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Thermal Behavior and Interaction Studies of Theophylline With Various Excipients

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SUMMARY. In preliminary preformulation studies, the evaluation of solid state interactions between an active component with different excipients is essential to guarantee the quality of the final product. Several investigations have been carried out using thermogravimetry (TG) and differential scanning calorimetry (DSC) as an important analytical tool to determine the compatibility of drug-excipients. In this study, the interaction between theophylline and a number of pharmaceutical excipients (microcrystalline cellulose, xanthan gum, guar gum, polyvinylpyrrolidone K-30, Eudragit® L100 and Opadry® Clear) were investigated using TG, DTG and DSC methods. Infrared spectroscopy was used as complementary technique to confirm possible interactions found on thermoanalyses. The TG/DTG and DSC curves were obtained and provided information on the thermal stability, decomposition and compatibility between theophylline and excipients used. The results showed possible interaction between theophylline and Eudragit® L100.

RESUMEN. "Comportamiento Termoanalítico y Estudio de la Interacción de la Teofilina von Varios Excipientes". En estudios preliminares de la preformulación, la evaluación de interacciones en el estado sólido entre un componente activo con diversos excipientes es esencial para garantizar la calidad del producto final. Varias investigaciones han sido realizadas usando la termogravimetría (TG) y la calorimetría exploratoria diferencial (DSC) como una importante herramienta analítica para determinar la compatibilidad del fármaco-excipientes. En este estudio se investigó la interacción entre la teofilina y varios excipientes farmacéuticos (celulosa microcristalina, goma xantana, goma guar, polivinilpirrolidona K-30, Eudragit® L100 y Opadry® Clear) usando termogravimetría (TG) y la calorimetría exploratoria diferencial (DSC). La espectroscopía infrarroja fue utilizada como técnica complementaria para confirmar interacciones posibles encontradas en el termoanálisis. Las curvas de TG/DTG y de DSC obtenidas proporcionaron información sobre la estabilidad térmica, la descomposición y la compatibilidad entre la teofilina y los excipientes utilizados. Los resultados demostraron una posible interacción entre la teofilina y el Eudragit® L100.

INTRODUCTION

The theophylline is a therapeutic agent belonging to the methylxanthine classes with various pharmacological actions. It provides relaxation in some muscular groups, stimulates the central nervous system and acts in kidneys as a diuretic drug. However, its effects are more frequently observed on the straight muscular groups. It's the most efficient broncodilatator among xanthine classes, in a certain way, does not only smoothes the blockage of the aerial ways in the acute asthma, but also diminishes the intensity of the symptoms and the time of lost work or school in the chronic asthma [1-3].

In the preformulation study of new drug delivery systems, it is essential to have readily available knowledge of the physicochemical properties of the active component and excipients. Pharmaceuticals excipients are applied in dosage forms to facilitate administration and release the drug, as well as to protect it from the environment [4-7]. The excipients are considered inert, but incompatibilities (solid state interactions) between drug and excipients are com-

KEY WORDS: Compatibility Studies; FTIR; Theophylline; Thermoanalysis
PALABRAS CLAVE: Estudios de Compatibilidad; Espectroscopia Infrarroja; Teofilina; Termoanálisis

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monly possible [8]. The inadequate use of pharmaceutical excipients in solid oral dosage forms can cause serious biopharmaceuticals implications, modifying the release mechanism, absorption as well as the biodisponibility [8-10].

Careful and fast evaluation of possible incompatibility is facilitated using the thermoanalytical techniques, which offers significant advantages in saving both time and substance [11]. The differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG) are extensively used in the pharmaceutical area. This thermoanalytical methods allows evaluation of thermal behavior, decomposition kinetics, purity determination and investigation of interactions between drug and excipients according to appearance, shift or disappearance of peaks and/or variations in the corresponding enthalpies of reactions [8,12-14]. In addition, fourier transform infrared spectroscopy analysis (FTIR) was used to evaluate the compatibility of mixtures. Changes in the position, intensity or width of the vibrational bands can be observed in spectra when an interaction between drug and excipient occurs [15].

Since our research involves the development of a delayed release multiparticle system containing theophylline, the preformulation study searching for interactions is crucial to select appropriate excipients to ensure the final formulation quality. The multiparticle system due to its numerous technological and pharmacokinetics advantages in relation to the single pharmaceutical dosage, was the chosen one. The extrusion/spheronization technological process was used to obtain theophylline pellets; therefore it was indispensable to select proper excipients capable to provide adequate characteristics for pellets production [16].

The purpose of this work is to report the compatibility study of theophylline with some excipients (microcrystalline cellulose, guar gum, xanthan gum, polyvinylpyrrolidone K-30, Eudragit® L100 and Opadry® Clear) by means of TG, DSC and FTIR.

MATERIALS AND METHODS

Materials

Theophylline (bulk material) was supplied by Labsynth. The microcrystalline cellulose NF M101 was purchased from All Chemistry Brazil Ltda. The guar gum and polyvinylpyrrolidone (PVP) K-30 was provided by Purifarma. The xanthan gum was obtained from D'Altomare Química Ltda. Eudragit® L 100 from Röhm GmbH & Co. and Opadry® Clear provided by Colorcon. The drug-excipient interaction study was performed using mixed samples of equal weights (1:1) of theophylline and each excipient (microcrystalline cellulose, guar gum, xanthan gum, PVP K-30, Eudragit® L 100 and Opadry® Clear). The physical mixtures were prepared using an agate mortar and pestle at room temperature. The binary mixture was kept into an amber glass vials for one week and them submitted to the thermal analysis.

Thermogravimetric and Differential Scanning Calorimetry Analysis

TG/DTG and DSC curves of theophylline individually and in each excipient were performed, as well as the binary mixtures. The TG/DTG curves were obtained on thermobalance TGA-60 (Shimadzu), under synthetic air atmosphere with the flow rate of 100 mL min-1. Approximately 7 mg of sample was placed in α-Al_2O_3 pan and heated from 30 to 900 °C at heating rate of 10 °C min^{-1}. The equipment was previously calibrated with standard reference of calcium oxalate. The DSC measurements were performed on Shimadzu DSC-60 cell. Approximately 4 mg of samples were mass out and placed in a sealed aluminum pan. The curves were obtained from 30 to 600 °C at heating rate of 10 °C min^{-1} under synthetic air atmosphere with the flow rate of 100 mL min^{-1}. The equipment was previously calibrated with standard reference of indium.

FTIR- Spectroscopy Analysis

The FTIR spectroscopy was used as supplementary technique in order to investigate the interaction between drug and excipient and to confirm the results obtained by the thermal analysis. The spectra of theophylline and the binary mixture were recorded using a Shimadzu spectrometer (FTIR-8400) over wavenumber range between 5000-400 cm^{-1}, using a nominal resolution of 4 cm-1 and an averaging of 32 scans. The samples were diluted with potassium bromide spectroscopic grade in ratio of 1:99 and the disks weighed about 200 mg were obtained by direct compress (8 kgf/cm^2). For each case, disks of pure drug and drug:excipient (1:1) mixtures were prepared. A background spectrum corresponding to pure potassium bromide disk was employed. The software used for differential analysis was GRAMS/32 V4.04 (Galactic Industries Corporation, Salem, NH, USA).

RESULTS AND DISCUSSION

Thermoanalyses

The TG/DTG and DSC curves obtained for pure theophylline are demonstrated in Fig. 1. The DSC curve exhibited an endothermic event between 30 and 80 °C corresponding to the dehydration of the drug. A sharp endothermic peak was observed between 277 to 281 °C characteristic of melting point process (T_{peak} = 277.47 °C and ΔH_{fusion} = -106.57 J/g). In addition the decomposition process started in 285 °C with peaks in 310 and 374 °C. The DSC data were confirmed by TG/DTG analysis, in which was observed a small mass loss (Δm = 6.8 %) up to 80 °C confirming theophylline dehydration. The decomposition process occurs in a single step with mass loss of Δm = 94%, DTG_{peak} = 330 °C.

The selection of adequate pharmaceutical excipients used in the preformulation study was based on the drug physical chemical characteristics and the compatibility with other components. Nowadays infinity of excipients are available in the market and it is known that the same active substance when produced with different excipients can cause serious biopharmaceuticals implications such as modifying the dissolution mechanism, absorption and biodisponibility [10, 17].

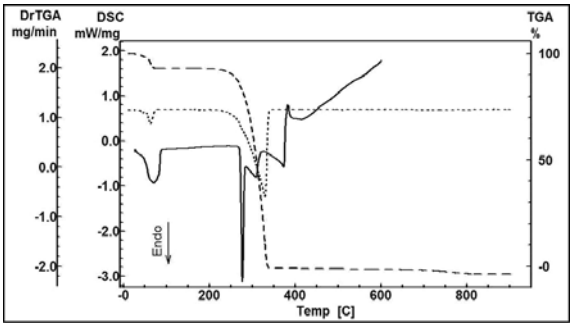

Figure 1. DSC and TG/DTG curves of pure theophylline obtained in sintetic air atmosphere of 100 mL min^{-1} at heating rate of 10 °C min^{-1}.

The DSC and TG curves of binary mixture (1:1) of drug and the following excipients: microcrystalline cellulose (CM), xanthan gum and guar gum are shown in Fig. 2. The thermoanalytical curves of the mixtures can be considered as a superposition of the curves of the theophylline active ingredient and excipients.

The DSC curves labeled 2, 3 and 4 in figure 2 showed an endothermic peak between 277 to 281 °C corresponding to the theophylline's melting point, following by exo and endothermic events characteristics of the decomposition process, which results are confirmed by mass loss observed in TG data. The TG curves indicated mass loss in two or three consecutive steps for binary mixtures up to 800 °C. The thermal behaviour of the pure drug was not significant modified in the mixtures, suggesting no interaction with these excipients.

The thermo analytical profiles for the mixtures theophylline-Opadry®, theophylline-Eudragit® and thephylline-PVP are given in Figure 3. The DSC curves showed differences in the thermal profile of the theophylline. The drug's melting peak in binary mixture disappears, suggesting a possible interaction but not necessary corresponding to incompatibility. It was evidenced from DSC and TG curves that the excipient influenced the decomposition process of the drug. In the case of theophylline and Eudragit® or PVP mixture, the disappearance of the drug fusion peak was observed in literature for others drugs, such as naproxen, ibuprofen and ketoprofen, indicating the occurrence of a strong interaction in the solid state with temper-

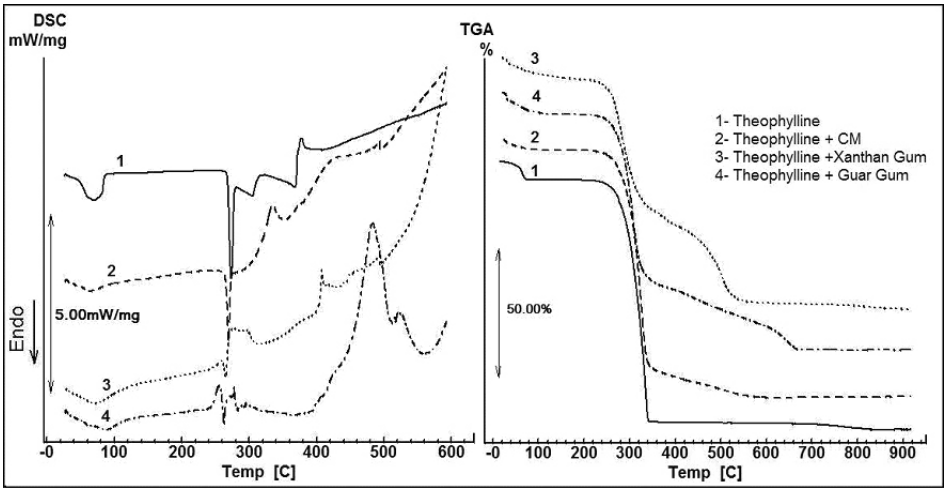

Figure 2. DSC and TG curves of pure theophylline and physical mixtures (1:1) obtained in sintetic air atmosphere of 100 mL min^{-1} at heating rate of 10 °C min^{-1}.

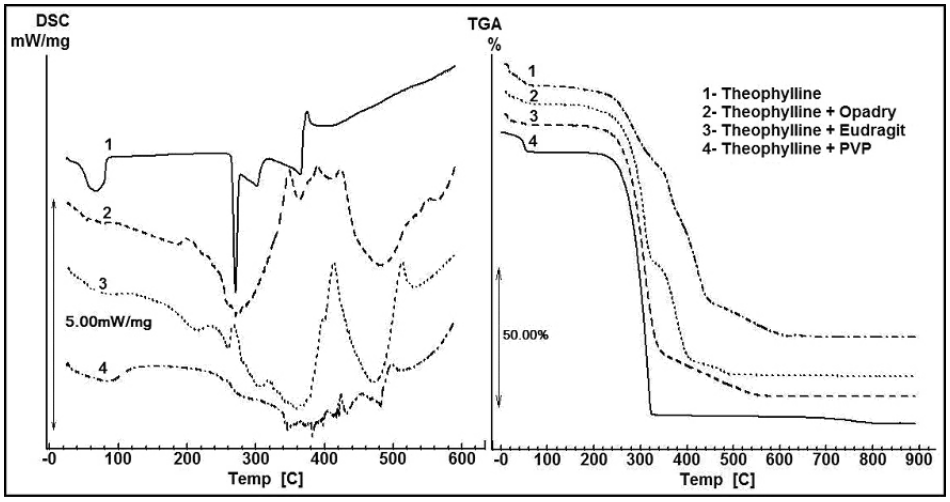

Figure 3. DSC and TG curves of pure theophylline and physical mixtures (1:1) obtained in sintetic air atmosphere of 100 mL min^{-1} at heating rate of 10 °C min^{-1}.

ature. However, the interaction is not indicative of an incompatibility between theophylline and Eudragit® or PVP, it can be justified as the dissolution of the drug into the excipient [18-20]. The endothermic peak related to theophylline's melting point in the mixture of theophylline and Opadry (labeled 2 in figure 3) is reduced because of the endothermic event of Opadry which occurs in the same temperature range, consequently hiding the drug's melting peak.

FTIR Spectroscopy Analysis

In formulations, solid-state interactions of the drug substance are great of interest. In some cases the excipients can accelerate the degradation process. In 1940s, the (IR) infrared spectroscopy becomes another technique utilized in the characterization of solid-solid interactions [21,22]. The FTIR spectroscopy was used as supplementary technique in order to investigate the interaction between drug-excipient and to confirm the results obtained by the thermal analysis. The spectra of all drug and excipient used in this study were collected for pure compounds and for the binary mixture (1:1) of drug:excipients. An additional so called differential analysis was carried out using the scaled subtraction function of the GRAMS software. In differential treatment, the spectra of the pure components (drug and excipient) were subtracted from the obtained for the corresponding binary mixture, and the resulting spectrum was analyzed to verify the existence of some residual band, that would be assigned as interaction evidence. The differential analysis represents a greater potential for the inquiry, since in the case of the absence of interactions, all bands are suppressed in the resultant spectrum.

The FTIR analyses were carried out for the pure drug, individual excipients and the binary mixtures (1:1), as investigated by thermoanalytical procedures. The results obtained by DSC and TG techniques were confirmed by infrared spectroscopy evidencing interaction only for theophyline-Eudragit® mixture. The chemical structure of pure theophylline and Eudragit® are given in Fig. 4. The spectra of theophylline and microcrystalline cellulose are shown in Fig. 5 and its vibrational bands are in accordance with the compounds structure. The cellulose spectra is dominated by the strong C-O and O-H absorption bands, and the absorption of carbonyl groups in the theophylline structure (figure 4b) are found at 1716 and 1666 cm^{-1}.

No significant residual band was found in the differential spectra (Fig. 6b) obtained by

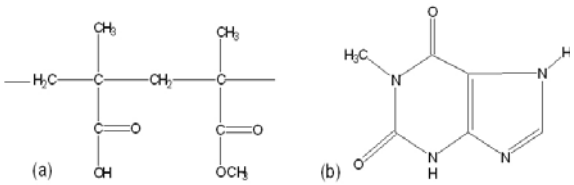

Figure 4. Chemical structures of (**a**) Eudagit® L100 and (**b**) theophylline.

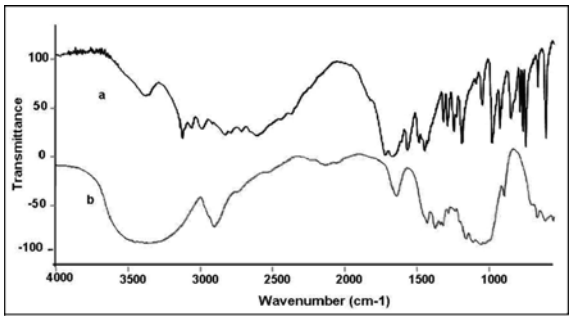

Figure 5. (**a**) Pure theophylline spectrum. (**b**) Pure microcrystalline cellulose spectrum.

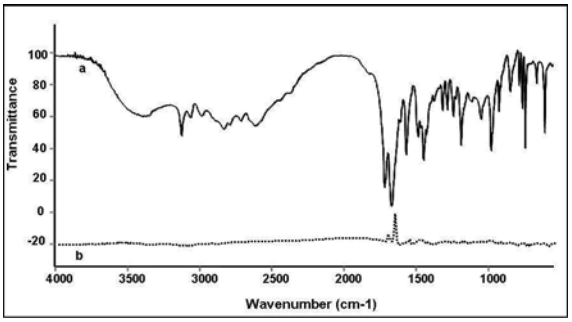

Figure 6. (**a**) Spectrum of the theophylline:microcrystalline cellulose binary mixture. (**b**) Differential spectrum obtained by subtraction of pure component spectrum from the spectrum of the binary mixture theophylline:microcrystalline cellulose.

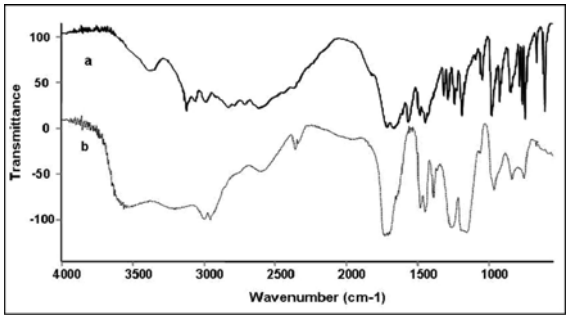

Figure 7. (**a**) Pure theophylline spectrum (**b**) Spectrum obtained from the Eudragit® excipient.

scaled subtraction of pure component spectra from the one obtained for the physical mixture (figure 6a). There are only bands corresponding to the strong absorption of theophylline´s spectrum, which could not be totally compensed due to the limitation of the pellet sampling method employed. The differential spectra of Fig. 6 represent the results obtained for all the mixtures which had no drug-excipient interaction (microcrystalline cellulose, xanthan gum, guar gum, PVP and Opadry®).

In the Fig. 7 are given the spectra of pure theophyline and Eudragit® compounds. The Eudragit® is a copolymer of meta-acrylic acid with many carboxylic groups, as shown in the figure 4a. The ratio of free to esterified carbonyl group is 1:1 in the L100 form. The peaks in the IR spectrum of the acid and ester form are found in the spectra at 1714 and 1736 cm^{-1} respectively, in accordance with the literature [23].

The spectroscopic evidence of drug-excipient interaction was found for the system theophyline-Eudragit®, as shown in the differential spectrum, presented in the figure 8b. The interaction between the drug:excipient is clearly evidenced, since residual peaks are found in many

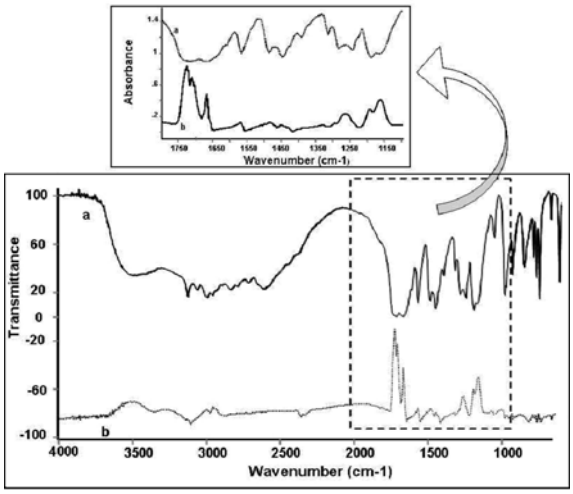

Figure 8. (**a**) Spectrum of the binary mixture theophylline:Eudragit® (1:1). (**b**) Differential spectrum obtained by subtraction of pure component from the mixture theophylline: Eudragit®.

parts of the spectrum and more intense in the 1716 and 1163 cm^{-1} range, related to the involvement of the acid group of the Eudragit®. The peak in the diferential spectra at 1163 cm^{-1} was not present in the pure theophylline spectrum and also a broader peak, compared to the pure drug, was found at 1716 cm^{-1}. The additional residual bands at 3364 and 3106 cm^{-1} range confirm the involvement of the OH acid group (excipient) and the NH group existing in the theophylline structure.

These results seem to be in accordance with reported by Lin *et al*., 1995 and Lin *et al*., 1996 that assigned the involvement of the carbonyl acid group in the interaction. The authors related a 1714 cm^{-1} absorption band for the acid group of the Eudragit® L-100 structure that would be more likely involved in the interaction than the ester group of the Eudragit® [23,24].

CONCLUSION

The thermoanalysis provided information about the thermal stability and decomposition of pure theophylline and the binary mixture. The results demonstrated the suitability of TG and DSC as a quick screening tool to select proper excipients at the early stages of a formulation design. The infrared spectroscopy was a valuable tool in the proof of the possible interactions demonstrated in the thermoanalysis.

Among the excipients used, the Eudragit® L100 interacted with theophylline. The interaction was observed by DSC curves, when disappearance of theophylline's melting point occurs in the binary mixture (1:1). The infrared spec-

troscopy studies evidenced arise of a band in 1163 cm^{-1}, broadening of 1716 cm^{-1} band and changes in the 3100 to 3400 cm^{-1} region. These results indicate that the interaction involves theophylline structure NH group with Eudragit® L100 carboxilic acid group. The present work will contribute to select appropriate excipients in order to develop a safe and stable theophylline delayed release multiparticle system.

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