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Thermoanalytical investigation of olanzapine compatibility with excipients used in solid oral dosage forms

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Abstract During preformulation studies of pharmaceutical solid dosage forms, thermal analysis techniques are very useful to detect physical or chemical incompatibilities between the drug and adjuvants of interest that might interfere with efficacy and safety of the final drug product. Differential scanning calorimetry (DSC) and thermogravimetry (TG) are useful tools for this purpose. The aim of this study was to investigate the thermoanalytical behavior of olanzapine (OLZ) when mixed with several excipients commonly used in solid dosage forms such as microcrystalline cellulose, croscarmellose, dicalcium phosphate dihydrate (DCPD), lactose, magnesium stearate, and povidone. Following DSC and TG analyses, powder X-ray diffraction tests were carried out. Thermoanalytical methods showed evidence of interaction between OLZ and magnesium stearate, lactose, and povidone. These results can be useful during the selection of excipients for pharmaceutical formulation development.

Keywords Compatibility · DSC · X-ray powder diffraction · Olanzapine · TGA · Solid pharmaceutical dosage forms

Introduction

When developing tablet formulations, during early preformulation studies, it is relevant to evaluate physical and chemical interactions between an active pharmaceutical ingredient (API) and excipients [1–3], since incompatibilities between drug and adjuvants may negatively affect both the stability and the bioavailability of drug products [1, 3–6]. A satisfactory formulation work must include a careful selection of excipients [3], taking into consideration that the "inert" substances commonly show interactions with APIs [7, 8].

There is no universally accepted protocol to evaluate compatibility between APIs and excipients [9]. Thermoanalytical methods such as differential scanning calorimetry (DSC) and thermogravimetry (TG) are frequently used in the same study [10–12] in order to obtain complementary data, demonstrating several advantages over traditional stability techniques [6, 13, 14]. Particularly, DSC has been used to investigate and predict physicochemical incompatibilities between API and excipients [2, 3, 15]. In addition, DSC and TG curves display information about several properties of the tested substances, such as purity, stability, and polymorphism [7, 16, 17].

DSC data can be more easily interpreted when they are supported by thermogravimetric curves [6]. In addition, due to the complexity of thermal analysis results, it is often necessary to combine X-ray diffraction data to accomplish proper interpretations [17]. In general, compatibility analysis is performed by analyzing alterations in DSC curves of the API mixed with the tested excipient in comparison to the individual API curve [18]. Mixtures are commonly prepared in 1:1 proportion with each excipient in order to maximize potential interactions [1, 2]. Modifications are expressed as appearance, shift, or disappearance of DSC peaks and/or variations in expected enthalpy values [19, 20]. It is important to note that the different techniques used to prepare drug–excipient mixtures may also affect the properties of the material, and therefore, different techniques have been used such as simple mixture and grinding [3].

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Physical or chemical interactions between APIs and excipients do not necessarily indicate incompatibility, but in general authors agree that a change in DSC curve is an undeniable evidence of interaction [18]. In certain cases, such interactions can be advantageous to the drug release system. However, when not expected, interactions can adversely affect the bioavailability of a drug [8].

In this study, interactions between olanzapine (OLZ) and several commonly used pharmaceutical excipients were investigated by thermal analysis and powder X-ray diffraction. OLZ is an atypical antipsychotic drug. Indications approved by the FDA include the monotherapy treatment of schizophrenia and bipolar mania [21]. OLZ has a distinctive market relevance, with sales reaching, according to the manufacturer Eli Lilly, US$ 8 billion in 2010. In fact, OLZ sales ranked among the top eight drugs each year from 2000 to 2007 [22, 23].

OLZ exhibits a complex solid state behavior and can crystallize in at least 25 different solid forms, including three polymorphic anhydrates, three polymorphic dihydrates, and a higher hydrate [24]. There is an anhydrous form that is considered the most stable polymorphic form, while the other anhydrous and hydrated polymorphs are metastable [24, 25]. Owing to this behavior, it is necessary to control manufacturing conditions of solid OLZ to avoid its ability to form polymorphs [26]. Polymorphic transitions during processing could affect stability and performance of the final product [27]. Although there have been numerous reports on OLZ polymorphism, there are no literature reports regarding preformulation studies to support the design of solid dosage forms containing OLZ.

In this study, DSC, TG, and XRPD techniques were applied with the purpose of evaluating compatibility of the stable, anhydrous polymorphic form (1) of OLZ with excipients commonly used in the manufacture of solid dosage forms, in order to subsidize the design of solid dosage forms for this drug, including the development of new generic formulations.

Experimental

Materials

Olanzapine was purchased from Galt Pharma Exports Private Limited, lot OL0031007. Excipients used were microcrystalline cellulose (Avicel PH-101®, FMC BioPolymer, USA), sodium croscarmellose (FMC, BioPolymer, USA), dicalcium phosphate dehydrate (Di-tab®, Innophos, USA), anhydrous lactose 22AN® (DMV-Fonterra, Germany), magnesium stearate (Shengzhou Light Industry Plastic Chemical Factory, China), and povidone K30® (Shanghai Dexiang Medicine Tech. Co., Ltd., China). All excipients were of pharmaceutical grade.

Preparation of samples

API–excipients binary mixtures of ratio 1:1 (w/w) were prepared by two different procedures: physical mixture and grinding. To prepare binary mixtures by physical mixture, each excipient was weighed and transferred to individual amber flasks containing the same weight of the API. The mixture was then homogenized in a vortex mixer for 2 min. Mortar and pestle were used to grind the second group of samples for 2 min each. Recently prepared samples were submitted to the analytical procedures.

Calorimetric studies

DSC was calibrated with indium and zinc. Baseline corrections were conducted according to instructions from the instrument's manufacturer. DSC curves were obtained in a Shimadzu DSC-60 cell using aluminum-sealed crucibles (about 2.0 mg samples) under dynamic N_2 atmosphere (flow rate of 50 mL min^{-1}) and heating rate of 283.15 K min^{-1} in the temperature range from 298.15 to 573.15 K. Tests were carried out individually with drug and excipients, then with recently prepared physical mixtures and grinded samples.

Thermogravimetric studies

TG curves were obtained in a Shimadzu DTG-60 thermobalance, under dynamic N_2 atmosphere (flow rate 50 mL min^{-1}) and heating rate of 283.15 K min^{-1} in the temperature range from 298.15 to 923.15 K. Samples (4.0–8.0 mg) were placed in platinum crucibles. Tests were carried out individually with drug and excipients, then with recently prepared physical mixture samples.

Powder X-ray diffraction

To characterize crystallinity, powder X-ray diffraction patterns (XRPD) were obtained with a Shimadzu LabX XRD 6000 diffractometer with CuKα radiation (voltage of 40.0 kW, amperage of 30.0 mA), over an angular range 5–40° (2θ) with scan speed of 2.0° min^{-1}, using powder method. Isolated drug, excipients, and physical mixtures were analyzed.

Results and discussion

DSC and TG/DTG curves for OLZ are shown in Fig. 1. DSC curve exhibits an endothermic melting peak

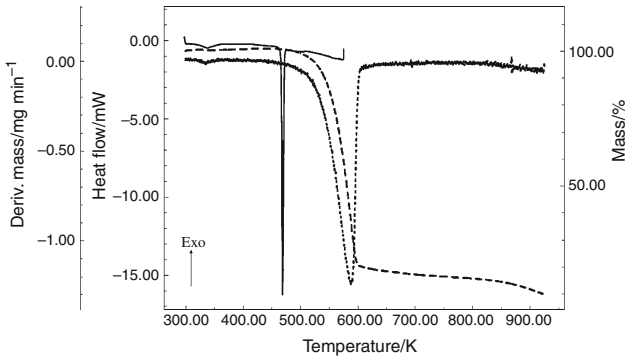

Fig. 1 DSC (*continuous line*) and TG (*dashed*) curves of OLZ and TG first derivative curve (*dotted*)

($T_{onset} = 466.6$ K), with a melting heat (ΔH_{fusion}) of -110 J g^{-1}. From the TG curve (Fig. 1), it can be observed that mass loss does not occur during the melting process, with degradation event starting after melting event is completed. According to Polla et al. [25], melting point is the only thermal event identifiable in DSC curve of OLZ form (1), the most stable anhydrous form. The DSC curve obtained in this study shows the same thermal behavior as described by these authors, which characterizes form (1) of OLZ.

TG first derivative shows one degradation event occurring approximately between 490 and 600 K, which is responsible for sampling an 80% weight loss.

X-ray diffraction pattern obtained from drug analysis is presented in Fig. 2, exhibiting four characteristic peaks that identify the OLZ polymorphic form (1): 8.6; 12.4; 14.4; and 17.0°, according to the previous literature reports [25].

Figure 3 exhibits DSC results from binary mixtures prepared by physical mixture and grinding procedures. DSC data referring to OLZ melting peak are presented in Tables 1 and 2. Melting temperature is highly reproducible even when OLZ is mixed with different excipients. Since the melting enthalpy for the drug corresponds to

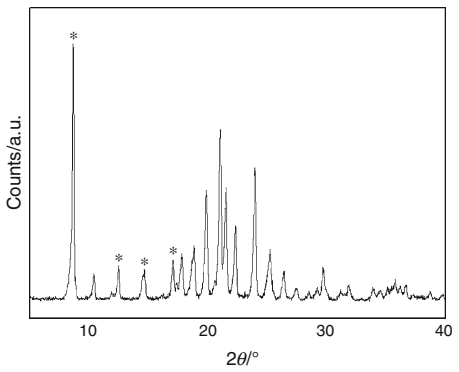

Fig. 2 X-ray diffraction pattern of OLZ (*Characteristic peaks of OLZ polymorphic form (1))

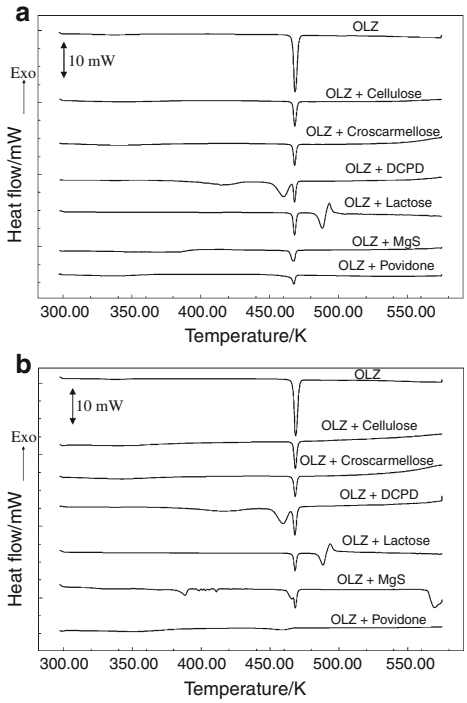

Fig. 3 DSC curves of olanzapine pure (**a**) and grinded (**b**) samples and 1:1 (w/w) olanzapine/excipient physical (**a**) and grinded (**b**) mixtures

Table 1 Peak temperature and enthalpy values for physical mixtures

Excipient in 1:1 mixture	T_{onset} DSC/K	T_{peak} DSC/K	ΔH/J g^{-1}
Cellulose PH-101	466.7	468.4	−57.16
Croscarmellose sodium	466.6	468.2	−67.10
Dicalcium phosphate dihydrate	464.2[a]	468.2	−29.54[b]
Lactose	466.7	468.2	−44.74
Magnesium stearate	464.4[a]	194.5[a]	−53.22
Povidone	464.7[a]	467.7[a]	−48.88
Olanzapine	466.6	468.7	−109.90

[a] Corresponds to variations over 0.5 K in relation to isolated drug

[b] Corresponds to variations over 25% in relation to 1/2 of isolated drug ΔH value

-109.90 J g^{-1}, the value expected in a 1:1 mixture is close to -55 J g^{-1}.

DSC curves of the binary mixtures of API and cellulose, croscarmellose, or DCPD (physical mixture and grinded samples) overlapped with the curves of pure components. In the case of binary mixture with DCPD (Fig. 4a), there are two events prior to OLZ melting, corresponding to a two-step dehydration of DCPD. A broad endotherm around 420 K is observed followed by an endothermic peak near 463 K, in agreement to previous reports in the literature [4]. The curve in Fig. 4a showed that the melting event of the OLZ in DCPD mixture occurred in a temperature range

Table 2 Peak temperature and enthalpy values for grinded mixtures

Excipient in 1:1 mixture	T_{onset} DSC/K	T_{peak} DSC/K	ΔH/J g^{-1}
Cellulose PH-101	466.5	468.3	−52.38
Croscarmellose sodium	465.7[a]	468.3	−62.55
Dicalcium phosphate dihydrate	466.1	468.2	−33.62[b]
Lactose	466.5	468.2	−46.99
Magnesium stearate	466.6	468.3	−53.38
Povidone	447.2[a]	459.1[a]	−31.72[b]
Olanzapine	193.4	195.5	−109.90

[a] Corresponds to variations over 0.5 K in relation to isolated drug

[b] Corresponds to variations over 25% in relation to 1/2 of isolated drug ΔH value

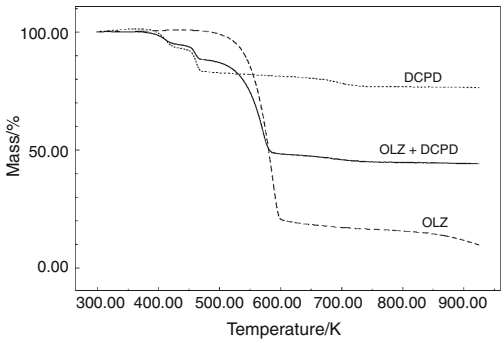

Fig. 5 TG curves of olanzapine (*dashed*), of DCPD (*dotted*), and of their 1:1 (w/w) physical mixture (*continuous line*)

similar to the pure OLZ melting. API melting enthalpy was lower in both mixtures with DCPD (Tables 1, 2); however, enthalpy decrease was probably due to the proximity of the second dehydration peak of DCPD.

TG analysis (Fig. 5) shows DCPD dehydration in two steps (385–428 and 428–477 K), which causes a weight loss of almost 20% in the sample containing the pure excipient. These events' intervals showed little or no noticeable change when DCPD was mixed with OLZ (388–431 and 431–478 K). Weight losses related to decomposition events showed that individual components decomposed individually in mixtures, indicating no interaction between them.

DSC curves of the binary mixtures between lactose and OLZ (Fig. 4b; Tables 1, 2) were similar to DSC curves of pure OLZ. Differences in the melting peak related to the mixture procedure were not observed. However, the T_{onset} for the melting peak of the anhydrous lactose in mixtures was lowered in comparison with pure lactose melting. Lactose melting peak was 513 K, also in accordance to the literature [28], but when mixed with OLZ, lactose melting peak was approximately 493 K. In addition, DSC curves of both mixtures showed an exothermic event right after lactose melting, which was not observed for none of the individual components, highlighting a possible interaction. Nevertheless, interactions cannot be assured in this case in light of literature reports of a thermal decomposition of lactose monohydrated, a different kind of α-lactose, which takes place right after its melting [18]. This decomposition event was also seen when lactose was mixed with captopril [29] and venlafaxine [30].

Figure 6 shows TG/DTG curves of lactose and lactose–OLZ mixture. Pure lactose degradation begins at 498 K, before the melting peak seen in the DSC curve (Fig. 4b). However, TG/DTG curve of the physical mixture showed that decomposition occurs before expected, dropping from 498 to 481 K, which also indicates interaction between OLZ and lactose. This is probably associated to the Maillard reaction, which occurs in lactose-containing tablets

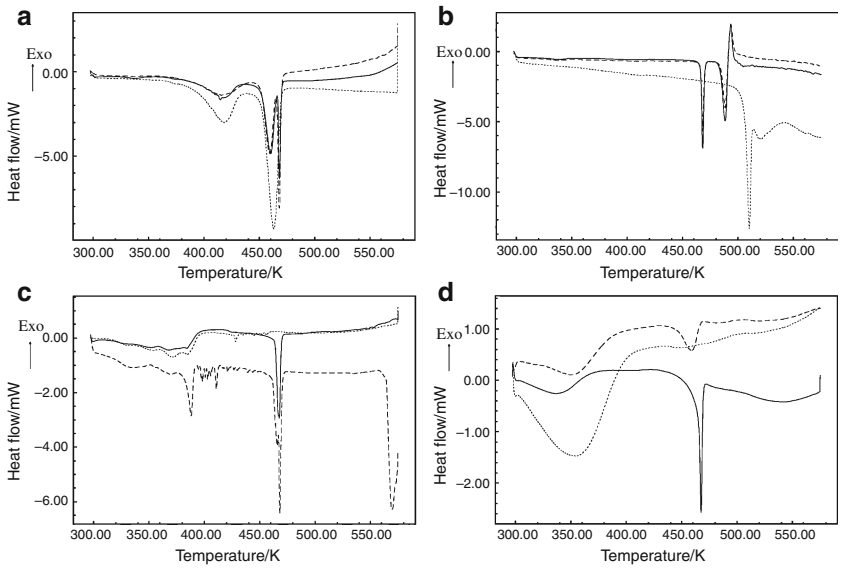

Fig. 4 DSC curves of excipients (*dotted*) DCPD (**a**), lactose (**b**), magnesium stearate (**c**), and povidone (**d**), and their 1:1 (w/w) olanzapine/excipient binary mixtures grinded (*dashed*) and physical mixture (*continuous line*)

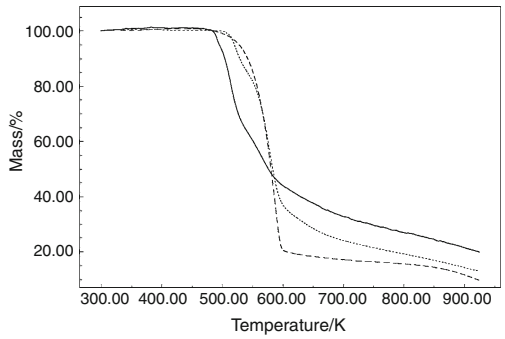

Fig. 6 TG curves of olanzapine (*dashed*), of lactose (*dotted*), and of their 1:1 (w/w) physical mixture (*continuous line*)

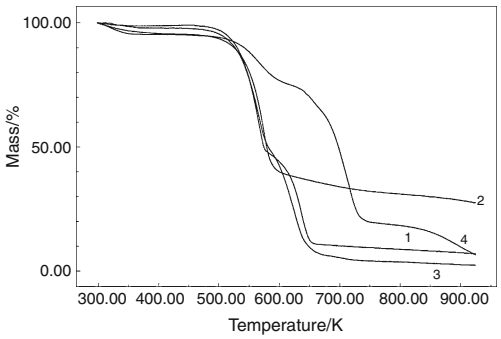

Fig. 7 TG curves of 1:1 (w/w) olanzapine/excipient physical mixtures with cellulose (*1*), croscarmellose (*2*), magnesium stearate (*3*), and povidone (*4*)

and was already studied for several drugs [31]. OLZ contains two secondary amines which can probably react with the sugar in the mixture.

Figure 4c exhibits DSC curves of magnesium stearate (MS) and the binary mixture. MS dehydration takes place in several steps in the temperature range 343–383 K [4, 29]. The grinded mixture curve showed an endothermic peak, probably related to dehydration process, around 383 K. MS melting starts at 383 K and an endothermic peak around 433 K can be observed in DSC curve of the pure excipient. According to Marini et al. [10], this peak is due to magnesium palmitate melting, commonly present in MS samples. In DSC curve of the grinded mixture, endothermic peaks are observed in the range 393–413 K, which may be attributed to MS and magnesium palmitate melting events. Meanwhile, OLZ melting peak in DSC curve of grinded mixture presented a shoulder, which can also be evidence of interaction. Regardless of changes in the peak shape, the melting enthalpy (Table 2) remained as expected. TG curve of this mixture (Fig. 7) shows that degradation onset is not altered, exhibiting a similar behavior as the curves of physical mixtures containing cellulose, croscarmellose, and povidone.

In Fig. 4d, it can be observed that povidone presents typical hygroscopic amorphous substance behavior, with a broad endothermic event due to water evaporation, ending around 393 K [3, 10]. Curve of grinded mixture shows that melting T_{onset} of OLZ is reduced and melting peak is broadened, which indicates solid–solid interaction. This behavior, a consequence of the grinding process, has been already described for other drugs, such as ibuproxam [3], piroxicam [7], and captopril [29], but does not necessarily indicate pharmaceutical incompatibility between povidone and the drug [29]. TG curve of this physical mixture did not support the evidence of interaction between OLZ and povidone (Fig. 7).

Physical mixtures were also analyzed by X-ray powder diffraction method. Results are presented in Fig. 8. X-ray patterns were obtained with the purpose of confirming

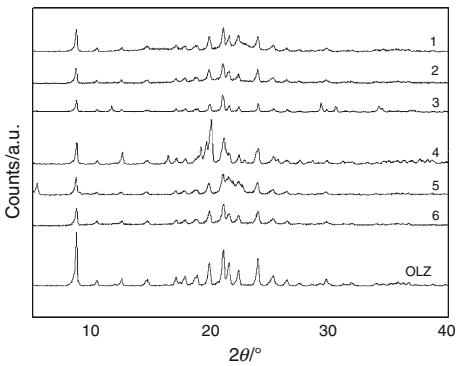

Fig. 8 X-ray diffraction patterns of 1:1 (w/w) olanzapine/excipient physical mixtures with cellulose (*1*), croscarmellose (*2*), DCPD (*3*), lactose (*4*), magnesium stearate (*5*), and povidone (*6*)

possible interactions suggested by thermal analysis. Results did not indicate new evidences of interaction in the solid state, since the peaks that identify OLZ (marked with * in Fig. 2) are still present in the X-ray patterns of the physical mixtures. X-ray patterns can be considered as the overlap of individual components without absence, shift or broadening of the peaks. Comparison between both mixtures containing the same excipients did not show any differences. It has been reported that DSC/TG techniques are considered to be more sensitive than XRPD [10]. In this study, interactions indicatives were only observed in thermal analysis results.

Conclusions

Based on thermal analysis results, DSC curves indicate that OLZ might interact with lactose, magnesium stearate, and povidone. TG analysis provides evidence of incompatibility only between OLZ and lactose. However, X-ray diffraction patterns of all physical mixtures tested did not exhibit modifications on crystalline structure of OLZ. Even though XRPD data did not reinforce the possible drug–

excipient interactions suggested by DSC and TG analysis, these results appoint for the usefulness of thermal analysis techniques as a relevant screening tool during formulation development.

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