Journal of Thermal Analysis and Calorimetry, Vol. 87 (2007) 3, 919–925

DEVELOPMENT OF THERMOGRAVIMETRIC METHOD TO QUANTITATIVE DETERMINATION OF MEBENDAZOLE

Ana Paula Barrêto Gomes, Lidiane Pinto Correia, Mônica Oliveira da Silva Simões and Rui Oliveira Macêdo[*]

Federal University of Paraíba UFPB, Unified Development and Medicine Assays Laboratories LUDEM, Cidade Universitária Campus I CCS, João Pessoa, Zipcode 58051-970, Paraíba, Brazil

The objective of this work was to develop and validate a fast and reproducible method able to determine the concentration of mebendazole in raw materials and tablets. The samples were analyzed by dynamic thermogravimetry, in the heating rates of 10, 20, 40, 60 and 80°C min^{-1}, in the atmospheres of nitrogen and nitrogen with synthetic air. Obtained data were used in the equations of Antoine and Langmuir, with the purpose to get the pressure curves of those. Vapor pressure curves of drug and tablet of mebendazole were evaluated using the mathematical indexes of difference factor, f_1, and similarity factor, f_2, to compare its profiles. The data showed that there is no significant difference between the vapor pressure profiles of drug and tablet of mebendazole in both environmental conditions studied, what confirms that the process is really vaporization. The concentration of mebendazole was determined in the raw material and tablets with the drug.

Keywords: *equation of Antoine, equation of Langmuir, mebendazole, thermogravimetry, vapor pressure*

Introduction

Mebendazole is a synthetic benzoimidazol with a large anti-helminthes spectral action and low incidence of adverse effects [1]. The thermal techniques have been demonstrating several applications: thermal characterization [2–4], study of drugs stability [5–9], preformulation studies [10, 11], as well measure the vapor pressure of substances [12–15]. The objective of this work was to develop a sensitive and fast method to quantitative analysis of mebendazole using thermogravimetry that has its fundamental determination in the vapor pressure of the drug.

Experimental

Materials

Methylparaben (pattern), mebendazole substance active in raw material and tablets containing 100 mg of mebendazole were used in this study.

Quantitative determination of mebendazole

Pattern curves of mebendazole drug diluted in microcrystalline cellulose were prepared in the rate of 20°C min^{-1}, in the concentrations of mebendazole: microcrystalline cellulose of 60:85, 80:65, 100:45, 120:25 and 140:5, in an environment of nitrogen and nitrogen with synthetic air. The raw material and the tablets of mebendazole were analyzed by the calibration curve, using the equation of the straight line.

Determination of mebendazole by Brazilian's pharmacopoeia

Twenty tablets of mebendazole were pulverized. After, it was weighed 145 mg of pulverized mebendazole and added to a volumetric balloon of 100 mL with 10 mL of formic acid, which was agitated in a vortex for 15 min. The volume of the balloon was completed with isopropyl alcohol, homogenized and filtered. An aliquot of 1 mL of the filtered solution was transferred to a volumetric balloon of 100 mL, then added 5 mL of 0.1 M chloride acid and completed the volume with isopropyl alcohol and homogenized it [16].

Methods

Calorimetric curves of methylparaben (pattern), mebendazole drug and its respective product were obtained using a Shimadzu calorimeter, model DSC-50, in a nitrogen atmosphere of 50 mL min^{-1}, in different heating rate (10, 20, 40, 60 and 80°C min^{-1}) up to 500°C of temperature.

Non-isothermal thermogravimetric curves of mebendazole raw material and tablets of 100 mg were obtained using a Shimadzu thermal balance, model

* Author for correspondence: ruiomacedo@ig.com.br

1388–6150/$20.00

Akadémiai Kiadó, Budapest, Hungary
Springer, Dordrecht, The Netherlands

TGA-50H, with rate heating of 10, 20, 40, 60 and 80°C min^{-1} up to the temperature of 900°C, with n=3, in an atmosphere of synthetic air, flow of 20 mL min^{-1}, and nitrogen 50 mL min^{-1}. Non-isothermal thermogravimetric curves of methylparaben were obtained in the same Shimadzu thermal balance, also the same heating rate up to the temperature of 400°C, when it finishes its mass loss, with n=3. The mass used was 8.0±0.5 mg, which was put in an alumina crucible. Curves were analyzed by TASYS program from Shimadzu, to characterize the mass loss stages.

Equation of Arrhenius

Thermogravimetric non-isothermal data were used to determination of reaction order by equation of Arrhenius [17].

$$k_{vap} = A e^{-E_{vap}/RT}$$

where E_{vap} is the vaporization energy, A is the pre-exponential factor, R in the universal gas constant, T is the absolute temperature and k_{vap} is the evaporation coefficient.

Equations of Antoine and Langmuir

Data obtained from thermogravimetric experiments of methylparaben were used to construct the vapor pressure curves, using the equation of Antoine, and after determine the value of 'k', which will be used to construct the vapor pressure curves of drug and tablets of mebendazole, using the equation of Langmuir, both presented following.

Antoine's equation [16] is presented as it follows:

$$\ln P = \frac{A-B}{T+C}$$

where P is the vapor pressure, T is the absolute temperature and A, B and C are the Antoine's constants in a temperature interval [17]. Antoine's constants registered to methylparaben are: A=5.23662, B=1159.34 and C=–220.03, to a temperature interval of 446–517 K [18].

The Langmuir's equation [16] is presented as it follows:

$$dm/dt = P\alpha(M/2\pi RT)$$

where (dm/dt) is the mass loss rate per area unit, P is the vapor pressure, α is the vaporization constant and M is the molecular mass of evaporation vapor.

Langmuir's equation can be modified to obtain the vapor pressure values of many simple components. The follow modification is described [16]:

$$P = [\alpha^{-1}(2\pi R)^{1/2}][(T/M)^{1/2}(dm/dt)] = k\upsilon$$

where $k=\alpha^{-1}(2\pi R)^{1/2}$ and $\upsilon=(T/M)^{1/2}(dm/dt)$.

If k is considered a constant t a group of data and it is independent of the used material, so the graphic of P *vs.* υ gives the value of k.

Method of Ozawa

Activation energy of non-isothermal TG curves of drug and tablet of mebendazole was determined by Ozawa's method [19].

Equations of f_1 and f_2

The equations of f_1 and f_2 are recommended by FDA as an acceptable method to compare the dissolution profiles; however, this method was used because it compares straight lines parallel bars, in which f_1 will define the difference between the straight lines and f_2 will define the similarity between them. Data from vapor pressure curves profiles to the drug and tablet of mebendazole in both environmental situations were applied in the equations of f_1 and f_2. The acceptance limits for two samples belong to the same population are: f_1 smaller than 15% and f_2 bigger than 50% [20].

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} \left| R_t - T_t \right|}{\sum_{t=1}^{n} R_t} \right\} \cdot 100\%$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} \omega_t (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\}$$

Results and discussion

Calorimetric characterization of mebendazole's drug and tablets

Calorimetric curves of mebendazole drug showed two endothermic processes (Fig. 1a). The first endothermic process begins in 246.02°C, which the maximum peak occurs in 263.72°C, and the second endothermic process that begins approximately in 318°C presented maximum peak in 326°C, in a heating rate of 10°C min^{-1}. According to the Merck Index, the melting of mebendazole drug occurs in 288.50°C, when in its synthesis is utilized as solvent the acetic acid and methanol. However, the analyzed mebendazole showed melting onset a lot distant form that value, even in the different rates used (20, 40, 60 and 80°C min^{-1}), what suggests the presence of the two polymorphs in the raw material. Mebendazole tablet showed four endothermic processes (Fig. 1b). The first process refers to the humidity loss, the second endothermic process begins in 218.78°C, which max-

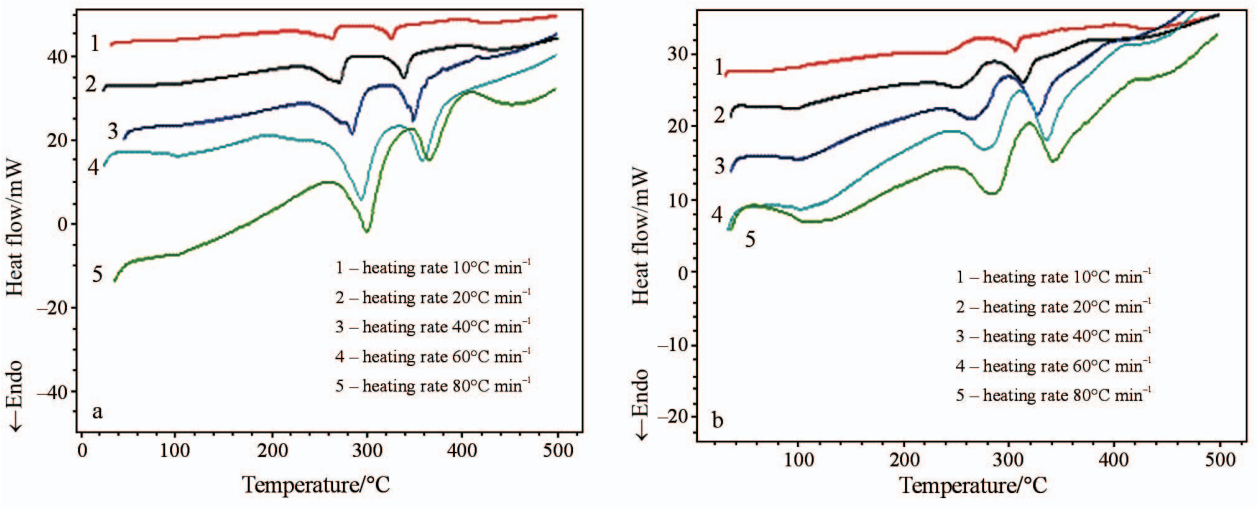

Fig. 1 DSC curves of mebendazole a – drug and b – tablet

imum peak occurs in 233.24°C, the third process begins in 295.27°C and the fourth process in 408.19°C, in a heating rate of 10°C min^{-1}. So, the tablet of mebendazole showed an anticipation of onset melting related to the drug what indicates the influence of formulation components in the thermal characteristics of the drug.

Thermogravimetric characterization of mebendazole's drug and tablets

Mebendazole drug in the atmospheres of nitrogen (Fig. 2a) and nitrogen with synthetic air (Fig. 2b) presented three stages of thermal decomposition in all heating rates studied. The mass loss were 13.8, 10.6 and 35.6%, respectively in the first, second and third

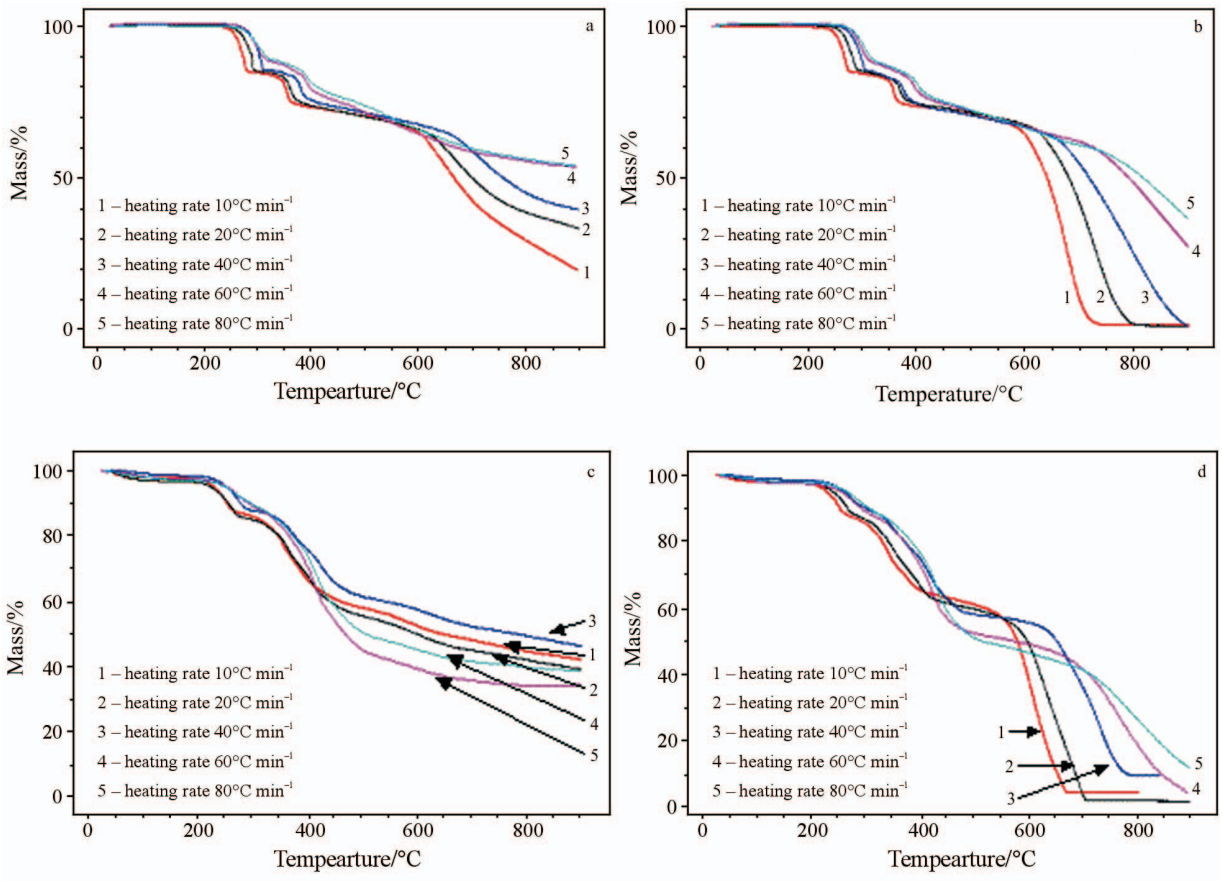

Fig. 2 TG curves at different heating rates of mebendazole drug in a – nitrogen and b – nitrogen with synthetic air atmosphere; and mebendazole tablet c – in nitrogen, d – nitrogen with synthetic air atmosphere

stages in nitrogen atmosphere; and 14.6, 11.1 and 62.6%, respectively in the first, second and third stages in nitrogen with synthetic air. The third stage of mebendazole drug resists to the volatilization process, what is confirmed by the lower mass loss when the heating rate is enhanced in the inert environment with nitrogen. Another relevant aspect that confirms the high resistance of polymorph to melt followed by volatilization refers to the higher mass loss in the third stage, when synthetic air is added to nitrogen flow, when compared to inert environment.

Mebendazole tablet in a nitrogen (Fig. 2c) and nitrogen with synthetic air (Fig. 2d) atmospheres showed four stages of thermal decomposition, with following mass loss, 2.21, 9.61, 31.38 and 15.44%, respectively in the first, second, third and fourth processes in nitrogen atmosphere; and 1.79, 9.53, 30.01 and 52.21% in nitrogen with synthetic air atmosphere. Data show that the heating rate enhance implies in the reduction of mass loss. The analysis suggest that the first two volatilization stages of mebendazole present polymorphs with lower thermal stability and the third stage is the most stable polymorph.

Determination of reaction order, activation energy and respective pressure curves to the drug and tablet of mebendazole

Methylparaben was used as pattern and presented a thermal process with kinetic of zero order, as foreseen to compounds that present vaporization process, as shown in literature [12]. The obtained values of '*k*' for methylparaben in the rates of 10, 20, 40, 60 and 80°C min^{-1} with synthetic air were 125555, 245191, 414034, 605841 and 714416, respectively. In an inert environment in the rates of 10, 20, 40, 60 and 80°C min^{-1}, the values of '*k*' were: 125413, 246932, 413676, 597515 and 709030. Mebendazole's drug activation energy, obtained by Ozawa's method in nitrogen and nitrogen with synthetic air atmosphere were respectively 142.7±4.4 kJ mol^{-1}, in a temperature interval from 227 up to 300°C and 116.0±3.8 kJ mol^{-1}, in a temperature interval from 235 up to 300°C. The activation energy of mebendazole's tablet in nitrogen and nitrogen with synthetic air atmosphere were respectively 101.4±7.5 kJ mol^{-1}, in a temperature interval from 197 up to 400°C and 104.3±4.1 kJ mol^{-1}, in a temperature interval from 201 up to 280°C.

The drug and the tablet of mebendazole also presented a zero order reaction kinetic, confirming a vaporization process. The values of '*k*' from methylparaben were used to obtain the vapor pressure values and its respective curves to mebendazole's drug and tablet in an environment of nitrogen and nitrogen with synthetic air, in the rate heating of 10, 20, 40, 60 and 80°C min^{-1} (Figs 3 and 4). Figures 3 and 4 showed that occurs an increase of vapor pressure with the increase of heating rate, however, it is worth to say that the vapor pressure presented to the drug is higher than that one to the tablet of mebendazole in both environmental situations and in all heating rates.

Table 1 shows that the values of f_1 and f_2 to the drug and the tablet of mebendazole are in the accepted limits to all heating rates, those are, f_1 is smaller than 15% and f_2 are higher than 50%, what confirms that there is no difference in behaviour between the drug and the tablet of mebendazole in both environmental conditions, confirming the process as volatilization.

Determination of mebendazole's contents in tablets

Data of average vapor pressure from drug and tablet of mebendazole in the rates of 10, 20, 40, 60 and 80°C min^{-1} and in the two environmental conditions were analyzed to obtain a factor. This factor was used as an analytical parameter to choose the best rate that defines the method, which it was the rate of 20°C min^{-1}. It was obtained a calibration curve to the environment of nitrogen (Fig. 5a) and nitrogen with

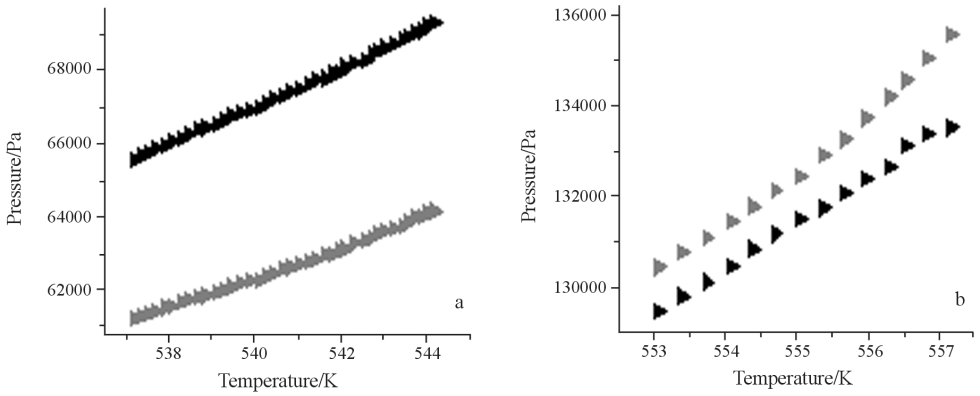

Fig. 3 Vapor pressure curves of mebendazole's drug in the heating rates of: a – 10, b – 20, c – 40, d – 60 and e – 80ºC min^{-1}, black triangle – in nitrogen and grey triangle – nitrogen with synthetic air atmospheres

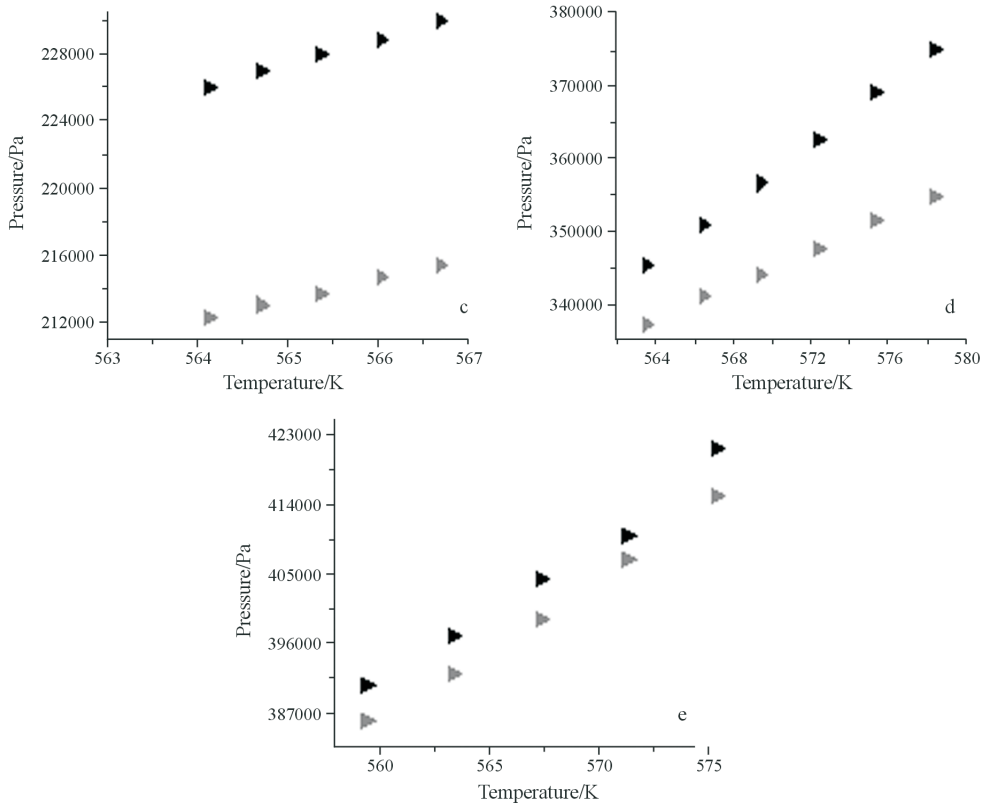

Fig. 3 Continued

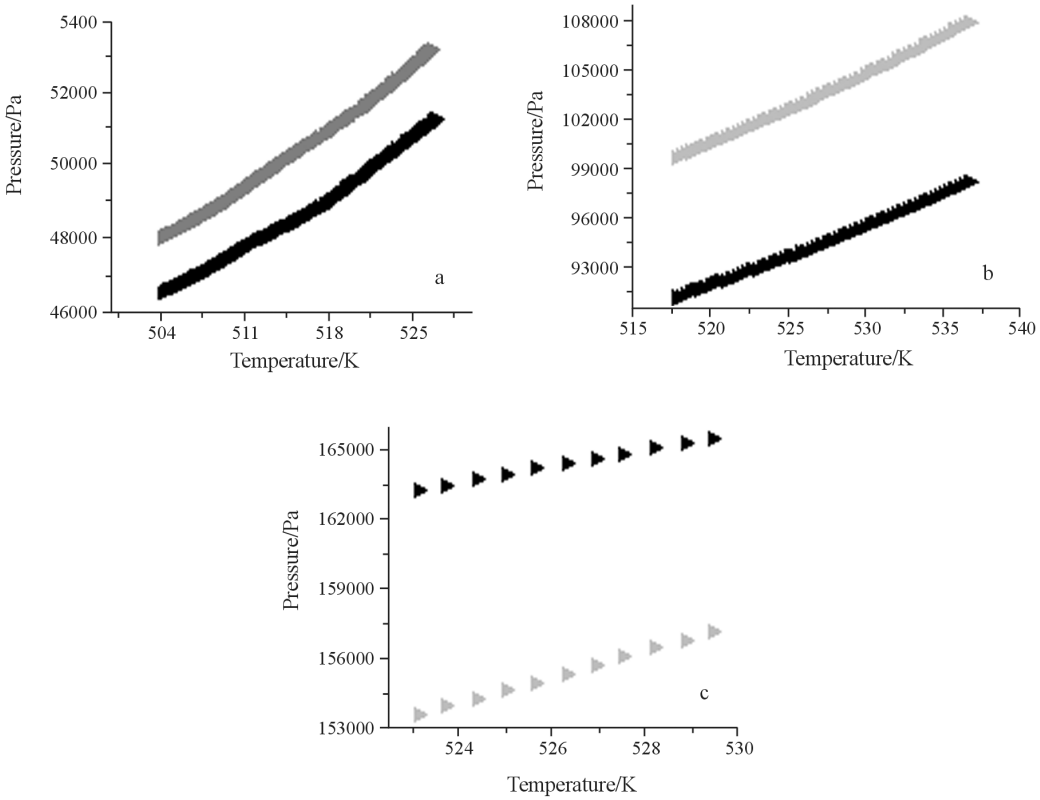

Fig. 4 Vapor pressure curves of mebendazole's tablet in the heating rates of: a – 10, b – 20, c – 40, d – 60 and e – 80ºC min^{-1}, black triangle – in nitrogen and grey triangle – nitrogen with synthetic air atmospheres

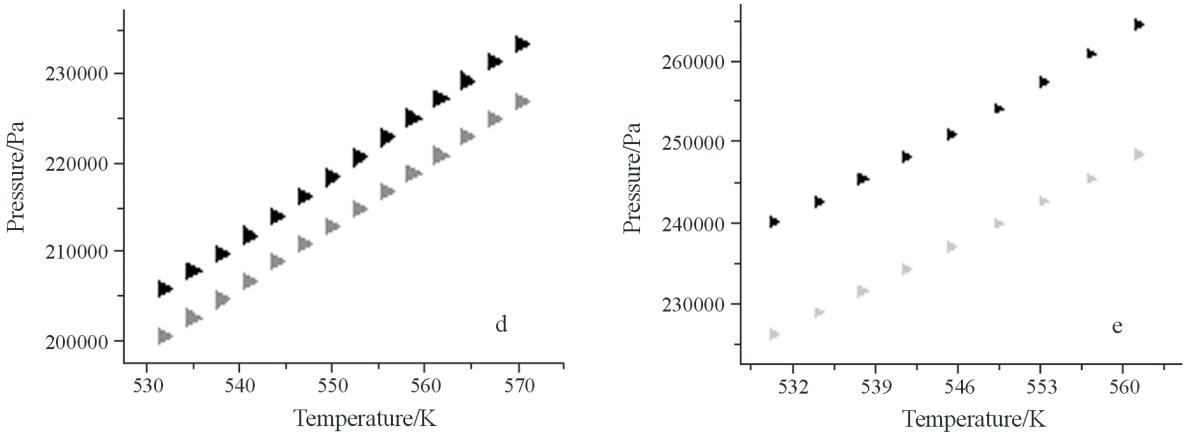

Fig. 4 Continued

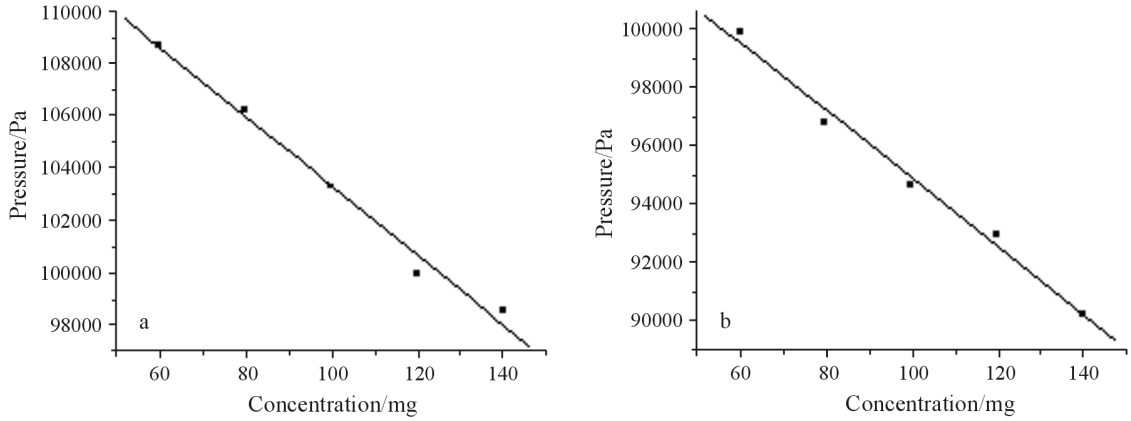

Fig. 5 Calibration curve of mebendazole + MC101 in a – nitrogen and b – nitrogen with synthetic air atmospheres

Table 1 Resultant data from equations of f_1 and f_2 to the drug and tablet of mebendazole in different heating rates

Mebendazole drug									
10ºC min^{-1}		20ºC min^{-1}		40ºC min^{-1}		60ºC min^{-1}		80ºC min^{-1}	
f_1	f_2	f_1	f_2	f_1	f_1	f_2	f_1	f_2	f_1
6.63	–81.91	3.25	–80.97	5.84	–106.11	2.33	–95.31	1.18	–83.17
6.74	–82.36	3.06	–79.75	5.81	–106.07	2.56	–97.59	1.21	–83.96
6.81	–82.66	3.16	–80.59	5.83	–106.18	2.90	–100.74	1.25	–84.84
6.88	–82.96	3.25	–81.26	5.87	–106.39	3.22	–103.39	1.12	–83.03
6.93	–83.19	3.28	–81.54	5.97	–106.81	3.54	–105.91	1.19	–84.64
Mebendazole tablet									
10ºC min^{-1}		20ºC min^{-1}		40ºC min^{-1}		60ºC min^{-1}		80ºC min^{-1}	
f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2
3.26	–59.01	9.37	–96.56	5.94	–99.35	2.43	–85.57	5.57	–107.27
3.29	–59.37	9.43	–96.89	5.86	–99.07	2.43	–85.80	5.61	–107.56
3.40	–60.35	9.50	–94.11	5.78	–98.81	2.45	–86.18	5.67	–107.95
3.53	–61.33	9.57	–95.18	5.69	–98.51	2.54	–87.20	5.74	–108.40
3.57	–61.80	9.64	–95.99	5.58	–98.12	2.59	–87.91	5.82	–108.84
3.26	–59.01	9.37	–96.56	5.94	–99.35	2.43	–85.57	5.57	–107.27

synthetic air (Fig. 5b), which linear regression of them permitted to obtain the following equations and respective variation coefficient: y=116582+(–132.6)x and R=0.9944, y=106531+(–116.5)x and R=0.9953. Utilizing the calibration curve it was determined the drug's concentration in tablet obtaining a content of 100.5 mg of mebendazole in nitrogen environment and 103.5 mg in nitrogen with synthetic air environment, which are respectively equivalent to 100.5 and 103.5% of labeled value. Data were compared with the values obtained by mebendazole's determination in the pharmacopoeia method [16], which the value was 99.5%.

Conclusions

Data analysis showed that mebendazole presented same constants of vapor pressure in atmosphere of nitrogen or nitrogen plus synthetic air. The values of the mebendazole concentration are similar if obtained by thermogravimetric method or Brazilian pharmacopoeial method.

References

1 B. G. Katzung, Farmacologia Básica & Clínica, Guanabara Koogan, Rio de Janeiro 2003, pp. 709–715, 778.
2 A. C. Schmidt, J. Therm. Anal. Cal., 81 (2005) 291.
3 F. I. Kanaze, E. Kokkalou, I. Niopas, M. Georgarakis, A. Stergiou and D. Bikiares, J. Therm. Anal. Cal., 86 (2006) 283.
4 F. S. Souza, A. P. B. Gomes and R. O. Macedo, J. Therm. Anal. Cal., 64 (2001) 739.
5 B. D. Glass, Cs. Novák and M. E. Brown, J. Therm. Anal. Cal., 77 (2004) 1013.
6 B. Marciniec, M. Kozak and K. Dettlaff, J. Therm. Anal. Cal., 77 (2004) 305.
7 R. O. Macedo, T. G. do Nascimento, C. F. S. Aragão and A. P. B. Gomes, J. Therm. Anal. Cal., 59 (2000) 1.
8 A. C. D. Medeiros, N. A. B. de Cervantes, A. P. B. Gomes and R. O. Macedo, J. Therm. Anal. Cal., 64 (2001) 745.
9 N. A. B. de Cervantes, A. C. D. Medeiros, A. F. O. Santos and R. O. Macedo, J. Therm. Anal. Cal., 72 (2003) 535.
10 P. Basu, K. S. Alexander and A. Riga, J. Therm. Anal. Cal., 83 (2006) 19.
11 G. G. G. Oliveira, H. Ferraz and J. S. R. Matos, J. Therm. Anal. Cal., 79 (2005) 267.
12 K Chartterjee, A. Hazra, D. Dollimore and K. S. Alexander, Eur. J. Pharm. Biopharm., 54 (2002) 171.
13 L. Burnham, D. Dollimore and K. Alexander, Thermochim. Acta, 367–368 (2001) 15.
14 T. V. Sorokina, D. Dollimore and K. S. Alexander, Thermochim. Acta, 392–393 (2002) 315.
15 S. Vecchio, A. Catalani, V. Rossi and M. Tomassetti, Thermochim. Acta, 420 (2004) 99.
16 A. Hazra, K. Alexander, D. Dollimore and A. Riga, J. Therm. Anal. Cal., 73 (2004) 317.
17 R. M. Stephenson and S. Malamowski, Handbook of the Thermodynamics of Organic Compounds, Elsevier, New York, p. 263.
18 T. Ozawa, Bull. Chem. Soc. Jpn., 38 (1965) 1881.
19 V. P. Shah, Y. Tsong, P. Sathe and L. Jen-Pie, Pharm. Res., 15 (1998) 6.
20 Farmacopéia Brasileira, 4th Ed. São Paulo, Atheneu 1988.

Received: June 20, 2006
Accepted: September 5, 2006

DOI: 10.1007/s10973-006-7741-9