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International Journal of Pharmaceutics 260 (2003) 303–314
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms

Adriano A.S. Araújo [a], Sílvia Storpirtis [a], Lucildes P. Mercuri [b], Flávio M.S. Carvalho [c], Mery dos Santos Filho [d], Jivaldo R. Matos [b,*]

[a] *Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, SP, Brazil*
[b] *Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo, Av. Lineu Prestes, 748, São Paulo, SP 05508-000, Brazil*
[c] *Departamento de Mineralogia e Geotectônia, Instituto de Geociências, Universidade de São Paulo, São Paulo, SP, Brazil*
[d] *Oxiteno S/A Indústria e Comércio, São Paulo, SP, Brazil*

Received 4 September 2002; received in revised form 1 May 2003; accepted 2 May 2003

Abstract

Modern thermal analysis techniques are frequently used because of their ability to provide detailed information about both the physical and the energetic properties of a substance. In the present work, the thermal decomposition of zidovudine (AZT) was studied using differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). Thermal analysis was supplemented using elemental analysis (C, H, and N), infrared (IR) spectroscopy, and X-ray powder diffraction to characterize the solid intermediates products. Volatile products of the thermal decomposition of AZT were studied by a system composed of the TG/DTA coupled gas chromatography/mass spectrometry (GC/MS). The physical–chemical properties and compatibilities of several commonly used pharmaceutical excipients with AZT were evaluated using thermal methods. The results showed that the product originated from the first thermal decomposition stage corresponds to the cleavage followed by elimination of the azide group and consequent formation of thymine. The second event corresponds to thermal decomposition of thymine. TG/DTA–GC/MS system identified thymine's decomposition products as furan and 2-furanmethanol like volatile species. Comparison of the thermoanalytical profiles of the mixtures with individual compounds did not give any evidence of interactions.

Keywords: Solid state interactions; Thermal analysis; Zidovudine (AZT); HIV/AIDS

1. Introduction

Acquired immune deficiency syndrome (AIDS) is a degenerative disease of the immune system caused by the human immunodeficiency virus (HIV), a *lenti-virus* belonging to the family of the *Retroviridae* (Barre-Sinoussi et al., 1983; Gallo et al., 1983; Breimer et al., 1994). Zidovudine, 3′-azido-3′-deoxy-thymidine (azidothymidine; AZT) was shown to inhibit HIV "in vitro" and to induce immunologic, virologic and neurologic improvements in HIV infected patients. HIV infection causes a severe depletion of CD_4 expressing cells which include T lymphocytes,

* Corresponding author. Tel.: +55-11-3091-3837.
E-mail address: jdrmatos@usp.br (J.R. Matos).

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doi:10.1016/S0378-5173(03)00288-6

monocytes, and macrophages, leading to a profound immunosuppression (Gambertoglio and Peter, 1998). AZT, the first compound that has been approved by the Food and Drug Administration (FDA-USA), was long used as monotherapy for HIV infection. This drug belongs to the class of nucleoside reverse transcriptase (RT) inhibitors. Several studies have demonstrated that the combination of AZT with other available compounds leads to a more sustained viral suppression (Gambertoglio and Peter, 1998; Fischl, 1989; Bardey et al., 1994).

The development of effective antiviral therapies for the treatment of individuals infected with the human immunodeficiency virus presents unique challenges (Hirsch and Daquila, 1993). The progress and strategies for HIV antiviral treatment research have as priorities the discovery and development of new antiretroviral compounds, new dosage forms, understanding the mechanisms of HIV resistance to antiretroviral agents, and study of combinations therapies (Steven and Pettinelli, 1997). Development of new dosage forms is facilitated by the use of thermal methods for characterization of pharmaceutical preparations with the directed application to the quality control (Ford and Timmins, 1986).

The term thermal analysis refers to a group of techniques in which a physical property of a substance and/or its reaction products is measured as a function of temperature whilst the substance is subjected to a controlled temperature program (Wendlandt, 1986). The most widely used techniques are differential thermal analysis (DTA), differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). These are techniques widely used in the pharmaceutical sciences for the characterization of solid drugs and excipients. DTA is a technique in which the difference in temperature between the sample and a thermally stable reference material is monitored against time or temperature, while the temperature is programmed in a specified atmosphere. DSC technique involves the application of a heating or cooling signal to a sample and a reference. When the sample undergoes a thermal event, the difference in heat flow to a sample (pan) and to a reference (pan) is monitored against time or temperature while the temperature is programmed in a specified atmosphere. Consequently, the temperature and energy associated with events, such as melting, oxidation and reduction reactions, glass transition, boiling, sublimation, decomposition, crystallization or gel to liquid crystal transition can be evaluated. When such events are evaluated for mixtures of drugs and excipients, possible interactions may be discerned (Wendlandt, 1986; Giron, 1998a,b). TG is a thermal analysis technique in which the change in sample mass is determined as a function of temperature and/or time whilst sample is subjected to a controlled temperature program. In DTG, the derivative of the mass-change with respect to time, dm/dt, is recorded as a function of time (t) or temperature (T). In other cases, the derivative of the mass-change with respect to temperature, dm/dT, is recorded as a function of time or temperature. In either case, the resulting curve is the first derivative of TG curve, giving a series of peaks, instead of a stepwise curve. A horizontal plateau in the TG curves gives a corresponding horizontal plateau in the DTG curve because dm/dt $= 0$. A maximum in the DTG curve is obtained when the TG curve has an inflection point where mass is being lost the most rapidly.

Thermal analysis techniques have been used for pharmaceuticals for more than 30 years. In preformulation studies, it is possible to derive information about potential physical or chemical incompatibilities between an active ingredient and so called “inert” excipients (Mura et al., 1998; Venkataram et al., 1995; Lotter et al., 1997; Gomes-Pinho et al., 1998). Additional information regarding the effects of storage at elevated temperatures can also be obtained. These reactions may or may not lead to inactivation of the active ingredient in the formulation. Several studies have already been done in this field. Venkataram et al. (1995), related the potential incompatibilities of various commonly used excipients with indomethacin using DSC. The evaluation of compatibility of tablet excipients with albendazole and closantel using DSC and high performance liquid chromatography (HPLC) has been made by Lotter et al. (1997). Gomes-Pinho et al. (1998), have published a study of application of thermoanalytical methods in preformulation of chlohydrate of metformin tablets. Mura et al. (1998), used thermal analysis as a screening technique in preformulation studies of picotamide solid dosage forms.

The objective of the present study was to evaluate the thermal stability and decomposition products of AZT. In this work thermal analysis was supplemented by using elemental analysis (C, H, and N), IR

spectroscopy and X-ray powder diffraction to identify the AZT, and its thermal decomposition products. The process of thermal decomposition was complemented by TG/DTA–GC/MS coupled system, which provided structural information about the decomposition products through identification of the evolved gas. DSC and TG/DTG were used to assess the compatibility of AZT with a number of common pharmaceutical excipients.

2. Experimental

2.1. Materials

The reference standard of AZT ($C_{10}H_{13}N_5O_4$; 3′-azido-2,3′-dideoxythymidine) was obtained from United States Pharmacopeia (lot: F). Thymine was obtained from Sigma (lot No. 129FO508). Excipients tested were: starch (Henrifarma), hydroxypropylmethylcellulose (Methocel®K100), magnesium stearate (Dyne), lactose (Henrifarma), colloidal silicon dioxide (Aerosil, Galena), polyethyleneglycol 6000 (Galena). The mixed samples consisted of equal weights of AZT and each excipient were individually weighed into amber glass vials to give composite weights of 20 mg. The physical mixtures was gently prepared at a 1:1 (AZT:excipient) weight ratio by simple mixing with a spatula.

2.2. Measurements

Carbon, hydrogen, and nitrogen contents were determined by elemental analysis using a Pekin–Elmer analyzer (Model 2400).

The IR absorption spectra of the AZT and products of thermal decomposition were obtained at room temperature in the range 4000–400 cm^{-1} in KBr pellets using a Nicolet spectrophotometer, model Magna 550.

DSC curves were obtained in a DSC-50 cell (Shimadzu) using aluminium crucibles with about 2 mg of samples, under dynamic nitrogen atmosphere (50 ml min^{-1}) and heating rate of 10 °C min^{-1} in the temperature range from 25 to 600 °C. The DSC cell was calibrated with indium (mp 156.6 °C; ΔH_{fus} = 28.54 J g^{-1}) and zinc (mp 419.6 °C). TG/DTG curves were obtained with a thermobalance model TGA 50 (Shimadzu) in the temperature range 25–900 °C, using platinum crucibles with ∼3 mg of samples, under dynamic nitrogen atmosphere (50 ml min^{-1}) and heating rate of 10 °C min^{-1}.

The DTG–GC/MS system was adjusted to operate at the following conditions: (i) DTG-50H used simultaneous TG/DTA modulus operating under dynamic atmosphere of helium (99.999%) at 50 ml min^{-1} and heating rate of 20 °C min^{-1} from 30 to 900 °C, with sample mass of about 2 mg; (ii) the evolved gaseous material was adsorbed to Tenax 60/80 mesh trap cooled at dry ice temperature. After that the trap was heated to 300 °C and the gaseous material was desorbed and separated a gas chromatograph (GC-14B series); and (iii) GC/MS-QP5000 system was composed of the chromatograph (GC-14B) with a MS detector operating under the helium atmosphere. The injection port was maintained at a constant temperature of 300 °C to introduce all released material into the column. The packed glass column containing 1.1 m × 3.2 mm i.d. and coated with Tenax 60/80 mesh was programmed to heat to 80 °C, was held for 5 min, followed by heating at a rate of 20 °C min^{-1} up to 300 °C, and held for 5 min. The Q-MS mass spectrometer was operated in the electron bombardment ionization (70 eV) mode and the *m*/*z* range of 16–300, which enabled the detection of the ions evolved from the sample. Spectral National Institute of Standards (NIST), chemical and structural database was used to assign the mass spectra of unknown evolved compounds.

The X-ray diffraction (XRD) patterns were obtained on a Siemens, model D5000, with tube of Cu Kα, in the range of 3–65° (2θ) and 1 s of pass time, using the powder XRD method.

3. Results and discussion

3.1. Thermal analysis of AZT and characterization of degradation products

DSC curve of AZT (Fig. 1) shows a sharp endothermic peak that corresponds to melting in the range of 120–124 °C (melting onset T_{onset} = 122.6 °C; enthalpy change (ΔH) = 123.6 J g^{-1}). After melting, two peaks are observed due to thermal decomposition. The first indicates an exothermic event in the range of 180–250 °C, presenting a high enthalpy value of

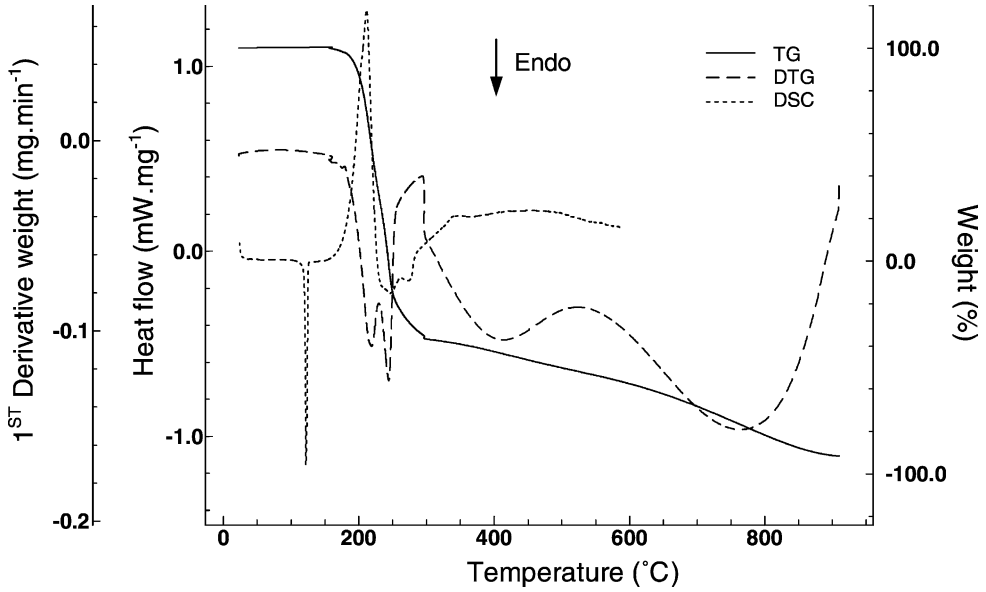

Fig. 1. DSC and TG/DTG curves of AZT in dynamic nitrogen and helium atmosphere, respectively (50 ml min^{-1}), and heating rate 10 °C min^{-1}.

905 J g^{-1}, while the second indicates an endothermic event in the range of 250–355 °C ($\Delta H = 165$ J g^{-1}). The TG/DTG curves indicate that the thermal decomposition process of AZT occurs in three stages in the following temperature range and weight losses: 153–249 °C ($\Delta m = 51.8\%$), 249–357 °C ($\Delta m = 20.3\%$), and 360–650 °C ($\Delta m = 28.2\%$).

The first event of weight loss represents 51.8% of the molecular mass of the AZT. The solid product of thermal decomposition at this stage has a molecular weight of about 129 g mol^{-1}. Comparing the calculated and experimental values suggests the formation of thymine ($C_5H_6N_2O_2$) followed by cleavage as the azide group and release of the 2-furanmethanol ring of AZT. Analytical data for percentages of C, H, and N in AZT (calc./found) are: C (44.94/45.12), H (4.89/5.46), N (26.21/26.39). The ratios of the calculated to the observed values for thymine by elemental analysis are: C (47.62/46.19), H (4.81/5.02), N (22.21/21.30). Using TG/DTG data, AZT was heated to a set temperature to isolate intermediate products at 249 °C (intermediate 1) and 357 °C (intermediate 2) for further characterization by IR, DRX, and DSC techniques.

The IR spectra of the AZT and products of thermal decomposition at various stages are shown in Fig. 2. The IR spectrum of AZT (Fig. 2a) shows the stretching bands in the 3500–3200 cm^{-1} wave number region assigned to ν_s and ν_{as} OH stretching, OH-bending mode at 1630–1600 cm^{-1}, a band at 2102 cm^{-1} assigned to νC=N=N=N (azide group), a band at 1694 cm^{-1} assigned to C=O, a band at 1385 cm^{-1} assigned to CH_2, and 1281 cm^{-1} assigned to C–O–C and C–OH. An examination of IR spectrum in Fig. 2b of thermal decomposition product isolated at 249 °C (intermediate 1) indicates bands in the wave number region of 3500 and 3300 cm^{-1} assigned to νO–H and νNH arising from AZT. This spectrum still presents the bands at 1694 and 1385 cm^{-1} which identify the functional groups as C=O and CH_2, respectively, in the thymine structure. Comparison to the spectrum of the standard thymine confirmed this intermediate as the thermal breakdown product of AZT.

Powder XRD patterns of AZT, intermediate 1, and intermediate 2 are shown in Fig. 3. XRD data were compared with the PDF-2 (JCDP-JCAPS) database library patterns which are attached to the computer program. The results identify AZT, thymine as intermediate 1, and residual thymine in the intermediate 2 (according to TG/DTG data and IR spectrum).

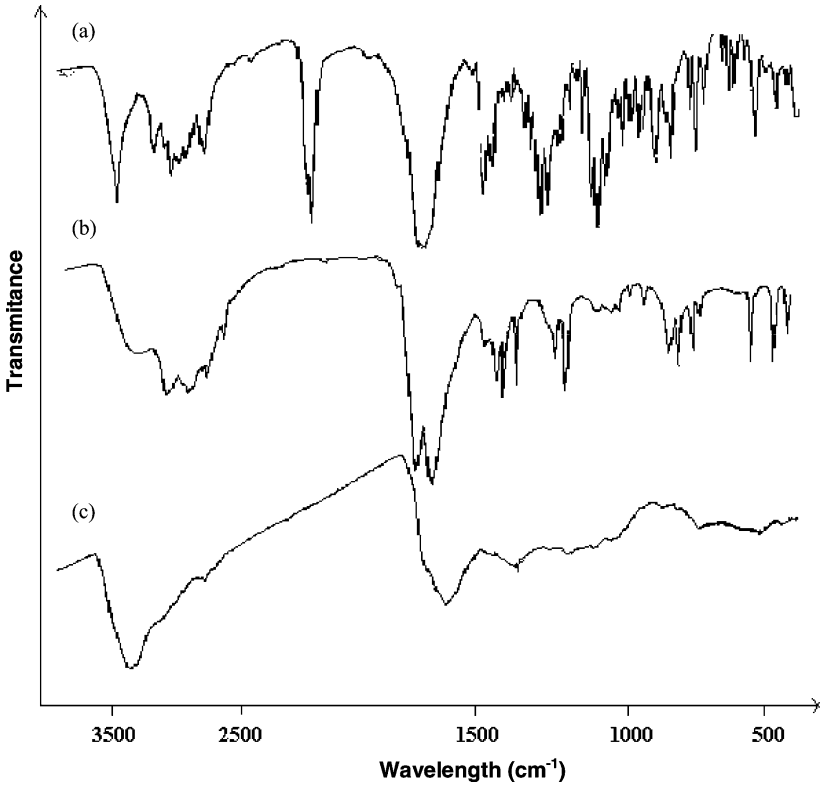

Fig. 2. The IR spectra of AZT (a) product of decomposition up to 249 °C (b) and product of decomposition up to 357 °C (c).

Fig. 4 shows the DSC profiles of AZT (a), intermediate 1 (b), standard thymine (c), and intermediate 2 (d). DSC curves of intermediate 1 show an endothermic event at 309 °C. This event is representative of the melting process of thymine (theoretical value 313–317 °C). DSC curve of the intermediate 2 compound did not show any thermal events, indicating that the generated thermal decomposition products (elemental carbon) are stable until 600 °C under dynamic N_2 atmosphere.

The TG/DTG curves of AZT obtained by TG/DTA–GC/MS coupled system are shown in Fig. 1. The data corroborate the weight loss obtained from conventional TG/DTG (not illustrated here). In addition, this coupled system gave the total ion chromatogram (TIC) of the volatile products derived from thermal decomposition (Fig. 5 and Table 1). Furthermore, the mass chromatograms (MC) indicated abundance of each molecular ion at its expected retention time (RT).

The experimental data obtained from the GC/MS of the coupled system also permitted the identification of the following products separated at respective retention time. The comparison of the *m*/*z* of the volatile products formed during thermal decomposition is shown in the Fig. 6. The identification of furan and 2-furanmethanol corroborated the results presented formerly in the characterization of solid intermediates of the thermal decomposition of AZT. These results suggest the use of the methodology for separation and identification of the volatile products recorded in the DTG–GC/MS coupled system as a screening tool for drugs and medicines.

3.2. Compatibility study with excipients

As seen in Fig. 7, the starch sample showed a major endothermic transition in the DSC curve between 30 and 130 °C corresponding to its dehydration (unbound water). However, this event was also shown in the TG

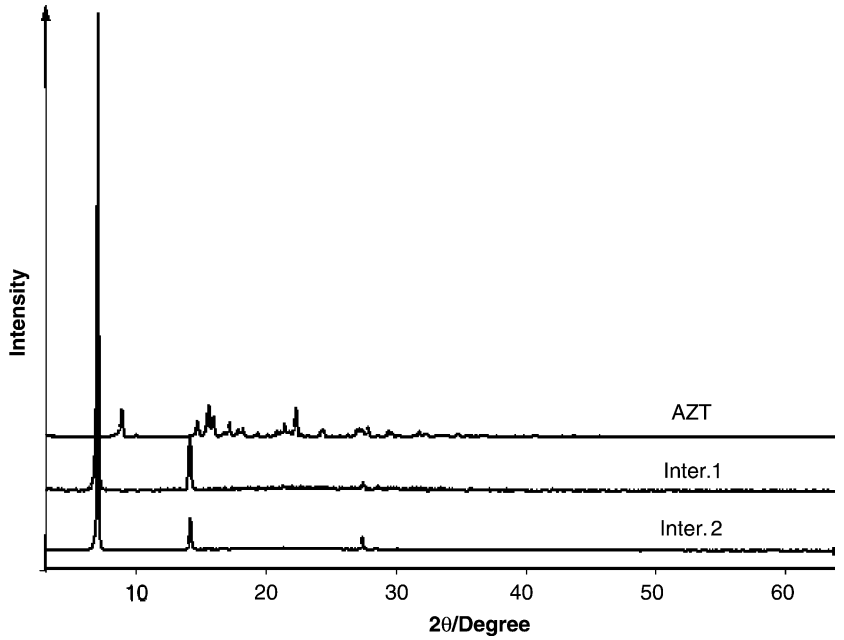

Fig. 3. X-ray diffraction of AZT, product of decomposition up to 249 °C (Inter. 1) and product of decomposition up to 357 °C (Inter. 2).

curve (Fig. 8) where a humidity loss of about 9.3% was verified. This excipient showed a thermal stability region between 140 and 260 °C, and an endothermic event indicated by broad peak at 311 °C, corresponding to the thermal decomposition of this material. The DSC and TG curves of the 1:1 physical mixture of the drug and of excipient (Figs. 9 and 10) correspond to the added signed from the pure components. These

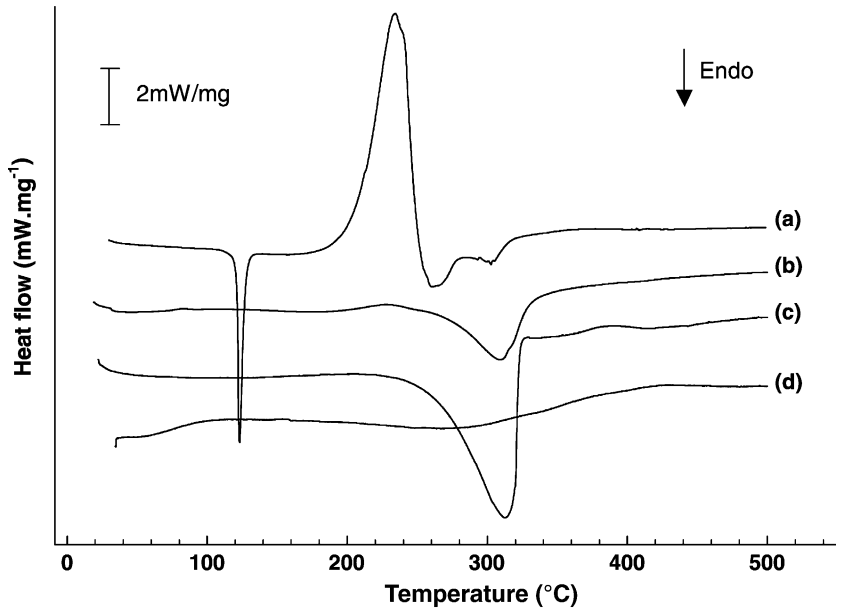

Fig. 4. DSC curves of AZT (a), intermediate 1 (b), standard thymine (c), and intermediate 2 (d).

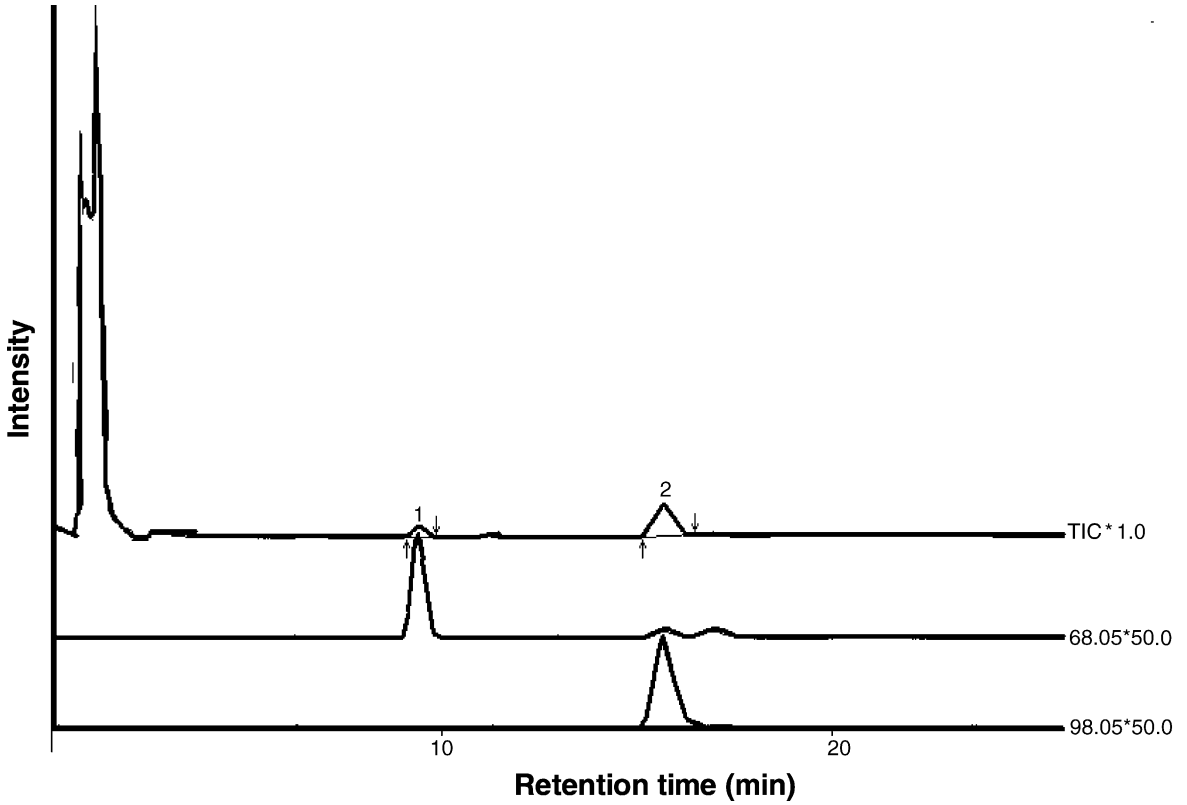

Fig. 5. TIC obtained from thermal decomposition of AZT. (1) Furan and (2) 2-furanmethanol.

results show that physical interaction of components did not occur within the mixture.

DSC and TG curves of HPMC (Figs. 7 and 8) presented a characteristic profile of elimination of water surface between 35 and 90 °C, thermal stability between 100 and 300 °C, following thermal decomposition as evidenced by the exothermic transition in temperature at about 375 °C. The thermogravimetric profile of the HPMC presented weight loss of 83.7% at 365 °C. Since the profile of DSC and TG curves of the AZT/HPMC mixture (Figs. 9 and 10) do not show characteristic changes introduced by the individual drug and excipient, we can conclude that there is no incompatibility between the compounds.

Table 1
Chromatographic data on the identification of the volatiles derived from thermal decomposition of AZT

Peak	Retention time (min)	*A*/*H* (s)	%Total	Identification
1	9.448	14324609	17.46	Furan
2	15.708	67740081	82.54	2-Furanmethanol

The DSC curve of magnesium stearate (Fig. 7) by itself had two endothermic transitions occurring at 81 and 110 °C that was assigned to dehydration (bound water). Magnesium stearate showed a thermal stability in the range of 130–300 °C and a broad peak relative to the endothermic event between 300 and 465 °C due to thermal decomposition. TG curve of magnesium stearate (Fig. 8) showed the dehydration (bound water) of excipient at a temperature of about 35 °C ($\Delta m = 4.3\%$), and confirmed that the endothermic event indicated above is relative to thermal decomposition of material in one step at about 305 °C ($\Delta m = 86.4\%$). The sum of representative curves of magnesium stearate and AZT (Figs. 9 and 10) correspond to the profile obtained from the physical mixture of these components, indicating that between components, there is not interaction.

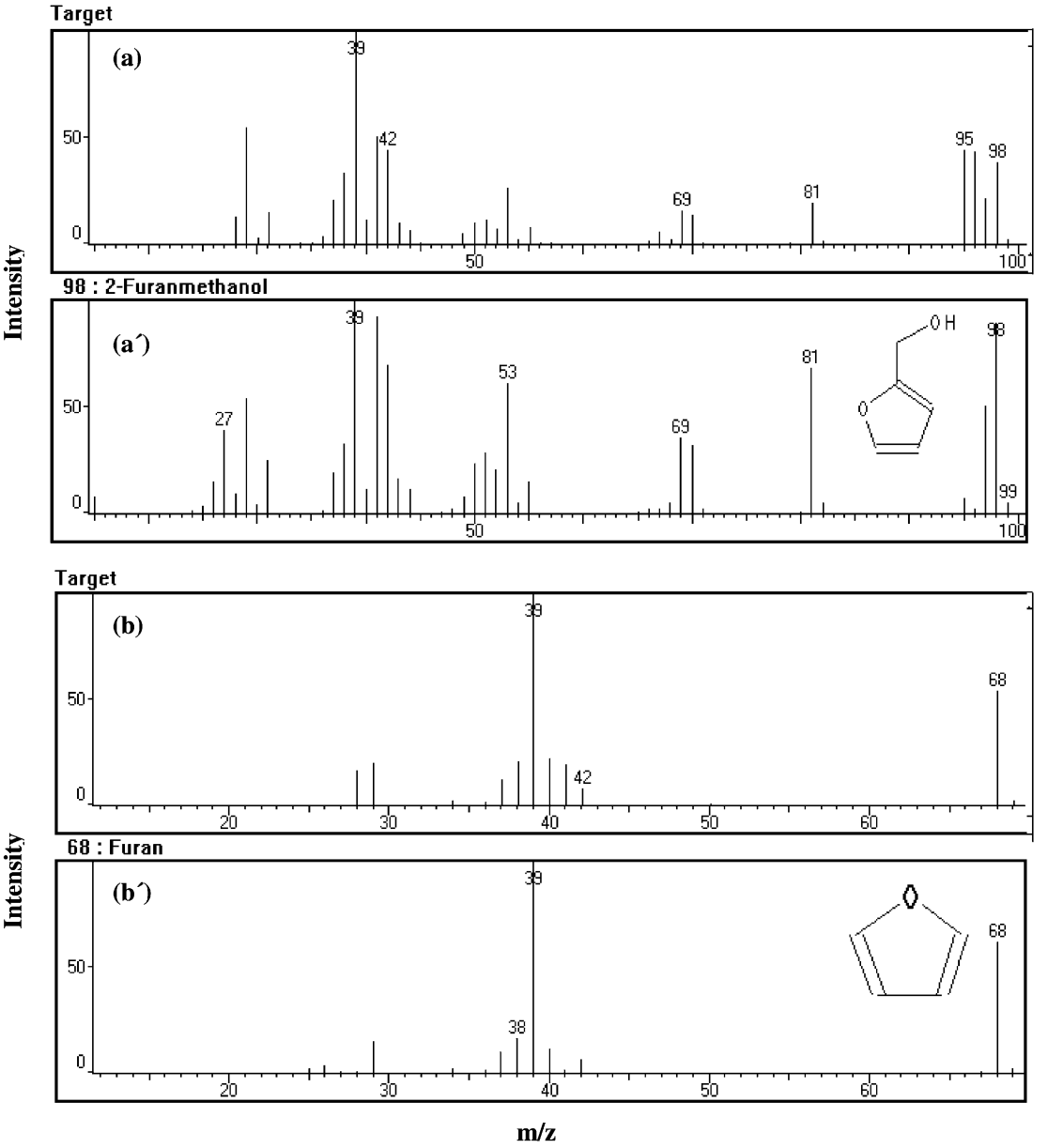

Fig. 6. Comparison of the mass spectra of the thermal decomposition of AZT (a, b) and the library (a′, b′), corresponding to 1 and 2 peaks of the TIC, respectively.

The thermal behavior of lactose is illustrated in the Figs. 7 and 8. The DSC curve shows a peak (endothermic event) corresponding to the dehydration (bound water) at 148 °C, an exothermic event due to crystalline transition (peak temperature at 176 °C), melting point at 217.9 °C, followed by thermal decomposition (Fig. 7). From TG/DTG curves four steps of weight loss can be observed: dehydration (Δm_1 = 5.4% and DTG_{peak} = 144 °C) due to water of crystallization, thermal decomposition (Δm_2 = 19.3% and DTG_{peak} = 248 °C; Δm_3 = 47.9% and DTG_{peak} = 306 °C), and carbonization initiating at about

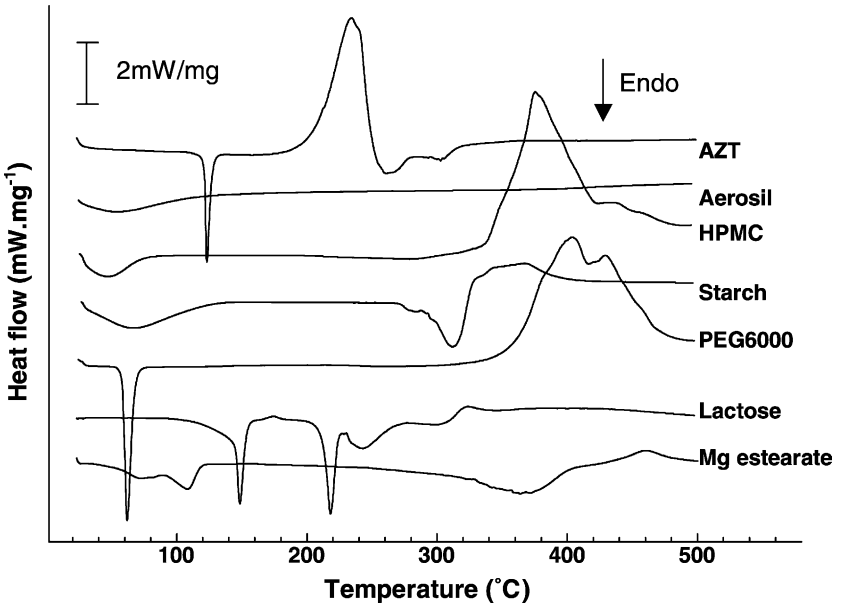

Fig. 7. DSC curves of AZT and excipients obtained in dynamic nitrogen atmosphere (50 ml min^{-1}) and heating rate 10 °C min^{-1}.

320 °C (Δm_4 = 32.7%) of the excipient (Fig. 8). The DSC and TG curves (AZT/lactose) presented in the illustrations 9 and 10, respectively, show that the events relative to AZT are not changed. Thus, there is no incompatibility between the two compounds.

Figs. 7 and 8 show thermal behavior of aerosil. From TG/DTG curves, a weight loss is observed, occurring in the temperature range of 25–100 °C and associated with desorption of physically adsorbed water vapor (e.g. surface H_2O) and possibly other gases

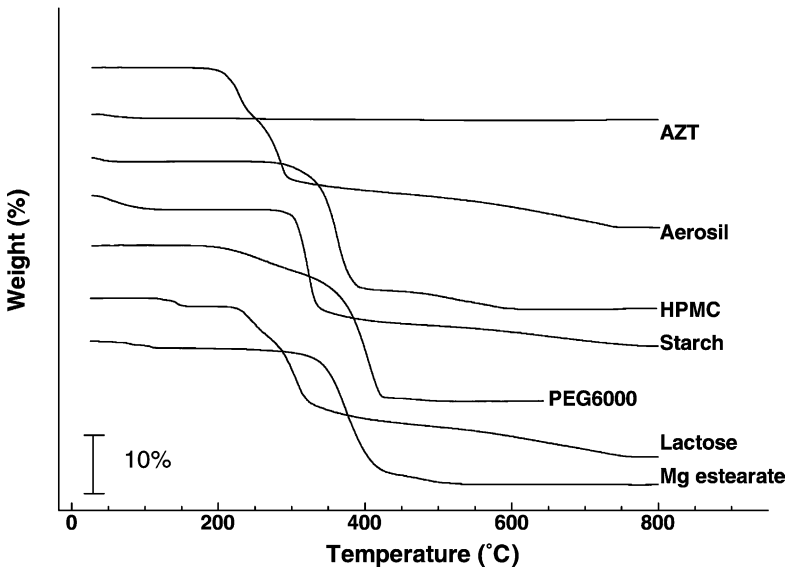

Fig. 8. TG curves of AZT and excipients obtained in dynamic nitrogen atmosphere (50 ml min^{-1}) and heating rate 10 °C min^{-1}.

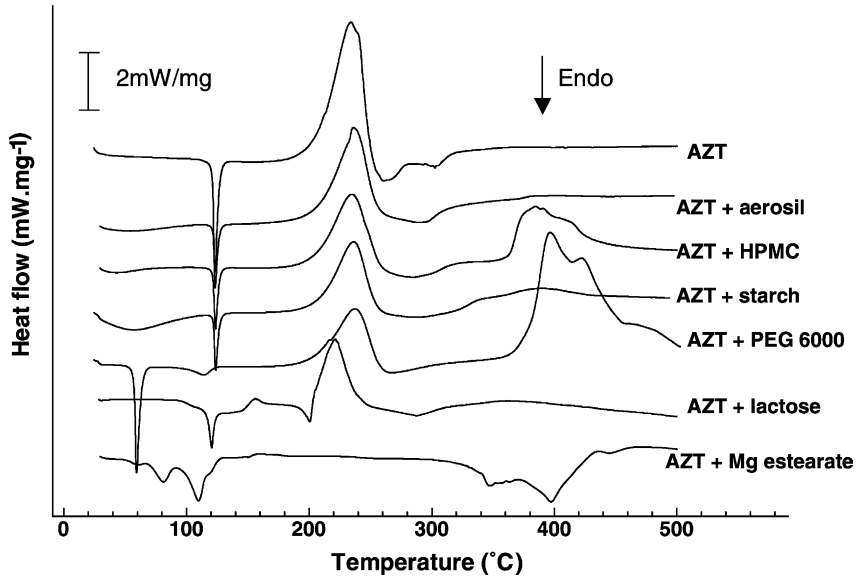

Fig. 9. DSC curves of AZT and 1:1 physical mixtures of drug and excipients obtained in dynamic nitrogen atmosphere (50 ml min^{-1}) and heating rate 10 °C min^{-1}.

on material surface. DSC data agree with TG/DTG results, indicating that this material is thermally stable up to 600 °C. The thermal behaviour of the binary mixture of AZT and aerosil (Figs. 9 and 10) show the endotherm and exotherm characteristic of drug, indicating the presumable absence of incompatibility.

DSC curve of polyethylene glycol (PEG 6000), Fig. 7, exhibit a single endothermic event indicated

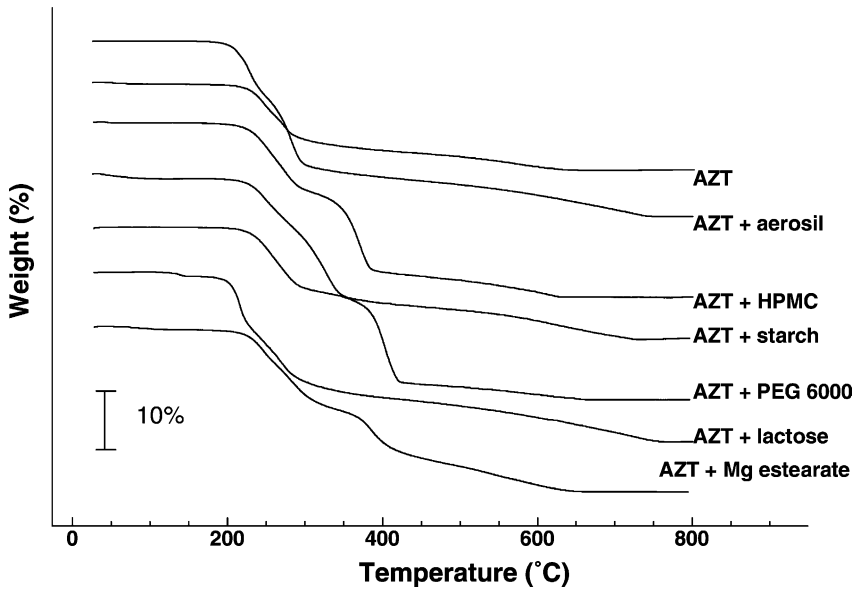

Fig. 10. TG curves of AZT and 1:1 physical mixtures of drug and excipients obtained in dynamic nitrogen atmosphere (50 ml min^{-1}) and heating rate 10 °C min^{-1}.

Table 2
Peak temperature and enthalpy values of AZT and binary mixtures with excipients

	T_{onset} (melting) (°C)	Enthalpy (fusion) J g^{-1}	$T_{onset\,TG}$ (°C)	$T_{onset\,DTG}$ (°C)	Weight loss (%)
Drug					
Zidovudine (AZT)[a]	122.6	123.6	225	229/284	32/40/**28**
Drug/excipients					
Starch	121.8	42.4	225	249/328	29/40/**25**
HPMC	121.3	50.2	228	271/370	39/45/**14**
Magnesium estearate	121.6	142.8[b]	223	247/284/385	20/25/31/**17**
Lactose	120.5	153.2[b]	124	216/270	36/33/**28**
Aerosil	121.4	48.2	225	247/273	18/20/**12**
PEG 6000	98.6	26.2	233	257/403	37/52/**9**

The values introduced in boldface represent the relative mass loss of the material due to carbonaceous elimination.
[a] Reference standard.
[b] Total value (AZT melting + excipient dehydration).

by a sharp peak corresponding to the melting of the polymer (T_{onset} = 62 °C and ΔH_{fus} = 206 J g^{-1}). Exothermic events were observed at 403 and 429 °C, relative to thermal decomposition. From TG curve of PEG (Fig. 8), three weight loss events of PEG 6000 can be observed (Δm_1 = 16.3% and DTG_{peak} = 257 °C; Δm_2 = 80.7% and DTG_{peak} = 404 °C; Δm_3 = 2.2% and DTG_{peak} = 460 °C). In the DSC curve representative of the mechanical mixture of AZT and PEG 6000, the characteristic melting endotherm of AZT was absent and a single endothermic peak, corresponding to the melting of the polymer, was observed (Fig. 9). The disappearance of the melting peak of drug is indicative of a strong interaction, but not necessarily corresponding to incompatibility. In fact, a similar effect was observed for other drugs, such as naproxen (Bettinetti et al., 1988; Mura et al., 1993), piroxicam (Fernandez et al., 1992), ketoprofen in mixtures with various PEGs, and was attributed to drug dissolution in the melted polymer (Botha and Lotter, 1989).

The values of the melting peak temperature, fusion enthalpy, and temperature range of thermal decomposition and weight losses (%) of AZT after mixing with excipients are listed in the Table 2.

4. Conclusion

Thermoanalytical methods have become important tools for the development of medicinal compounds. There are several advantages in using these techniques; small quantities of samples, quick scanning technique for solid state stability studies, and information about physical and chemical properties. This study shows the application of thermal analysis as a quick and efficient technique in the characterization of AZT and evaluation of the compatibility with excipients used in solid dosage forms. Combined techniques with elemental analysis (C, H, and N), IR spectroscopy, and X-ray powder diffraction allowed identification of the solid intermediates of the thermal decomposition of drugs. AZT alone was shown to decompose in three steps, where the first intermediate product of thermal decomposition was thymine and the subsequent steps involved the decomposition of thymine and elimination of a residue of carbon. The application of the TG/DTA–GC/MS coupled system in the evaluation of the degradation process and characterization of volatile products of the thermal decomposition of AZT proved valuable. Formation of furan and 2-furanmethanol were deduced which corroborated the characterization of the solid intermediates, and created a new perspective on the method of evaluation of the decomposition pathway and stability of drugs.

Thermoanalytical results supported as absence of incompatibility using physical mixtures of AZT and excipients (e.g. starch, hydroxypropylmethylcellulose, magnesium stearate, lactose, aerosil, and PEG 6000). The 1:1 physical mixtures of these excipients with AZT showed the characteristic AZT peak, except for the case of PEG 6000. The heats of fusion in all cases were close to the expected values. None of the samples

had thermoanalytical curves with additional events or news peaks.

Acknowledgements

The authors acknowledge to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for the financial support (Proc. Number 00/03130-2).

References

Bardey, V., Constant, H., Leboucher, G., 1994. Zidovudine: retrovir. Lyon Pharmaceut. 45, 31–33.

Barre-Sinoussi, F., Chermannj, C., Rey, F., Nugeyre, M.T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vezinet-Brun, F., Rozinoux, C., Rezenbaum, W., Montaignier, L., 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immunodeficiency syndrome (AIDS). Science 220, 868–871.

Bettinetti, G.P., Mura, P., Liguori, A., Bramanti, G., Giordano, F., 1988. Solubilization and interaction of naproxen with polyvinylpyrrolidonein aqueous solution and in the solid state. Fármaco Ed. Pr. 43, 331–343.

Botha, S.A., Lotter, A.P., 1989. Compatibility study between ketoprofen and tablet excipients using differential scanning calorimetry. Drug Dev. Ind. Pharm. 15, 415–426.

Breimer, D.D., Boer, A.G., Langemeijer, M.W.E., Jaehde, U., Maserreuw, R., 1994. In vitro and in vivo transport of zidovudine (AZT) across the blood–brain barrier and the effect of transport inhibitors. Pharmaceutic. Res. 11, 324–330.

Fernandez, M., Rodriguez, I.C., Margarit, M.V., Cerezo, A., 1992. Characterization of solid dispersions of piroxicam/polyethylene glycol 400. Int. J. Pharm. 84, 197–202.

Fischl, M.A., 1989. State of antiretroviral therapy with zidovudine. AIDS 3, 137–143.

Ford, J.L., Timmins, P., 1986. Pharmaceutical Thermal Analysis. Technique and Applications. Wiley-Interscience, New York.

Gallo, R.C., Sarin, P.S., Gelmann, E.P., Robert-Guroff, M., Richardson, E., Kalyanaramamv, S., Mann, D., Sidhu, G.D., Stahlr, E., Zolla-Pazzne, S., Leibowitch, J., Popovic, M., 1983. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). Science 220, 865–867.

Gambertoglio, J.G., Peter, K., 1998. Intracellular phosphorylation of zidovudine (ZDV) and other nucleoside reverse transcriptase inhibitors (RTI) used for human immunodeficiency virus (HIV) infection. Pharmaceutic. Res. 15, 819–825.

Giron, D., 1998a. Contribution of thermal methods and related techniques to the rational development of pharmaceuticals—Part 1. Pharmaceutic. Sci. Technol. Today 1, 191–199.

Giron, D., 1998b. Contribution of thermal methods and related techniques to the rational development of pharmaceuticals—Part 2. Pharmaceutic. Sci. Technol. Today 6, 262–268.

Gomes-Pinho, J.J.R., Matos, J.R., Mercuri, L.P., Miyano, M.H., Storpirtis, S., 1998. Application of the thermal analytical methods in pre-formulation study of metformin hydrochloride tablets. Anais. Assoc. Bras. Quím. 47, 305–307.

Hirsch, M.S., Daquila, R.T., 1993. Therapy for human immunodeficiency virus infection. N. Engl. J. Med. 328, 1686–1695.

Lotter, A.P., Malan, C.E.P., Villiers, M., 1997. Evaluation of compatibility of tablet excipients with albendazole and closantel using DSC and HPLC. Drug Dev. Ind. Pharm. 23, 533–537.

Mura, P., Bettinetti, G.P., Bramanti, G., Manderioli, A., 1993. Thermal behavior of naproxen in mixtures polyethylene glycol. Acta Symp. Pharm. Thermal Anal. Freiburg, March 10–16.

Mura, P., Faucci, M.T., Manderioli, A., Furlanetto, S., Pinzauti, S., 1998. Thermal analysis as a screening techniques in preformulation studies of picotamide solid dosage forms. Drug Dev. Ind. Pharm. 24, 747–756.

Steven, M.S., Pettinelli, C.B., 1997. Strategies and progress in the development of antiretroviral agents. In: DeVita Jr., V.T., Hellman, S., Rosenberg, S.A. (Eds.), AIDS: Biology, Diagnosis, Treatment and Prevention. Lippincott-Raven Published, Philadelphia, pp. 467–475.

Venkataram, S., Khohlokwane, M., Wallis, S.W., 1995. Differential scanning calorimetry as a quick scanning technique for solid state stability studies. Drug Dev. Ind. Pharm. 21, 847–855.

Wendlandt, W.W., 1986. Thermal Analysis, 3rd ed. Wiley, New York.