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Thermal compatibility studies of nitroimidazoles and excipients

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Abstract Nitroimidazoles are heterocycle imidazoles with a nitrogen group incorporated in its structure. The objective of this study was to develop a model to characterize possible interactions between active substances and excipients using: Thermogravimetry, Differential Thermal Analysis, Differential Scanning Calorimetry, and DSC coupled to photovisual system. It was used three nitroimidazoles (metronidazole, secnidazole, and tinidazole) and two types of microcrystalline cellulose with different particle size (Microcel and Avicel). The binary mixtures were prepared in proportion (w/w) 1:1 (nitroimidazole:excipient). Thermogravimetric data demonstrated that the tinidazole was the nitroimidazole with better uniformity. The nitroimidazoles obeyed the zero order kinetic reaction, evidencing its vaporization processes. Differential thermal analysis data showed nitroimidazoles compatibility with the different microcrystalline celluloses studied, showing that microcrystalline celluloses stabilized the active substances. Calorimetric data of secnidazole showed two melting points, characteristic of the polymorphs presented in raw material. The vaporization constants values of nitroimidazoles studied were secnidazole > metronidazole > tinidazole and for the binary mixtures these values followed the order tinidazole > metronidazole ≥ secnidazole.

Keywords Nitroimidazoles · Thermal analysis · Compatibility studies · Binary mixtures

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Introduction

Nitroimidazoles are heterocycle imidazoles with a nitrogen group incorporated in its structure. Examples of these compounds are metronidazole, secnidazole, and tinidazole. These nitroimidazoles have been used to combat anaerobic bacterial and parasitic infections [1–4]. The structures of the three drugs are given in Fig. 1.

The compatibility studies of active pharmaceutical ingredients with excipients are very important in the development of formulations. The rational planning of a pharmaceutical formulation should, therefore, to start with the physical characterization of the active and excipients, in order to optimize parameters of quality of the dosage form [5–9].

Microcrystalline cellulose (MCC) is one of the best compactable excipients used for tableting, e.g. [10, 11]. The produced tablets show already at low densification high crushing forces. In 1964, MCC was introduced into the market [12]. It is produced by acid hydrolysis of the milled pulp and subsequent spray drying of the resulting solution. MCC is partially crystalline (70%) and partially amorphous (30%) [13–15]. Cellulose of different pulp and origin are used to produce materials of different density [16].

Thermal analysis is used in the pharmaceutical industry as a quick and reliable technique for quality control and for the development of new pharmaceutical formulations

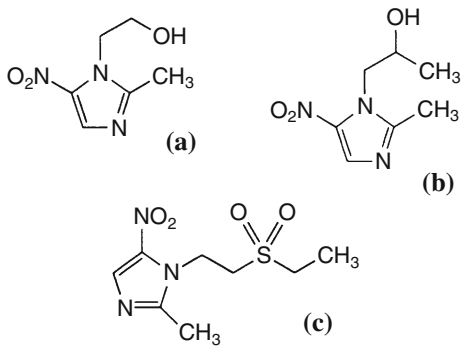

Fig. 1 Chemical structures of nitroimidazoles (**a**) metronidazol, (**b**) secnidazole and (**c**) tinidazole

[17–22]. The number of publications dealing with the use of thermal analysis in pharmaceuticals increases considerably in the last years [23].

The objective of this study was to develop a model to characterize possible interactions between active substances and excipients using thermal techniques (TG, DTA, DSC, and DSC coupled to photovisual system).

Experimental

Samples

Metronidazole (MTZ), pharmaceutical grade 99.46%; Secnidazole (SCZ), pharmaceutical grade 99.30%; Tinidazole micronizated powder (TNZ), pharmaceutical grade 100.70%.

Microcrystalline cellulose (Microcel 101 (MCL 101); Microcel 102 (MCL 102); Avicel pH 101 (AVC 101), Avicel pH 102 (AVC 102)). The samples Microcel are produced by Blanver Farmoquímica and Avicel by FMC Corporation.

Binary mixtures

The binary mixtures were obtained with nitroimidazoles and microcrystalline cellulose that were weighed individually in the quantity of 500 mg each. Physical mixtures were prepared in proportion (w/w) 1:1 (nitroimidazole:excipient) by simple mixing during 20 min into polypropylene container.

Methods

Thermogravimetry (TG)

The TG dynamic curves of nitroimidazoles were performed in a thermobalance Shimadzu model TGA-50H at a heating rate of 10, 20, and 40 °C/min until 900 °C, in an atmosphere of synthetic air and nitrogen, with flow of 20 and 50 mL min^{-1}, respectively. The mass used was 5.00 mg (±0.05), which was put in an alumina crucible. The TG instrument was calibrated using calcium oxalate monohydrate. The conditions to TG dynamic curves of mixtures were similar, using only a heating rate of 20 °C/min. Curves were analyzed by TASYS program from Shimadzu, to characterize the mass loss stages.

Ozawa equation was applied using TG kinetic analysis program installed in Shimadzu data acquisition system to calculate activation energy (E_a) and reaction order (n). Three different heating rates were used: 10, 20, and 40 °C/min in an atmosphere of synthetic air and nitrogen, with flow of 20 and 50 mL min^{-1}, respectively.

Differential thermal analysis (DTA)

The DTA curves of nitroimidazoles were recorded in differential thermal analyzer Shimadzu, model DTA-50, at a

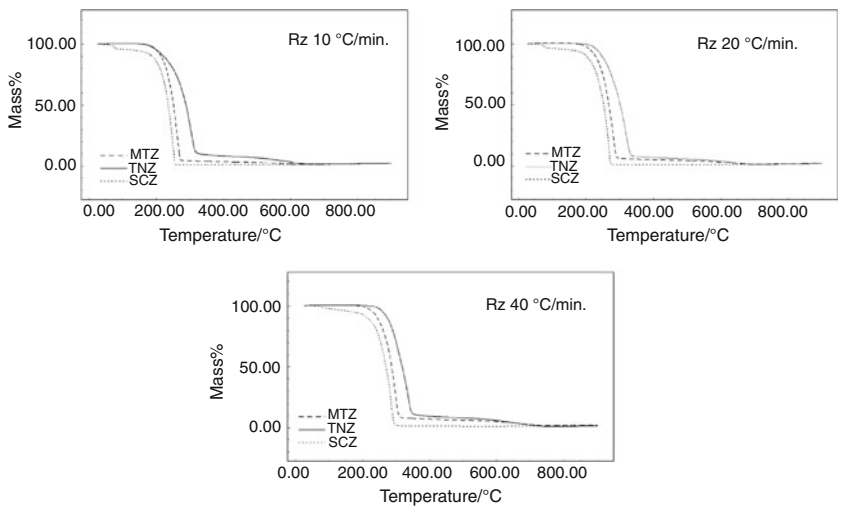

Fig. 2 Dynamic thermogravimetric curves of nitroimidazoles metronidazole (MTZ), tinidazole (TNZ) and secnidazole (SCZ), at heating rates of 10, 20 and 40 °C/min

Table 1 Thermogravimetric data of binary mixtures (1:1, w/w) metronidazole (MTZ), tinidazole (TNZ) and secnidazole (SCZ) with each type of microcrystalline cellulose (Avicel 101 (AVC 101); Microcel 101 (MCL 101); Avicel 102 (AVC 102); Microcel 102 (MCL 102)) in heating rates of 20 °C/min

Mixtures 1:1, w/w		Decomposition step											
		1			2			3			4		
		T_i/°C	T_f/°C	Mass loss/%	T_i/°C	T_f/°C	Mass loss/%	T_i/°C	T_f/°C	Mass loss/%	T_i/°C	T_f/°C	Mass loss/%
MTZ	AVC 101	183.76/± 0.96	275.07/± 1.04	47.20/± 2.93	329.88/± 0.67	378.45/± 0.41	30.19/± 2.00	378.45/± 0.41	616.47/± 2.17	13.74/± 4.32	[a]		
	MCL 101	185.41/± 2.00	278.46/± 1.13	54.07/± 8.46	325.93/± 0.32	391.03/± 1.50	21.94/± 11.43	391.03/± 1.50	624.79/± 2.27	16.02/± 11.78			
	AVC 102	182.11/± 1.27	278.46/± 0.66	52.64/± 4.37	329.66/± 1.44	380.11/± 1.64	25.68/± 7.63	380.11/± 1.64	617.18/± 2.27	13.78/± 8.51			
	MCL 102	184.45/± 2.61	276.42/± 0.37	50.34/± 1.57	320.49/± 2.21	389.56/± 0.17	24.62/± 3.19	389.56/± 0.17	625.81/± 2.14	17.19/± 2.87			
TNZ	AVC 101	226.43/± 0.46	307.20/± 0.16	45.25/± 0.65	307.20/± 0.16	355.62/± 0.94	33.04/± 3.34	355.66/± 0.92	624.31/± 1.41	17.51/± 5.56	[a]		
	MCL 101	213.56/± 2.52	303.97/± 0.84	45.30/± 1.62	304.00/± 0.86	365.86/± 1.21	29.39/± 2.35	365.86/± 1.21	620.77/± 0.21	20.94/± 6.43			
	AVC 102	225.77/± 1.10	306.87/± 0.15	44.12/± 1.51	306.87/± 0.15	351.73/± 2.44	33.09/± 6.68	351.73/± 2.44	620.99/± 0.72	18.66/± 6.33			
	MCL 102	221.74/± 1.31	306.35/± 0.25	45.97/± 0.73	306.32/± 0.27	366.34/± 0.82	31.58/± 3.34	366.34/± 0.82	623.75/± 0.25	18.31/± 4.14			
SCZ	AVC 101	61.49/± 5.50	90.22/± 4.92	2.32/± 10.36	166.81/± 7.11	257.38/± 1.28	47.21/± 10.66	329.52/± 1.28	362.30/± 0.96	38.62/± 13.34	362.30/± 0.96	61.49/± 5.50	90.22/± 4.92
	MCL 101	60.08/± 2.57	87.84/± 2.89	2.32/± 12.10	173.52/± 0.62	258.18/± 0.38	48.55/± 6.10	317.59/± 0.97	373.08/± 0.40	30.36/± 7.29	373.08/± 0.40	60.08/± 2.57	87.84/± 2.89
	AVC 102	59.96/± 5.19	87.62/± 5.46	2.14/± 11.47	175.29/± 4.24	257.07/± 0.72	44.52/± 6.70	329.00/± 0.23	362.88/± 0.55	40.09/± 6.50	362.88/± 0.55	59.96/± 5.19	87.62/± 5.46
	MCL 102	61.60/± 4.96	88.05/± 3.13	2.24/± 11.42	174.40/± 1.66	258.57/± 0.06	49.32/± 2.31	323.19/± 2.60	373.12/± 0.31	28.47/± 7.23	373.21/± 0.28	61.60/± 4.96	88.05/± 3.13

[a] Step no observed; ±*CV* coefficient of variation, T_i initial temperature, T_f end temperature)

heating rate of 10, 20, and 40 °C/min until 900 °C, in an atmosphere of nitrogen, flow of 50 mL min^{-1}. The mass used was 8.00 mg (± 0.05), which was put in an alumina crucible. The conditions to DTA curves of mixtures were similar, using only a heating rate of 10 °C/min. The temperature and heat flow of the DTA instrument were calibrated by the melting point and enthalpy of indium and zinc standards. The DTA curves were analyzed by TASYS program from Shimadzu.

Differential scanning calorimetry (DSC)

The DSC curves of nitroimidazoles were recorded in a differential scanning calorimeter Shimadzu, model DSC-50, in nitrogen (flow rate: 50 mL min^{-1}), at a heating rate of 2, 5, 10, 20, and 40 °C/min until 350 °C. The mass used was 2.0 mg (± 0.1), which was put in an aluminum crucible then the cell was sealed hermetically. The pictures of thermal behavior of nitroimidazoles were obtained with DSC 50 calorimeter coupled to a photovisual system (an Olympus microscopy connected to a Sanyo camera, model VCC-D520). The temperature and heat flow of the DSC instrument were calibrated by the melting point and enthalpy of indium and zinc standards. The DSC curves were analyzed by TASYS program from Shimadzu.

Results and discussion

Thermogravimetry

The thermal decomposition of nitroimidazoles raw materials (MTZ, TNZ, and SCZ) presented one major step of mass loss corresponding to 94.60, 88.44, and 94.60%, respectively. The second mass loss was observed in MTZ and TNZ corresponding to the ash residues. In the SCZ was observed the presence of volatile product in the beginning of the thermogravimetric curve relative to the water loss (Fig. 2).

The kinetic data calculated by Ozawa equation showed that nitroimidazoles obeyed the kinetic process of zero order, evidencing possibly that mass loss can be due to the vaporization process of the metronidazole, secnidazole, and tinidazole. The activation energy showed to be similar for metronidazole and secnidazole, the obtained values were of 88.00 kJ/mol, while to the tinidazole were of 104.50 kJ/mol.

The vaporization constant data, calculated by Antoine and Langmuir equation [24], for secnidazole, metronidazole, and tinidazole were: 138034, 135569, and 124278, respectively. The metronidazole vapor pressure showed to be similar with data obtained by Gomes et al. [24] and Medeiros et al. [25]. The secnidazole and tinidazole were studied in this study and its vaporization constants when compared in the group of nitroimidazoles presented the vaporization constants order: secnidazole > metronidazole > tinidazole.

The thermal decomposition of MTZ, TNZ, and SCZ with different microcrystalline celluloses presented mass loss values near 50.00%. The TG data are presented in Table 1, where it is possible to verify that MTZ and SCZ showed less uniformity in the mass loss than TNZ. The fact can be explained due the TNZ raw material be micronizated while MTZ and SCZ, in the crystalline form.

The binary mixtures of MTZ, TNZ, and SCZ showed changes in the vaporization processes when compared with the raw materials. The vaporization constants presented small values in all binary mixtures for each active pharmaceutical ingredient and they presented the vaporization constant order: tinidazole > metronidazole ≥ secnidazole

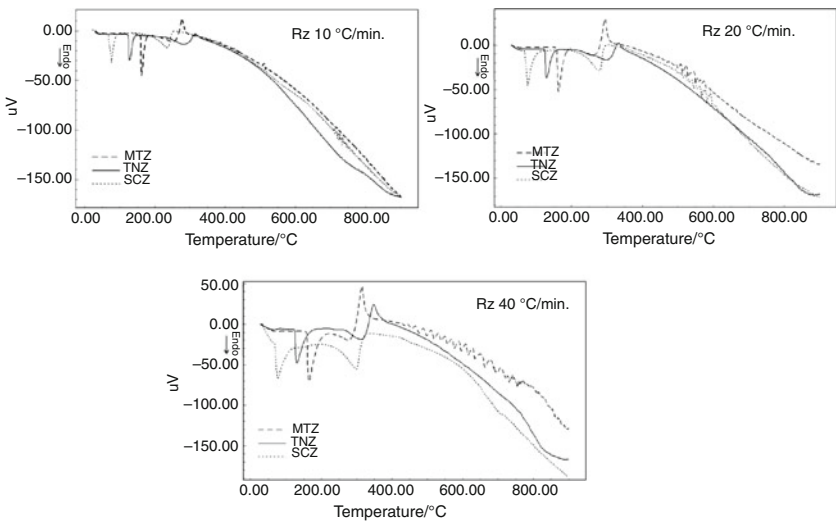

Fig. 3 DTA curves of nitroimidazoles metronidazole (MTZ), tinidazole (TNZ) and secnidazole (SCZ), at heating rates of 10, 20 and 40 °C/min

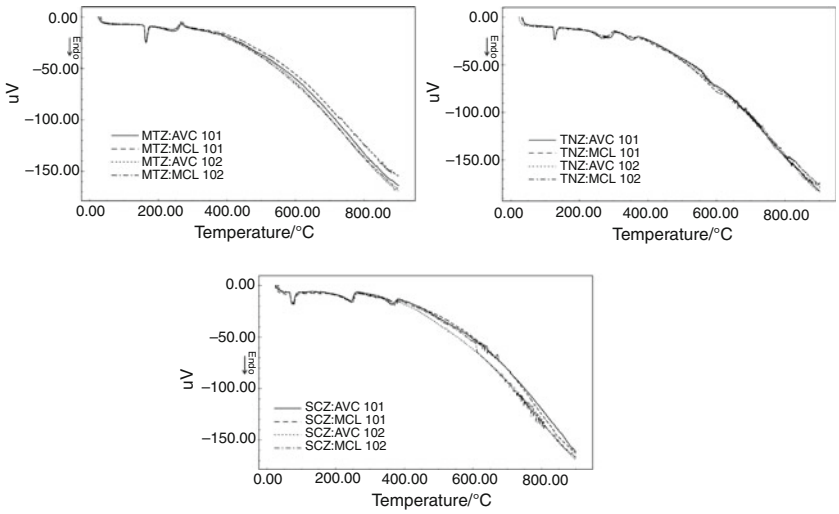

Fig. 4 DTA curves of binary mixtures (1:1, m/m) metronidazole (MTZ), tinidazole (TNZ) and secnidazole (SCZ) with each type of microcrystalline cellulose (Avicel 101 (AVC 101); Microcel 101 (MCL 101); Avicel 102 (AVC 102); Microcel 102 (MCL 102)) in heating rate of 10 °C/min

evidencing that microcrystalline celluloses stabilize the active substances. The tinidazole showed to be less stable because its micronized form.

Differential thermal analysis

DTA curves of nitroimidazoles and their binary mixtures are presented in Figs. 3 and 4, respectively. The MTZ raw material showed a melting point in the temperature of 161.89 °C and heat of reaction (J/g) of −228.75. In the binary mixtures containing MTZ and different microcrystalline celluloses were verified an increasing in the melting point temperature about 3 °C and a decreasing in heat of reaction about 137.00 J/g. This fact evidenced the more protection of MTZ by microcrystalline cellulose. The TNZ raw material presented a melting point in the temperature of 128.16 °C and heat of reaction (J/g) of −170.00. In the binary mixtures containing TNZ with different microcrystalline celluloses were observed the same melting point temperature while it showed a decreasing in heat of reaction about 103.00 J/g. The SCZ raw material presented a melting point in the temperature of 76.87 °C and heat of reaction (J/g) of −211.25. In the binary mixtures containing SCZ and different microcrystalline celluloses presented the same melting point temperature while they showed a decreasing in heat of reaction about 121.00 J/g. The microcrystalline cellulose protects MTZ and SCZ more than TNZ.

Differential scanning calorimetry

DSC curves of nitroimidazoles are showed in Fig. 5. The MTZ raw material showed a melting point at about 159 °C with displacement of temperature between heating rate 2 and 40 °C at about 5 °C. The TNZ raw material presented a melting point at about 125 °C with 6 °C of displacement between 2 and 40 °C. The SCZ raw material showed two melting points in heating rate of 2 and 5 °C evidencing two

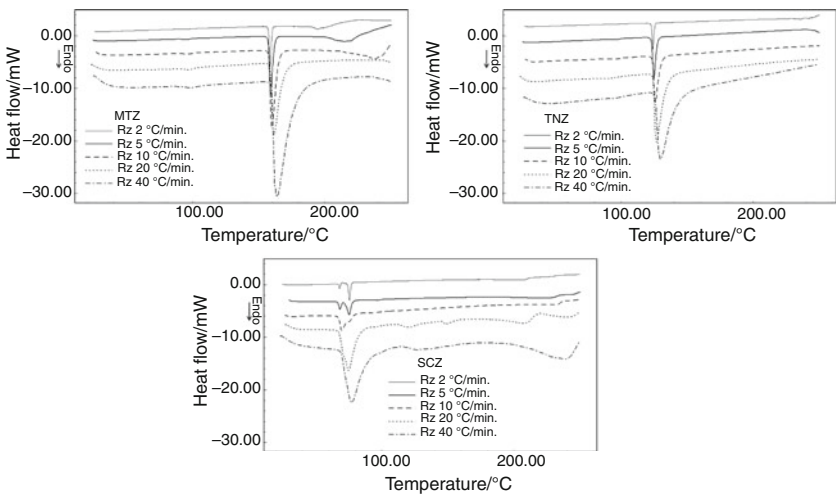

Fig. 5 DSC curves of nitroimidazoles metronidazole (MTZ), tinidazole (TNZ) and secnidazole (SCZ), at heating rates of 2, 5, 10, 20 and 40 °C/min

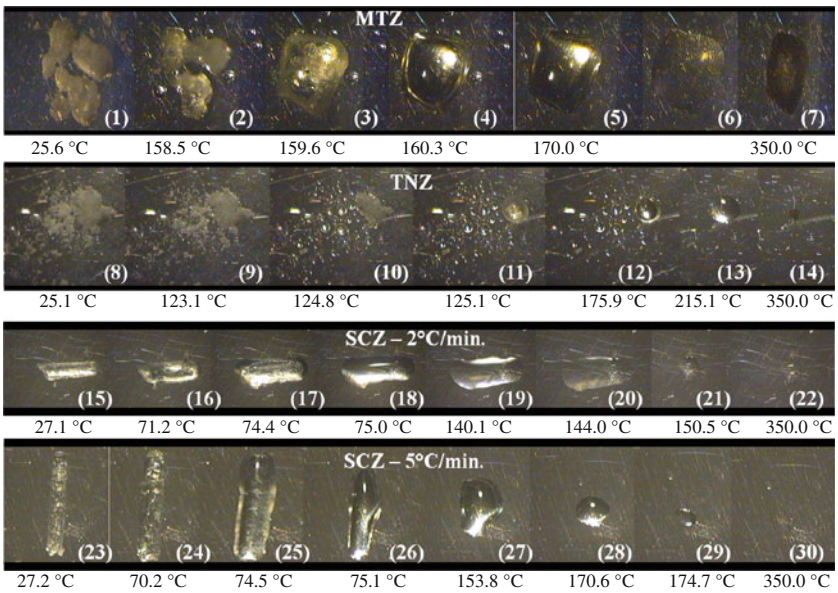

Fig. 6 DSC photovisual of nitroimidazoles metronidazole (MTZ), tinidazole (TNZ) at heating rate of 10 °C/min and secnidazole (SCZ) at 2 and 5 °C/min

polymorphs in the temperatures at about 68 and 75 °C, respectively. In the heating rate of 40 °C showed a variation about 10 °C when compared with heating rate of 2 °C.

It was possible to determine the melting points of secnidazole by DSC curves presenting the values of 68.30 and 75.50 °C, corresponding to the first and second polymorphs, respectively, in the heating rate of 2 and 5 °C/min. The heating rates of 10, 20, and 40 °C/min presented only a melting point in the DSC curves, evidencing low sensibility in these heating rates to discriminate the presence of polymorphs.

DSC coupled to photovisual system

The DSC coupled to photovisual system confirmed the events of fusion and volatilization of the drugs (Fig. 6). The SCZ exhibited two endothermic peaks at a heating rate of 2 and 5 °C/min, corresponding to two different melting points, possibly due the different crystal sizes in the sample. Through the images obtained by DSC coupled to photovisual system in the same condition it was not possible to visualize the two endothermic events due the lower uniformity distribution of temperature in the samples, because this technique uses open cells. It was observed the drug melting point at about 75 °C, temperature corresponding to the second endothermic peak of conventional DSC (Fig. 6—pictures 17 and 18 at a heating rate 2 °C/min; pictures 25 and 26 at a heating rate 5 °C/min).

The data comparison of the different thermal techniques showed to be possible to difference the interactions between different molecules of nitroimidazoles. This fact was confirmed by vaporization constants of raw materials and binary mixtures of nitroimidazoles with microcrystalline celluloses.

Conclusions

Thermogravimetric data demonstrated that MTZ and SCZ showed less uniformity in the mass losses than TNZ. The nitroimidazoles obeyed the kinetic process with reaction of zero order evidencing its vaporization processes. DTA data showed compatibility of nitroimidazoles with different microcrystalline celluloses. DSC data showed melting point of secnidazole for the polymorphs present in raw material. The vaporization constants for nitroimidazoles raw materials studied was: secnidazole > metronidazole > tinidazole and for binary mixtures with microcrystalline celluloses the vaporization constants order was: tinidazole > metronidazole ≥ secnidazole.

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