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Preformulation studies of itraconazole associated with benznidazole and pharmaceutical excipients

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ABSTRACT

Recent studies have shown that the antifungal itraconazole (ITZ), when in associations with benznidazole (BNZ), is a potential treatment for Chagas disease. Therefore, the objective of the present study was to evaluate the compatibility of ITZ with BNZ and with selected pharmaceutical excipients. Differential scanning calorimetry (DSC), derivative thermogravimetry (DTG), Fourier transform infrared spectroscopy (FTIR), optical microscopy and kinetic analyses under isothermal conditions were performed. The results showed thermal interactions between ITZ and the excipients hydroxypropyl methylcellulose and polyvinylpyrrolidone. The FTIR data together with complementary tests revealed signs of drug decomposition in the presence of these materials. Thus, these excipients were considered incompatible with ITZ and should be avoided in solid dosage forms containing this drug. Moreover, it was found that associations between ITZ and BNZ are potentially unstable. Therefore, it is necessary to develop a pharmaceutical dosage form that avoids the processing of these drugs together and allows a stable pharmaceutical formulation to be obtained.

1. Introduction

The morbidity and mortality associated with Chagas disease are some of the most pressing health problems found in developing countries and affect over eight million people, according to the World Health Organization [1]. Chagas disease is a zoonosis caused by the protozoan *Trypanosoma cruzi*; it is treated with benznidazole (BNZ), a BCS Class IV drug, which causes strong side effects [2–5]. Recent studies have demonstrated an important synergic effect when benznidazole is associated with others drugs [6–8]. Azole antifungals such as itraconazole (ITZ) have demonstrated efficacy against this disease; however, due to its low solubility in water (1 ng/mL) and low bioavailability (55%), high doses are required for solid dosage forms [9,10].

In this context, antichagasic therapy could be improved by new formulations containing associations of BNZ and ITZ, together with technological innovations such as inclusion complexes in cyclodextrins to overcome solubility issues [11]. Therefore, preformulation studies are essential to developing appropriate pharmaceutical forms.

Thermal analysis is frequently utilized in preformulation studies because of its ability to provide prompt and accurate data regarding physical characteristics and energetic properties, including melting points, degradation, decomposition, crystallization temperatures and glass transitions. Recently, the use of thermal analysis has become the method of choice to evaluate compatibility among drugs and excipients because it is easily implemented in routine analysis [12–14].

The aim of this research was to study the compatibility of ITZ with BNZ and with selected pharmaceutical excipients. Therefore, thermal techniques such as differential scanning calorimetry and derivative thermogravimetry were used, supported by Fourier transform infrared spectroscopy and optical microscopy. Additionally, kinetic analyses were performed under isothermal conditions.

2. Experimental

2.1. Materials

Itraconazole (ITZ; lot 00569488) was kindly donated by Janssen-Cilag Pharmaceutica (Geel, Belgium). Benznidazole (BNZ; lot 13871) was obtained from Roche (Basel, Switzerland). Pharmaceutical grades of the following excipients were used: β-cyclodextrin (βCD), hydroxypropyl-β-cyclodextrin (molar substitution 2.7, HPβCD), hydroxypropyl methylcellulose (HPMC), magnesium

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stearate (MgSt), polyvinylpyrrolidone (PVP) and randomly methylated β-cyclodextrin (substitution degree of 12.6, RMβCD).

2.2. Sample preparation

Physical mixtures (PM) were prepared with binary equal mass mixtures (1:1) of ITZ plus BNZ and selected excipients.

Wet mixtures (WM) were prepared by adding a few drops of purified water into the PM in order to form a wet mass. A vortex mixer was used to homogenize the distribution of the liquid in the powder. Samples were dried in an oven at 30 °C for 6 h.

Photostressed samples (PS) were obtained by submitting the material to light stress in a photostability chamber (CARON® UV/Vis light), following Guideline ICH Q1B [[15]].

In addition, binary mixtures were heated to 160 °C in the DSC for further evaluation. This treatment was proven to be non-destructive for the isolated materials, which maintained their physical and chemical properties. Those samples have been denoted as heated mixtures (HM).

2.3. Differential scanning calorimetry (DSC)

This analysis was performed in a DSC-60A (Shimadzu, Japan) using approximately 4.0 mg of each sample placed in aluminum-sealed crucibles under a dynamic N_2 atmosphere at a heating rate of 10 °C min^{-1} from 30 °C to 250 °C. The DSC was calibrated with indium and zinc.

2.4. Derivative thermogravimetry (DTG)

The decomposition ranges and the weight loss variations of the samples were evaluated using a Shimadzu DTG-60 thermobalance under a nitrogen flow of 50 mL min^{-1} at a heating rate of 10 °C min^{-1} from 30 °C to 400 °C. The tests were carried out individually, with samples of approximately 5.0 mg placed in platinum crucibles.

2.5. Fourier transform infrared spectroscopy (FTIR)

Spectra were recorded on a Varian 640-IR FTIR spectrometer (Varian Inc., Brazil) between 4500 cm^{-1} and 600 cm^{-1} at an optical resolution of 4 cm^{-1} using an ATR imaging accessory. All spectral manipulations were performed using Resolutions PRO Suite software.

2.6. Optical microscopy

The morphological characteristics of the samples were analyzed using an Olympus SZ60 (Opelco, Japan) microscope connected to an Olympus DP12 video camera (Opelco, Japan). Image processing was performed using Image Analysis software version 3.2.

2.7. Isothermal thermogravimetric studies

Kinetic investigation of the drug degradation was obtained using isothermal thermogravimetric experiments [16]. Samples placed in platinum crucibles were heated at a rate of 20 °C min^{-1} in a Shimadzu DTG-60 thermobalance under a N_2 atmosphere (flow rate of 50 mL min^{-1}) until reaching a temperature close to the initial decomposition temperature of the drug. Once reached, this temperature was held constant for the period of time to reduce the sample weight by 5%. The isothermal temperature range for ITZ was 290–330 °C, while the temperature range for BNZ was 190–230 °C. Evaluations of the ITZ–BNZ PM were also performed in the temperature range of 190 °C to 230 °C. An Arrhenius plot was established based on the experimental data to determinate the activation energies.

Table 1
DSC data of ITZ and BNZ as supplied, and binary mixtures containing ITZ with BNZ and selected excipients. Thermal events with significant changes are in bold type.

Sample	T_{peak} (°C)	Range (°C)	ΔH (J g^{-1})	Thermal interaction[a]
ITZ				
Pure	167.89	166–171	85.97	–
PS	168.54	165–171	87.70	–
BNZ				
Pure	190.91	189–195	139.30	–
PS	189.60	187–193	116.55	–
ITZ + βCD				
PM	168.12	165–171	43.20	0
WM	167.05	**163–170**	40.40	+
PS	167.87	164–171	42.24	0
ITZ + BNZ				
PM	**158.82**	**156–162**	49.59	+++
WM	**158.40**	**156–161**	45.64	+++
PS	**157.42**	**153–171**	46.03	+++
ITZ + HPβCD				
PM	168.31	165–171	42.44	0
WM	167.31	164–171	**39.84**	**+**
PS	167.78	164–171	**33.06**	+
ITZ + HPMC				
PM	168.02	165–171	42.03	0
WM	**170.13**	165–174	**34.60**	++
PS	167.78	164–171	**33.48**	+
ITZ + MCC				
PM	167.81	165–170	40.61	0
WM	167.52	165–171	40.93	0
PS	167.80	165–171	40.55	0
ITZ + MgSt				
PM	167.58	165–170	40.27	0
WM	167.45	165–170	42.88	0
PS	167.49	166–170	45.04	0
ITZ + PVP				
PM	167.97	165–171	40.08	0
WM	**163.54**	**153–167**	**37.82**	+++
PS	167.26	164–170	39.20	0
ITZ + RMβCD				
PM	168.04	165–171	42.06	0
WM	**166.90**	164–170	40.15	+
PS	167.82	164–171	45.70	0

[a] (0): none; (+): minor; (++): medium; (+++): strong.

3. Results and discussion

Recent studies have suggested that the association of ITZ and BNZ in the same pharmaceutical form can lead to significantly improved antichagasic therapy [7]. Therefore, compatibility studies between those compounds and pharmaceutical excipients are of great importance in obtaining a stable dosage form and are the focus of this study.

To reveal possible incompatibilities between the studied components, the binary mixtures were subjected to different treatments (PM, WM, PS and HM) simulating pharmaceutical production and aging processes.

The DSC data of ITZ and its mixtures PM, WM and PS are shown in Table 1. The thermal parameters and degree of interaction for each binary mixture studied were analyzed.

The DSC curve of ITZ showed a unique endothermic signal at 167.9 °C, corresponding to the melting peak appearing from 166–171 °C (Fig. 1, Table 1). This behavior confirms the crystalline structure of the drug, in agreement with previous studies [17]. Additionally, the results of the DTG analyses demonstrated that ITZ remains stable until 330 °C, when decomposition begins, culminating with a mass loss of 61.22% in the first stage of decomposition. The peak related to the BNZ melting temperature is well defined