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Weak interactions in clobazam–lactose mixtures examined by differential scanning calorimetry: Comparison with the captopril–lactose system

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ABSTRACT

The thermal behaviour of binary mixtures of two drugs (clobazam and captopril, respectively) and a pharmaceutical excipient (lactose monohydrate) was measured with differential scanning calorimetry to determine thermodynamic and kinetic parameters (dehydration and melting enthalpies and dehydration and glass-transition activation energies) which might be affected by intermolecular interactions.

A kinetic study showed that lactose dehydration is not a single-step conversion and that clobazam contributed to reduce the energy barrier for the bulk dehydration of the excipient.

On the other hand, the physical interactions between metastable liquid clobazam and crystalline anhydrous α-lactose obtained from monohydrate dehydration gave rise to the recrystallisation of clobazam.

In the captopril–lactose system, the liquid captopril influenced the lactose dehydration: a sharp increase of the dehydration enthalpy and a concurrent reduction of the dehydration temperature were observed.

Finally, it turned out that solid-phase transitions were enhanced by the contact with a liquid phase.

1. Introduction

Studies of active drug/excipient compatibility represent an important phase in the preformulation stage in the development of drug dosage formulations. The potential physical and chemical interactions between drugs and excipients can alter the chemical nature, stability and bioavailability of drugs and thereby may affect efficacy and/or safety [1–6].

Drug–excipient incompatibilities occur with both strong and weak interactions. Strong interactions have been described to occur between numerous drugs and excipients [1,7–10]. In some cases, they involve the formation of a more complex compound with a reaction between the drug and the excipient; in other cases, strong interactions can promote the intrinsic degradation of the drug via hydrolysis or oxidation. Alternatively, weak physical interactions (e.g. Van der Waals) do not cause the formation of new impurities but they may involve changes in physico-chemical properties that affect the dissolution profile or the crystallinity degree of the drug.

Differential scanning calorimetry (DSC) is a rapid and sensitive technique that has been successfully used for evaluating drug–excipient interactions [1–6]. Strong interactions are detected whether temperature shifts or relevant changes in enthalpy values occur for characteristic endothermic or exothermic peaks. In contrast, weak interactions among components typically produce small variations of peak temperatures or of the associated enthalpies. Although interaction can sometimes be beneficial to achieve specific design purposes, strong interactions generally involve striking incompatibility among the components of a mixture. Weak interactions, too, were claimed to put into question the compatibility of components of a pharmaceutical formulation [11].

Clobazam (7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4 (3H,5H) dione) is a psychotropic drug, essentially used for its anticonvulsant effects. A 1,5-benzodiazepine has nitrogen atoms in the 1 and 5 positions of the heterocyclic ring: this chemical structure was designed to produce a pharmacological profile different from that of 1,4 benzodiazepine which is used for sedation and tranquilisation [12,13]. In fact, clobazam is active in a wide spectrum of disorders and is highly effective in several types of refractory epilepsies [14]. Captopril (1-(3-mercapto-2-methyl-1-oxopropyl)-(S)-L-proline is an angiotensin converting enzyme inhibitor that has been used to treat hypertension and congestive heart failure [15,16].

In this study, we used DSC to investigate the physical interactions between clobazam or captopril and a pharmaceutical excipient, monohydrate lactose, which is commonly used in the development of solid formulations.

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2. Experimental

2.1. Materials

Clobazam (CEP quality), captopril (CEP Quality) and lactose monohydrate (Ph.Eur. quality) were purchased from Inresa and used without further purification.

After weighting pure components, binary mixtures were prepared by grinding samples with pestle and mortar for 5 min. The final formulations ranged from 10 to 98 mol% of active drug in mixtures with lactose monohydrate.

In order to prepare mixtures by double weighing, an analytical high-precision balance (model Precisa 40 SM-200A) equipped with a stability detector was used. The instrument, which lay on an anti-vibration support, was used in its 0–200 g range; the legibility was 10^{-2} mg and the loss of linearity 4×10^{-2} mg. Considering that the mass of each binary mixture was 100 mg, the uncertainty on composition was estimated not to be higher than 1% in the case of mixtures containing less than 10% of one component. For mixtures containing more than 10% of each component uncertainty was lower. These uncertainties are smaller than the one involved in DSC measurements, which was estimated to be 2% after device calibration.

2.2. Apparatus, experimental errors and measurement conditions

DSC studies were performed with an 823^e Mettler Toledo differential scanning calorimeter (GmbH, Switzerland). The melting temperature and enthalpy of indium were used as references to calibrate the instrument.

Similarly, the experimental errors, intended as the day-to-day repeatabilities on enthalpy and temperature measurements, respectively, were evaluated by founding upon a series of 13 experiments which were carried out on a sample of pure indium within the period of 1 month, without performing, at that time, any calibration of the DSC device. Repeatability was 2.4% for melting enthalpy and 0.1% for melting temperature. It can be noticed that the enthalpy repeatability is in agreement with the uncertainty claimed for the DSC device after calibration. The corresponding uncertainties were associated to experimental values reported in the first four tables.

Samples of approximately 1–10 mg were weighted, placed in non-hermetically sealed aluminium crucibles provided with pierced lids and submitted to heating and cooling scans at the rate of $\pm 10\,\mathrm{K\,min^{-1}}$ under a dynamic nitrogen atmosphere (gas flow: $80\,\mathrm{ml\,min^{-1}}$) in the temperature range between 298 and 473 K and occasionally between 213 and 473 K.

In order to determine the activation energies for the clobazam glass transition and the lactose monohydrate dehydration, scan rates were performed within a sufficiently restricted low-rate range ($2–20\,\mathrm{K\,min^{-1}}$) to ensure that the activation energy was at least independent on heating rate, according to what suggested by Abu-Sehly et al. [17] in a previous DSC study performed on amorphous selenium, where the same scan rates were used. Thermal analysis of each sample was repeated at least three times.

In the study of the thermodynamic parameters of the drug–excipient interaction, dehydration and fusion temperatures were read at the intersection point between the baseline and the line tangent to the ascending profile of the endothermic peak (for crystallisation the second line was tangent to the descending profile of the exothermic peak).

Conversely, in the kinetic study of the lactose monohydrate dehydration, temperatures T_α attained for achieving different extents of dehydration were computed. The computing method was based upon the experimental evidence that a transition is already completed before the DSC signal newly reaches the peak baseline. Accordingly, the end of a DSC-studied transition corresponds to a point on the thermal profile which is situated at a temperature slightly higher than that of the peak maximum. In this work, this temperature was made correspond to that, named T_e, of a minimum point on the curve of the first derivative of the DSC profile, which becomes negative for temperatures higher than the peak-maximum temperature: hence, T_e was assumed to be the dehydration-end temperature. Consequently, the extent of conversion α at a given temperature T_α was expressed as the ratio of the area of the portion of the transition peak truncated at this temperature T_α (by a line perpendicular to the baseline) to the area of the dehydration peak truncated at the dehydration-end temperature T_e.

In order to corroborate the reliability of the method, thermogravimetric (TGA) profiles were reproduced by using computed $(1-\alpha)$-values (which represent extents of non-dehydrated lactose monohydrate) and their features compared to those of experimental TGA curves. In Fig. 1A and 1B, the $(1-\alpha)$ vs. T data for pure lactose monohydrate and for a clobazam–lactose monohydrate mixture (clobazam molar fraction $x = 0.924$), respectively, both investigated at different scan-rates, are reported. It must be noticed that the $(1-\alpha)$ vs. T profiles exhibit maxima of dehydration rates at about 2/3 of the dehydration process, which is a characteristic of the thermogravimetric profiles. Besides, the shift of the dehydration curves towards higher temperatures with increasing the heating rate is also systematically reproduced.

However, for a sake of accuracy, in Fig. 2A we have compared the $(1-\alpha)$ vs. T curve derived from a DSC measurement on lactose monohydrate at the $5\,\mathrm{K\,min^{-1}}$ heating rate with the one obtained from a thermogravimetric measurement at the same heating rate [18]. For the former, the maximum of dehydration rate was calculated to be at a dehydration extent $\alpha = 0.72$ whereas for the latter to be at $\alpha = 0.62$. It can be noticed that the curve derived from DSC measurement is shifted of, on average, 5 K towards lower temperatures with respect to the other for α-values comprised within 0.15 and 0.85. From a qualitative point of view, it can also be noticed that the main difference between the two curves involves the final stage of dehydration. As a matter of fact, the decreasing of the $(1-\alpha)$ values with increasing temperature is much steeper for the profile derived from DSC measurement than is for the profile obtained by thermogravimetry. This is a straight consequence of our choice of the dehydration-end temperature, T_e, according to the properties of a DSC transition peak, which have been already discussed. Moreover, as dehydration ranges may depend on the particular experimental conditions of each experiment, in order to quantitatively discriminate about the two curves, a normalising thermal parameter of the dehydration range we named r:

$$r = \frac{T_\alpha - T_{\min}}{T_{\max} - T_{\min}},$$

where $T_{\min}$ and $T_{\max}$ are the temperature limiting the dehydration range and T_α that corresponding to a given dehydration extent α, has been reported in Fig. 2B as a function of α. It must be noticed that in the α-value range comprised between 0.45 and 0.85 parameter r is systematically higher for the DSC-derived profile than for the thermogravimetry-derived one (Δr is about 0.1).

Glass transition temperatures T_g of clobazam were taken as the inflection points in the DSC profiles that corresponded to the endothermic baseline shifts; these were proportional to specific-heat changes ΔC_P. Repeatability for T_g measurements was determined to be 0.15%; it resulted from a series of 7 measurements, each of which being performed on a different sample of the same clobazam batch at the same scan rate ($10\,\mathrm{K\,min^{-1}}$). The masses of the samples varied between 1.5 and 5 mg.