied in order to determine whether they contained polymorph C. The physicochemical properties of these powders were also compared. DSC, XRD, IR, particle size, and powder dissolution studies were performed to evaluate the samples. The crystal form present in mebendazole tablets commercially available in South Africa was also determined using IR spectroscopy.

MATERIALS AND METHODS

Materials

The mebendazole powders were obtained from four suppliers (Petropharm, batch no. 410330; Rokadia Chemical, batch no. 069; Cipla, batch no. 410330; Qure, batch no. ERM369) and were identified as samples 1–4. Commercially available tablets that were tested were Anthex™ (Rolab, South Africa, batch no. 92E01), D-worm™ (Triomed, South Africa, batch no. 1826), Vermox™ (Janssen-Cilag, South Africa, batch no. 662HDIA), and Wurmgo™ (Lennon, South Africa, batch no. MLB87490).

Infrared Spectrophotometry

The infrared spectra were recorded on a Fourier transform infrared spectrophotometer (Shimadzu, FTIR-4200, Shimadzu, Japan) over a range of 600–4000 cm^{-1}. The KBr disk technique was used to measure the IR spectra of the tablets. The tablets were crushed in a mortar with pestle and the tablet powder was used to prepare KBr tablets.

XRD

The XRD profiles were obtained at room temperature with a Philips PM9901/0 diffractometer (Philips, Netherlands). The measurement conditions were target, Co Kα; filter, Fe; voltage, 40 kV; current, 20 mA; slit, 0.2 nm; scanning speed, 2°/min. Approximately 200 mg of sample was loaded into an aluminum sample holder; care was taken not to introduce a preferential orientation of the crystals.

Particle Size Analysis

Particle size distributions in suspension were measured with a Galai-Cis-1 (Galai, Israel) particle size analyzer, which combines laser diffraction and image analysis for particle sizing. Powder samples were suspended in chloroform. A small magnetic stirrer inside the measuring cuvette prevented sedimentation of the particles. The acquired data were used to compute means, medians, and standard deviations based on the total particle population (3).

DSC

DSC thermograms were recorded with a Shimadzu DSC-50 instrument (Japan). The measurement conditions were sample weight, approximately 2 mg; sample holder, aluminum crimp cell; gas flow, nitrogen at 20 ml/min; heating rate, 10°C/min.

Powder Dissolution

Powder dissolution was measured using Method 2, paddle, of the USP 23 (4). The paddle was rotated at 50 rpm and samples were taken at 7.5, 15, 22.5, 30, 45, 60, and 90 min. The powder sample, 100 mg, was rinsed from the glass weighing boat into a 10-ml test tube with exactly 2 ml of the dissolution solution. Glass beads, 50 mg, with a mean size of 0.1 mm, were added to the suspension and the mixture was agitated for 60 sec using a vortex mixer. The contents of the test tube were transferred to the dissolution medium, 900 ml (0.1 M hydrochloric acid), and the dissolution rate was measured. The concentration of dissolved powder was calculated from the UV absorbency values obtained at 253 nm. Results are the mean of six determinations.

RESULTS AND DISCUSSION

According to Himmelreich et al. (1) the IR absorption spectra of the various polymorphic forms show characteristic differences in the detailed shape and intensities of some of the major absorption bands. Specifically, the carbonyl (carbamate) stretching frequency (1700–1730 cm^{-1}) and –NH stretching frequency (3340–3410 cm^{-1}) were different in each form and were used to identify the three polymorphs. The specific frequencies of interest are listed in Table 1.

The main absorbencies in the IR spectra of the four raw material samples are given in Table 1. According to these values and results reported by Himmelreich et al. (1) samples 2–4 are identified as most probably form C and sample 1 is either form A or form B, or a mixture of form A and B. The x-ray powder diffractograms, Fig. 1, of the mebendazole samples also differed significantly. The XRD pattern of samples 2–4 corre-

Table 1

Main Absorbencies in the IR Spectra of the Mebendazole Samples (cm^{-1})

Sample	-NH	-C=O
Polymorph A (1)	3370	1730
Polymorph B (1)	3340	1700
Polymorph C (1)	3410	1720
Sample 1	3349	1703
Sample 2	3403	1719
Sample 3	3403	1719
Sample 4	3403	1717

sponds with that of polymorph C (2). The pattern of sample 1 fits the published data (2) for polymorph B reasonably well, although not unambiguously.

The DSC thermograms (Fig. 2) of the four samples show some differences in the range 250–315°C, but it was not possible to establish, after comparison with published thermograms (2), the polymorphic form of the four samples.

The powder dissolution rates of the raw materials are given in Fig. 3. All of the samples dissolved slowly and at completion of the dissolution tests suspended particles were visible in the dissolution medium. Sample 1 dissolved slower than the samples identified as form C (samples 2, 3, and 4). The median particle diameters by volume of the samples were small and quite similar (sample 1 = 6 μm; sample 2 = 5 μm; sample 3 = 7 μm; sample 4 = 6 μm). Differences in the dissolution rates of the samples were therefore not attributed to particle size differences.

If sample 1 was polymorph B it should have dissolved faster than samples 2, 3, and 4, form C, because it is reported (1,2) that polymorph B is more soluble than polymorph C in both water and 0.03 M hydrochloric acid. Based on closer examination of IR and XRD evidence, Figs. 1 and 2, it was concluded that sample 1 contained predominantly polymorph A. Polymorph A has the slowest dissolution rate.

To ascertain the possible occurrence of different mebendazole polymorphs in commercially available tablets, the mebendazole polymorphic form present in four tablet formulations currently sold in South Africa was tested. Results listed in Table 2 showed that these products contained polymorph C, the pharmaceutically preferred crystal form.

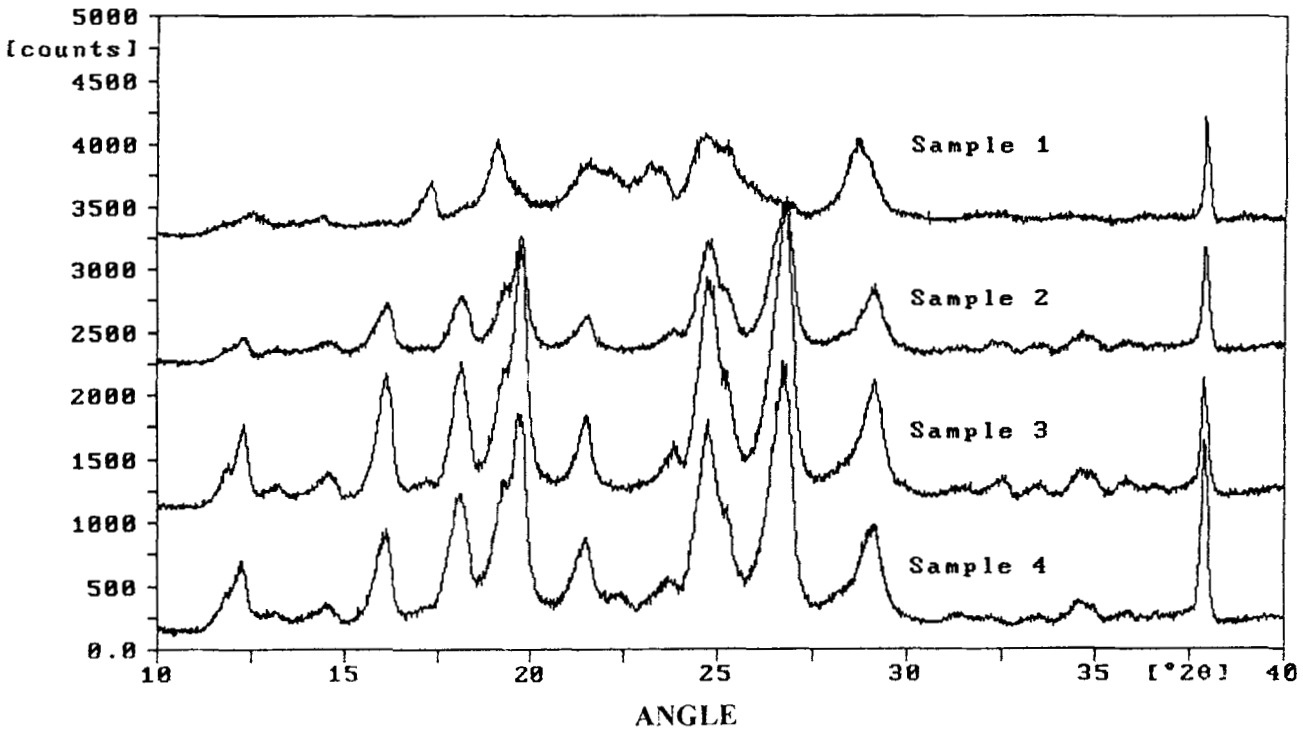

Figure 1. X-ray powder diffractograms of the mebendazole raw materials.

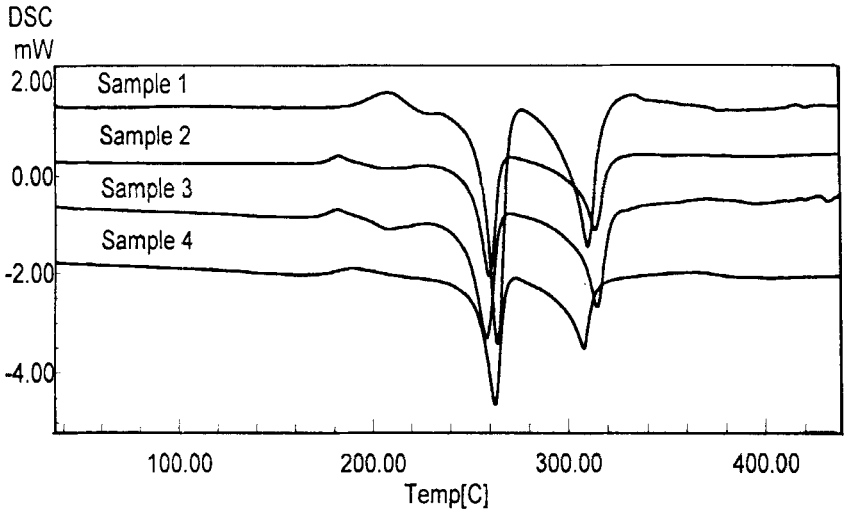

Figure 2. DSC thermograms of the mebendazole raw materials.

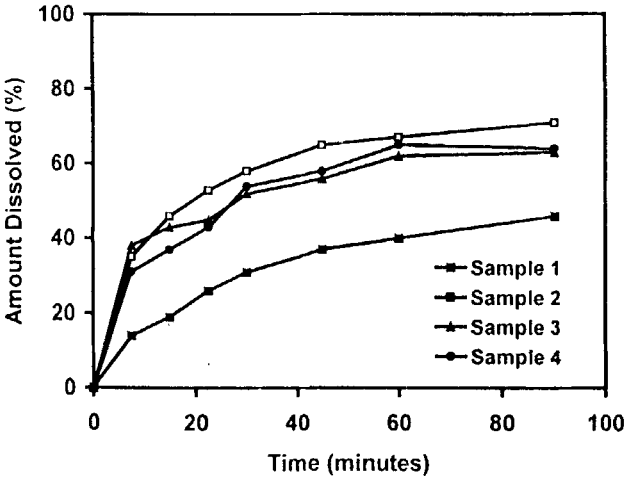

Figure 3. Powder dissolution curves of mebendazole raw materials in 0.1 M HCl solution according to Method 2, paddle, of the USP.

Table 2

Main Absorbencies in the IR Spectra of the Mebendazole Samples (cm^{-1})

Sample	-NH	-C=O
Anthex	3403	1719
D-worm	3403	1719
Vermox	3404	1719
Wormgo	3403	1719
Polymorph C	3410	1720

CONCLUSION

Although literature suggests that one should use polymorph C of mebendazole, there are still other polymorphic forms available on the generic market. In this study four raw material samples available in South Africa were tested. According to x-ray and IR identification three of the samples were identified as polymorph C. Dissolution rate measurements suggested that the remaining sample was most likely polymorph A. Generic manufacturers should be aware of the possibility that different polymorphs of mebendazole are available on the market. A complete preformulation is necessary before a decision on the use of any mebendazole raw material can be made. The use of just one technique might not unambiguously identify the polymorphic form. The currently available mebendazole tablets sold in South Africa all contained polymorph C, the preferred crystal form.

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