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COMPATIBILITY STUDIES BETWEEN CAPTOPRIL AND PHARMACEUTICAL EXCIPIENTS USED IN TABLETS FORMULATIONS

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Captopril (CAP) was the first commercially available angiotensine-converting enzyme (ACE) inhibitor. In the anti-hypertensive therapy is considered the selected drug has to be therapeutically effective together with reduced toxicity. CAP is an antihypertensive drug currently being administered in tablet form. In order to investigate the possible interactions between CAP and excipients in tablets formulations, differential scanning calorimetry (DSC) and thermogravimetric (TG) analysis completed by X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR) were used for compatibility studies. A possible drug-excipient interaction was observed with magnesium stearate by DSC technique.

Keywords: *captopril, compatibility, FTIR, thermoanalytical techniques, X-ray powder diffraction*

Introduction

Captopril (CAP) that corresponds to 1-(3-mercapto-2-methyl-1-oxopropyl)-,(*S*)-*L*-proline (Fig. 1), is an angiotensin-converting enzyme inhibitor that has been used to treat hypertension congestive failure. When administered, CAP exerts its antihypertensive effect by inhibition of the conversion of angiotensin I to angiotensin II. After CAP oral administration of therapeutic doses (12.5 to 100 mg), absorption occurs, with maximum plasma levels at about one to two hours and the reduction of blood pressure usually reaches its highest level later than 60–90 min [1–3].

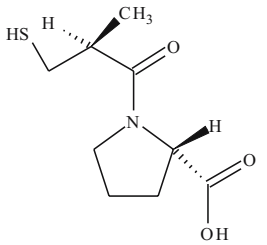

Fig. 1 Structural formula of captopril

The successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients. Most drugs intended for oral administration requires formulation with excipients to allow adequate administration, to facilitate the manufacture of the product, to increase the stability of the formulation, for aesthetic reasons or for identification. Although excipients traditionally have been thought of as being inert, excipients have shown that they can interact with the drug, preventing its absorption and bioavailability [4, 5].

During the formulation of new products or to reformulation of existing products, it is advantageous to have knowledge on any physical and/or chemical interactions between drug and excipients [6]. Drug-excipient interaction is an important exercise in the development of a stable dosage form [7]. The identification of possible incompatibilities between drug and excipients is one of the basic tasks to be dealt with in a pre-formulation laboratory. In this sense, devising a quick and accurate method to test and select the best candidates for stable dosage forms would constitute a real breakthrough in the pre-formulation pharmacy [8].

Thermoanalytical techniques measure changes in physical or chemical properties of the sample as a function of temperature. There are many possible applications in pharmaceutical industry, for example, identification, characterization of active and inactive ingredients, routine analysis, quality control and stability study [9].

In recent years, applications of thermoanalytical techniques in the pre-formulation stages in solid dosage form development have increased immensely. In particular differential scanning calorimetric has been proposed as a rapid method for evaluating physicochemical interactions between components of the formulation and therefore selecting excipients with suitable compatibility [5, 10].

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The present study was undertaken to establish the compatibility of CAP with a number of commonly used tablet excipients, using thermoanalytical techniques with the support of X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR).

Experimental

Materials

CAP was purchased from Shenyang Fine Chemical Co., China (lot number 55867). The excipients donated by Brazilian Industries and examined were: microcrystalline cellulose (granulometry 101 and 102, Avicel®), ethylcellulose (Ethocel 10 STD®), methylcellulose (Methocel 15PR®), monohydrated lactose, lactose Supertab®, stearic acid, magnesium stearate, polyvinylpyrrolidone (PVP K 30) and colloidal silicon dioxide (Aerosil®).

Methods

Differential scanning calorimetry (DSC)

DSC curves were obtained in a Shimadzu DSC-50 cell using aluminum crucibles with about 2 mg of samples, under dynamic N_2 atmosphere (flow rate: 100 mL min^{-1}) and at a heating rate of 10°C min^{-1} in the temperature range from 25 to 500°C. DSC cell was calibrated with indium (*m.p.* 156.6°C; ΔH_{fus}=28.54 J g^{-1}) and zinc (*m.p.* 419.6°C).

DSC analysis have been performed using sample pure CAP, single excipients, binary mixtures formed by CAP with only one excipient using 1:1 mass/mass ratio with all excipient samples.

Thermogravimetric analysis (TG)

TG curves were obtained with a Shimadzu model TGA-50 thermobalance in the temperature range of 25–600°C, using platinum crucibles with 4.0±0.1 mg of sample, under dynamic N_2 atmosphere (50 mL min^{-1}) and at a heating rate of 10°C min^{-1}. TG analysis have been performed using pure sample of CAP, single excipients, binary mixtures formed by CAP and only one excipient keeping 1:1 mass/mass ratio between active drug and all the excipient samples.

X-ray powder diffraction (XRPD)

For characterization of crystallinity, X-ray diffraction patterns were obtained on a Siemens model D 5000, with tube of CuK_α, voltage of 40 kV and current of 40 mA, in the range of 3–65 (2θ), using the powder XRD method. XRPD analysis has been performed using sample of pure CAP, single excipients, binary mixtures formed by CAP and only one excipient with 1:1 mass/mass ratio.

Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared (FTIR) spectra was recorded on a PerkinElmer Model 1600 apparatus using KBr discs in the range of 4000–400 cm^{-1}. FTIR analysis has been performed using sample of CAP, magnesium stearate, binary mixture formed by CAP and magnesium stearate at 1:1 mass/mass ratio.

Results and discussion

The thermoanalytical curves (DSC and TG) of CAP are illustrated in Fig. 2. The DSC curve of CAP showed a first endothermic event between 105 and 112°C (ΔH_{fusion}= –93.8 J g^{-1}), with a melting temperature of (T_{onset}=106.3°C). The TG curve exhibited 84.3% of mass loss between 150 and 350°C.

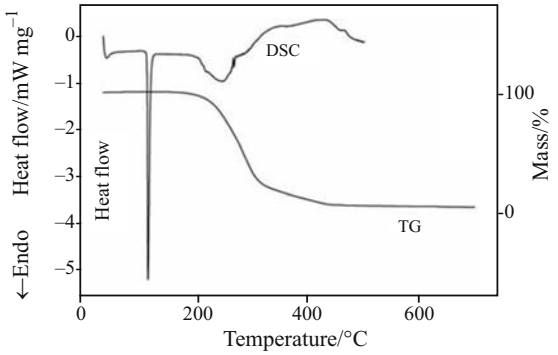

Fig. 2 DSC and TG curves of CAP

The selection of adequate excipients for the formulation was based on the characteristic of the drug and its compatibility with other components. Nowadays, it has infinity kinds of excipients and it is evidenced that the same drug, when manufactured with different excipients can presents distinct dissolution profile and bioavailability, which can prevent the desired pharmacologic effect [11].

Microcrystalline cellulose is composed of porous particles with white color, without odor, being widely used in pharmaceutical formulations (tablets and capsules) as diluent. It can be found in different sizes and degrees of mixture in the market which characterizes ones applications [12].

The natural modified polymers, such as the cellulose derivatives, like ethyl- and methylcellulose, present binder properties as viscosity increasing agent and coating in dust form for direct compression, while its solutions has adhesive properties [12, 13].

DSC and TG of CAP and 1:1 drug:excipient physical mixtures are shown in Fig. 3. Most of thermal profiles of mixtures can be considered as a superposition of DSC and TG curves of pure captopril and excipients evidencing the absence of incompatibility between CAP with different forms of celluloses, ethylcellulose and methylcellulose.

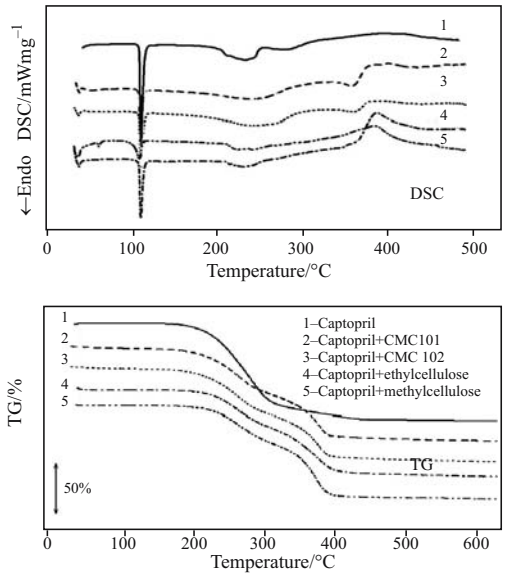

Fig. 3 DSC and TG curves of CAP and 1:1 physical mixtures (CAP, microcrystalline celluloses 101 and 102, ethylcellulose and methylcellulose)

Some types of lactose are commercially available, having different physical properties e.g. flowing and compressing abilities. Due to its physical properties Supertab® lactose is a product can be used for direct compression.

Thermal behavior of physical mixtures of CAP and lactose monohydrate and Supertab® are similar (Fig. 4). The DSC curve presents an endothermic peak corresponding to dehydration process in a temperature around 141°C. In the 173°C range was observed an exothermic event due to crystalline transition suffered by the lactose from α to β one [14]. After this event, an endothermic peak at 217°C represents the fusion followed by immediate thermal decomposition. In the TG curves a Δm=63.9% mass loss was observed between 234 and 347°C. The DSC and TG curves of the physical mixtures demonstrated there is no alterations in the thermoanalytical profiles of the drug.

Stearic acid and magnesium stearate are used as lubricant to prevent tack to improve the flowing properties of the mixture and reducing the attrition during compression [12, 13]. Magnesium stearate is widely used as an excipient in the tablet making since it decreases friction between the surface of the tablet and die wall during the ejection process [15].

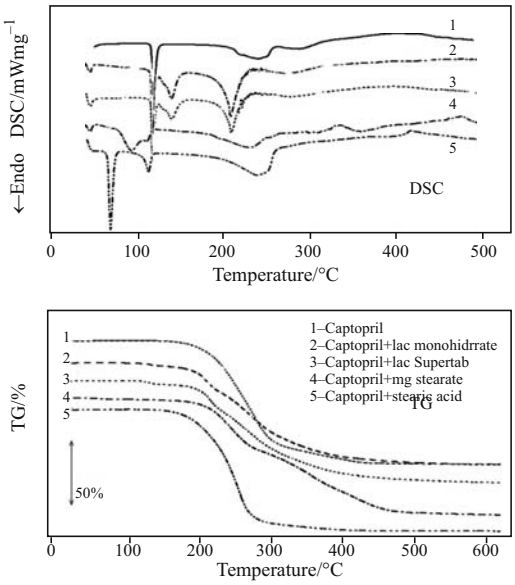

Fig. 4 DSC and TG curves of CAP and 1:1 physical mixtures (CAP, lactose monohydrate and Supertab®, magnesium stearate and stearic acid)

DSC curve of CAP and magnesium stearate (Fig. 4) presented two endothermic events in the 71–109°C temperature range which is characteristic for the dehydration process of magnesium stearate. The DSC curve of the binary mixtures indicate the occurrence of a possible incompatibility by the disappearance of the characteristic CAP fusion peak.

In the literature other interactions between drugs and magnesium stearate are detailed. Pyramides *et al.* [16] observed differences in the DSC curves of the melting point of atenolol in mixtures of drug:magnesium stearate and Oliveira *et al*. [17] reported it for glibenclamide.

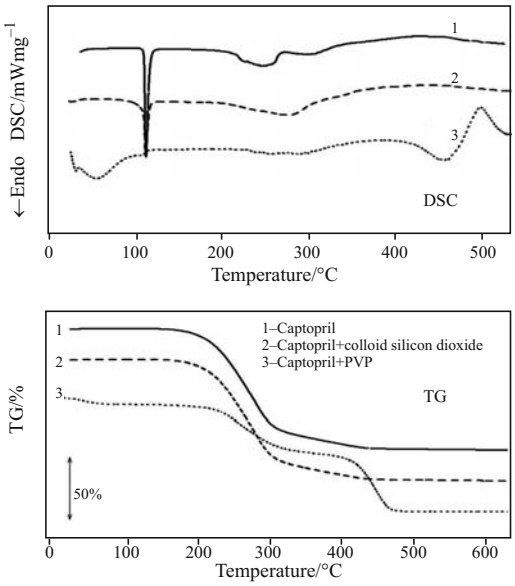

Fig. 5 DSC and TG curves of CAP and 1:1 physical mixtures with PVP and colloidal silicon dioxide

Table 1 Thermoanalytical data of captopril and drug:excipient physical mixtures

Samples	DSC		Enthalpy (fusion)/J g^{-1}
	T_{onset} (fusion)/°C	T_{peak} (fusion)/°C	
Drug			
Captopril	106.33	108.26	93.82
Drug/excipient			
Microcrystalline cellulose 101	106.26	108.06	67.93
Microcrystalline cellulose 102	106.03	107.89	51.42
Ethylcellulose	106.11	108.11	52.21
Methylcellulose	104.70	106.46	21.28
Monohydrated lactose	105.81	107.69	74.38
Supertab® lactose	105.86	107.85	54.36
Stearic acid	98.27	102.96	28.25
Magnesium stearate	–	–	–
Polyvinylpirrolidone	–	–	–
Colloidal silicon dioxide	106.31	108.26	48.75

The missing values cannot be calculated due to the infinite presence or the absence of the melting peak of CAP.

The DSC curve of CAP and stearic acid (Fig. 4) showed an endothermic peak at 57°C which is characteristic for the melting of the excipient. In agreement with the thermoanalytical curves of the physical mixture it can evidence a slight displacement of CAP melting peak, which does not seem to be an incompatibility.

The colloidal silicon dioxide is widely used in pharmaceuticals products. Its small particle size and large specific surface area provides its desirable flow characteristic which is exploited to improve the flow properties of dry powders in several processes, like tablet making [12]. The thermal behavior can be seen in Fig. 5, the binary mixture of CAP and colloidal silicon dioxide did not show incompatibility between these substances.

Polyvinyl pyrrolidone (PVP) is a synthetic colloid, water soluble and diverse organic solvent, having a high viscosity and the capacity to form complex. The DSC curve of the physical mixture CAP with PVP (Fig. 5) demonstrated the disappearance of

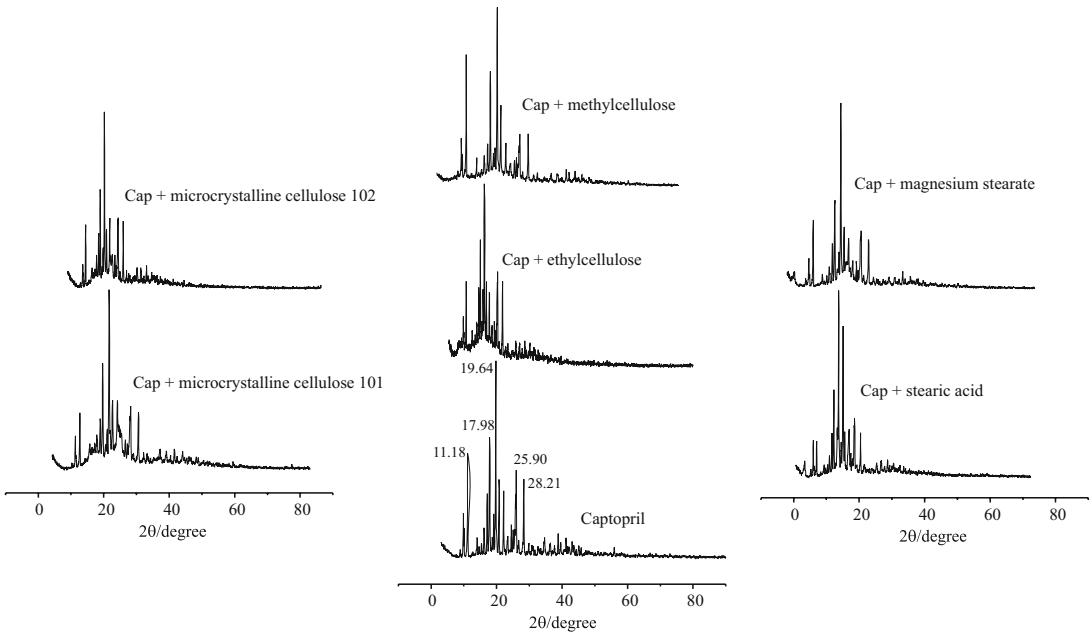

Fig. 6 X–ray diffraction spectra of CAP and 1:1 mass/mass blends as simple physical mixtures of CAP and microcrystaline cellulose 101, microcrystalline cellulose 102, ethylcellulose, methylcellulose, magnesium stearate and stearic acid

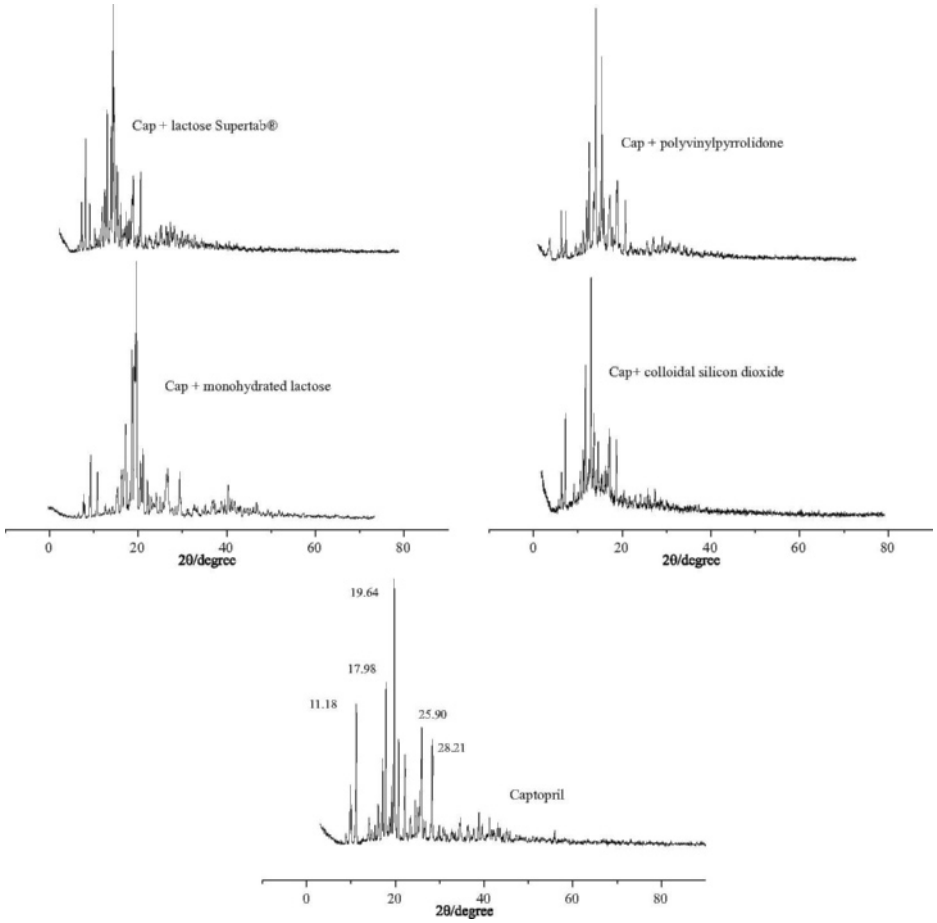

Fig. 7 X–ray diffraction spectra of CAP and 1:1 mass/mass blends as a simple physical mixtures of CAP and lactose monohydrate, Supertab® Lactose, polyvinyl pyrrolidone and colloidal silicon dioxide

the characteristic CAP fusion peak. This was also verified in the literature for mixtures of PVP with other drugs, as naproxen, ibuprofen and cetoprofen indicating the occurrence of a strong solid-solid interaction upon heating. However, this observation does not indicate an incompatibility between CAP and PVP. It can be rather explained as the dissolution of the drug in PVP [15, 18, 19, 20]. In the TG curve the sample was stable up to 300°C, followed by thermal decomposition, with a corresponding mass loss of 87.4%.

The results taken from DSC curves of binary mixtures are collected in Table 1.

X-ray diffraction studies were then performed, in order to obtain more information and to support DSC and TG results.

The studied drug has crystalline characteristics. The 2θ values of the more intensive peaks for CAP are 2θ=11.18; 17.98; 19.78; 25.99 and 28.21. In Figs 6 and 7 the X-ray diffractograms of CAP and the binaries can be observed.

According to our experiences, XRPD did not evidence incompatibility between CAP and the used excipients since the diffraction peaks of CAP remained unaltered in the physical mixtures. Incompatibility

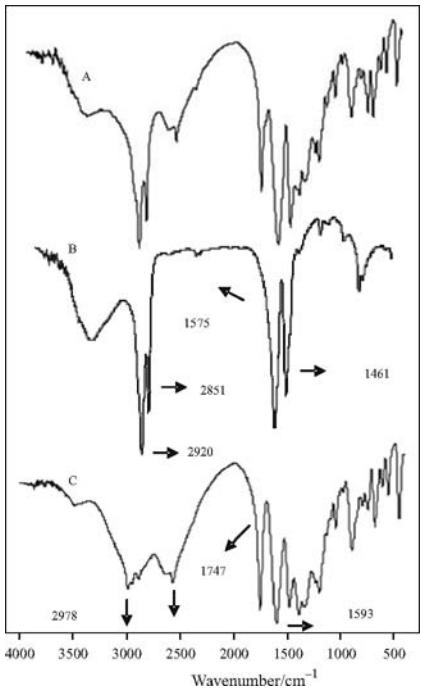

Fig. 8 FTIR spectra of physical mixture of A – CAP and magnesium stearate, B – pure magnesium stearate and C – pure CAP

observed by DSC between CAP and magnesium stearate was not observed by this assay.

The subsequent step of the present study was to analyze the FTIR spectra of CAP, magnesium stearate and the binary mixtures (1:1 mass/mass) of these components in order to identify a possible chemical interaction between them. The FTIR spectra are collected in Fig. 8.

In agreement with Huang *et al.* [21] the FTIR spectra (Fig. 8) CAP has three bands in the region of 2978 and 2870 cm^{-1} that correspond to the $–CH_2$ and $–CH_3$ groups. At 2561 cm^{-1} a band indicating the presence of –SH group. The carbonyl vibration band –COOH and amide band were demonstrated in the 1747 and 1593 cm^{-1} region, respectively. Magnesium stearate presents a strong CH_2–CH_3 vibration in region of 2920 up to 2851 cm^{-1}. At 1575 and 1461 cm^{-1} an asymmetric stretching was showed corresponding to the COO^- group.

The FTIR spectra of CAP and magnesium stearate did not show evidence on chemical interaction in the solid state. Moreover, the spectra of binaries did not show the absence or shift of vibration bands of CAP, only a superposition of the individual ones. It explains the absence of chemical interactions between CAP and magnesium stearate, suggesting that the obsevation showed by DSC curves is related to a possible physical interaction.

Conclusions

The results demonstrated the applicability of DSC as a fast screening tool for excipients at the early stages of a preformulation process. Based on the results of DSC/TG, XRPD and FTIR, majority of the excipients were found to be compatible with CAP. On the other hand, in accordance with the results of the present study a possible incompatibility was observed between CAP and magnesium stearate showed by DSC analysis, which was not confirmed by other techniques.

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