Journal of Thermal Analysis and Calorimetry, Vol. 68 (2002) 561–573

DRUG-EXCIPIENT COMPATIBILITY STUDIES
Search of interaction indicators

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Abstract

This paper is the first one of a research project aimed to find and optimize methods by which drug-excipient compatibility can be reliably and quickly assessed.

A number of experimental techniques (simultaneous TG-DSC, FT-IR spectroscopy, X-ray powder diffraction, scanning electron microscopy) have been used to investigate the compatibility between a novel tricyclic β-lactam antibiotic developed by GlaxoWellcome (now GlaxoSmithKline), GV118819x, and some commonly used excipients (poly(vinylpyrrolidone), magnesium stearate and α-lactose). Binary mixtures of two different compositions have been analyzed: drug:excipient=80:20 and 20:80 (mass/mass). Both qualitative and quantitative interaction indicators have been identified. It is shown that simultaneous thermal analysis is the best suited technique in the search of interaction indicators. With a proper selection of experimental conditions it is able to reveal the thermal changes brought about by the early stages of interaction, i.e. those occurring during the measurement on physical mixtures not previously annealed under stress conditions. Such an ability is discussed, in particular, with respect to the role of the water vapour, which has been found to be a critical parameter for all our systems.

Keywords: drug-excipient compatibility, humidity, simultaneous TG/DSC, solid state interaction

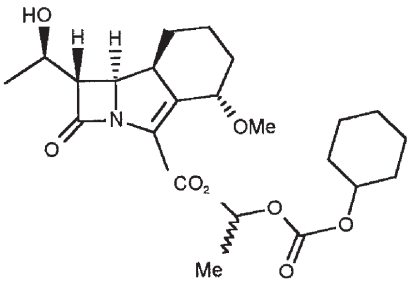
Introduction

The identification of possible incompatibilities between drug and excipients is one of the basic tasks to be dealt with in a preformulation laboratory [1]. 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 preformulation pharmacy. The procedure employed so far is mostly based on the annealing of binary mixtures under stress conditions and on the chromatographic analysis of the annealed mixtures [2–4]. This, besides requiring large amounts of drug, is time-consuming and ultimately very expensive. Thermoanalysis offers significant advantages in saving both time and substance as, in principle, makes it possible to detect compatibility/incompatibility directly on physical mixture, avoiding the time consuming step of the annealing of the mixtures under stress conditions [5, 6]. There are probably two main reasons of the origin of the low use and success that thermal methods have reached up to now in

1418–2874/2002/ $ 5.00
Akadémiai Kiadó, Budapest

compatibility studies. The first one is the lack of attention to the quantitative aspects of DSC results [7–9]. The second one, perhaps also more important, is an unsuitable selection of the measuring atmosphere, i.e. the overlooking of the role of the relative humidity on drug stability [10, 11].

This work reports the first results of a research project, the target of which is a new and quick method of as high as possible predictive ability for drug-excipient incompatibilities. Our plan is to apply simultaneous thermal analysis (STA) as well as X-ray powder diffractometry (XRPD), Fourier transform infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM) to a number of drug-excipient systems with the aim to find and validate reliable interaction indicators. Here we report the results obtained in the study of the interaction between some common excipients (Poly(vinylpyrrolidone) (E8 in the following), magnesium stearate (E16 in the following) and α- lactose monohydrate (E17 in the following)) and a tricyclic β-lactam antibiotic, GV118819x (A1 in the following), recently developed by GlaxoWellcome [12–15].



GV118819x

Experimental

A1 comes from a batch of industrial production and it has been ever since stored in closed vials kept under dark at 4°C. The excipients have been provided through GlaxoWellcome. Drug-excipient physical mixtures have been prepared by weighing the appropriate amounts of the components and mixing them manually in a plastic vial. Binary physical mixtures of two different compositions have been prepared, with drug:excipient (mass ratio) 20:80 and 80:20. These compositions were selected to study the influence of the relative amount of excipient in a rather wide range but using reasonable amounts of drug. The mixtures have also been stored at 4°C in the dark.

Different aliquots of drug, excipients and physical mixtures have been subjected to the following treatments:

– annealing in oven (RH<32%) at 65°C in closed glass containers for 6 days;

– ageing at room temperature (23°C, r.t.) at relative humidity >90% for different periods of time.

Simultaneous TG/DSC measurements have been carried out on pure components and mixtures (as prepared and treated in temperature or humidity) by a STA

625 apparatus (Polymer Laboratories, UK). Samples (about 7 mg) have been heated, in open Al pans, at a scanning rate of 2 and 5 K min^{-1}, under a flow (3 L h^{-1}) of dry nitrogen or of nitrogen bubbled through water at r.t. (wet nitrogen). At least three replicates have been made for each measurement.

XRPD diffraction spectra have been collected in air by a D5005 apparatus (Bruker Siemens, Germany) equipped with a goniometer and a graphite bent crystal monochromator (CuK_α radiation). The angular range between 5 and 35°2θ has been scanned in the step scan mode (step width: 0.02°2θ, counting time: 5 s, 40 kV, 30 mA).

Diffuse reflectance FT-IR spectra have been recorded at r.t. with a FT-IR Mod. 730 Nicolet Spectrometer (Nicolet, USA) equipped with a diffuse reflectance attachment (Drift Collector by Spectra Tech, UK) co-adding 256 scans at 2 cm^{-1} resolution. The spectra (4000–400 cm^{-1}) have been collected under a flow of dry nitrogen on samples dispersed (1–2% by mass) in a KBr matrix by a 2 -min milling in an agate mortar.

SEM microphotographs have been collected at r.t. with a Cambridge Stereoscan 200 Scanning Electron Microscopy on gold-sputtered samples.

Results and discussion

Tricyclic -β-lactam:polyvinylpyrrolidone (A1:E8)

A1:E8=20:80 (mass/mass)

Figure 1 reports TG/DSC curves recorded on the 20:80 physical mixture (curves c) at 5 K min^{-1} in dry nitrogen. The same figure also reports the curves of the pure components (a and b). The qualitative thermal behaviour of the mixture represents just the sum of those of the pure components. The following features are to be noted:

– an initial mass loss (nearly 10%) associated with a broad endothermic effect due to dehydration of the excipient;

– an endothermic peak followed by a shoulder, in the 90–125°C temperature range, attributable to A1. A previous work on A1 [15] showed that these thermal effects are due to melting of the eutectic mixture of two diastereoisomers followed by melting of the excess component.

– a weak thermal effect at about 160°C due to a glass transition of the excipient.

As concerns the quantitative aspects, measurements performed in dry nitrogen show a very good agreement between experimental and expected (12.84 J g^{-1}) melting enthalpies. It can be concluded that no interaction evidence is obtained by thermal measurements. The same is true by observing XRPD and FT-IR spectra, which look like the sum of the components spectra.

A totally different result is obtained by performing thermal measurements on the physical mixture under wet nitrogen: a melting enthalpy is obtained (6.72±0.66 J g^{-1}) which is nearly half of that expected meaning that, due to the presence of water vapour during the run, an interaction occurs.

The effect of humidity has been confirmed by examining the samples stored (r.t.) at RH>90%. Indeed 2 h storage reveals (Fig. 2) that several particles of A1 are partially in-

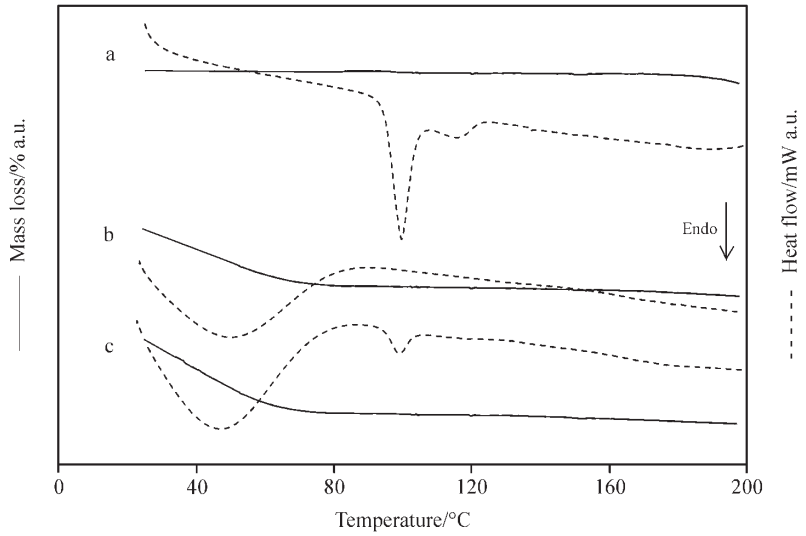


Fig. 1 TG/DSC traces recorded in dry nitrogen at 5 K min^{-1} on a – A1, b – E8, c – physical mixture A1:E8 20:80 (mass ratio)

corporated both inside and on the surface of the spherical particles of the excipient. Moreover TG/DSC scans recorded in dry nitrogen show, already after 30 min of storing at RH>90%, a 30% decrease of the melting enthalpy of A1 and, after two hours of storing, the disappearance of the A1 melting evidence. Note that the only change shown by pure components after having being stored at RH>90% is a larger water intake by E8. FT-IR spectra confirm that an interaction takes place which is induced by water vapour.

For the mixture annealed at 65°C, a 60% decrease of A1 melting enthalpy is obtained in the measurements recorded in dry nitrogen: note that this very same annealing does not affect the thermal behaviour of the pure components. It could be thought that temperature also acts to induce interaction. This point will be further discussed in the following. We note here that a clear evidence of interaction has been obtained on a physical mixture by a proper selection of the measuring atmosphere.

The quantitative results obtained from the STA measurements performed (5 K min^{-1}, dry nitrogen) on the 20:80 treated mixtures are summarized in Table 1.

Table 1 Enthalpy changes of the system A1:E8 20:80 (mass/mass) as a function of the treatment

Treatment of the sample	ΔH/J g^{-1}
30 min at RH>90%	9.01±0.24
2 h at RH>90%	No peak
6 days at 65°C	4.36±0.30
Expected value	12.84

A1:E8=80:20 (mass/mass)

Also for the mixture with high drug content the thermal measurements in dry nitrogen indicate an additive behaviour (i.e. no interaction). However, differently from expected, an additive behaviour is obtained, in this case, even in wet nitrogen. The comparison with the results obtained for the previous composition suggests that the humidity promotes interaction through the excipient: it is likely that the interaction is determined by the extent of surface contact between A1 and E8, as suggested by SEM micrographs (Fig. 2), and, as a matter of fact, only when the excipient is the prevalent component the interaction becomes evident on physical mixtures.

An additive behavior is obtained as well for the mixture stored 30 min at RH>90%. While confirming the reliability of the indication from the measurements on physical mixtures, the lack of interaction indicators on mixtures stored at RH>90% puts into evidence the role that system composition may play on drug-excipient interaction. Testing only one composition, as usual in compatibility studies, might lead to false-positive or false-negative results.

Annealing at 65°C does not promote any evidence of interaction, either, while, as previously noted, an indicator of interaction was found for the composition 20:80. In our opinion the effect of temperature was only apparent and at the origin of the interaction in the 20:80 samples annealed at 65°C, was the water vapour released by E8 and entrapped

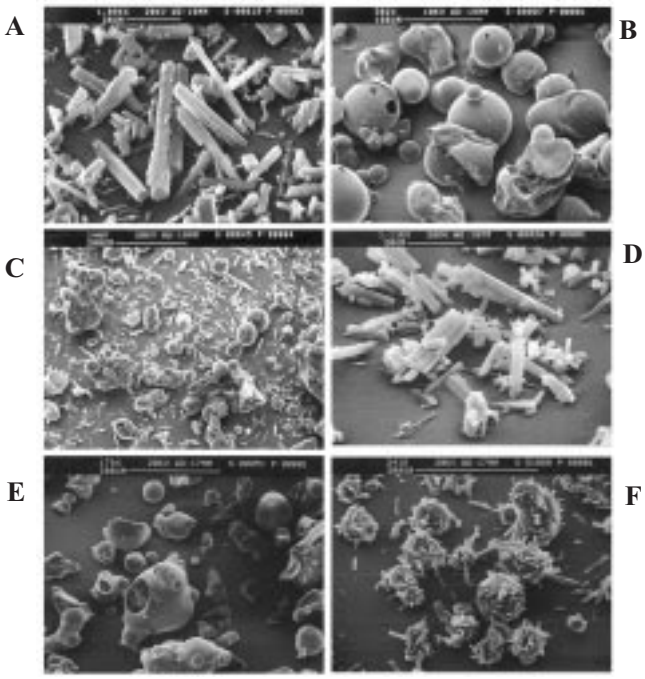


Fig. 2 SEM micrographs of samples a – A1, b – E8, c – physical mixture A1:E8 20:80 (mass ratio) and of the same samples stored 30 min at RH>90%, room temperature (respectively micrographs d, e and f)

into the vials. The absence of interaction in the 80:20 mixture could be explained as a direct consequence of composition and throws new light on the importance of this parameter in the interaction: a) there is much less water released by the excipient that is now present in a lower amount; b) there is lack of extended surface contact.

Tricyclic β-lactam:magnesium stearate (A1:E16)

A1:E16=20:80 (mass/mass)

Figure 3 reports TG/DSC traces recorded on the 20:80 physical mixtures at 5 K min^{-1} in dry nitrogen (Fig. 3c). These reflect the features of the single components (Figs 3a and 3b): three endothermic peaks, not well separated, are evident between 60 and 160°C (with a minor one at higher temperature). The first peak has a left shoulder reasonably due to released 'surface' water from E16 (Δm=0.5%). The first two peaks represent the dehydration of E16 (Δm=3.5%) and the second peak is superimposed, in the mixture scan, to the A1 melting. The third peak is due to the fusion of magnesium stearate (its right shoulder reflects melting of Mg palmitate impurity) [16]. In the scan performed on the same sample but under wet nitrogen (Fig. 4) a better separation of dehydration peaks is realized and a partial overlapping with melting of the excipient occurs. By heating at 2 K min^{-1}, the dehydration peaks move toward lower temperatures, thus allowing the reappearance of the third peak. However, the total enthalpy change (ΔH_{tot}) is 191±6.5 J g^{-1} while the expected one is 201.9 J g^{-1} (calculated as weighted mean of the enthalpies of pure components). We believe that the difference is too low to be considered as a reliable interaction indicator. Moreover, FT-IR and XRPD spectra indicate an additive behaviour.

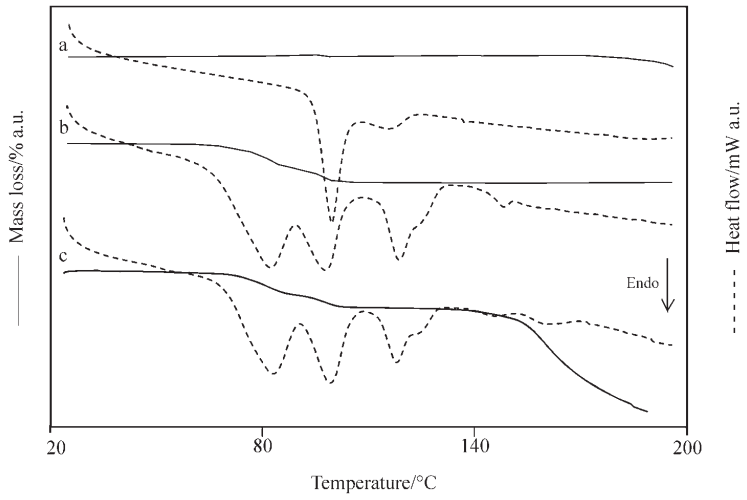


Fig. 3 TG/DSC traces recorded in dry nitrogen at 5 K min^{-1} on a – A1, b – E16, c – physical mixture A1:E16 20:80 (mass ratio)

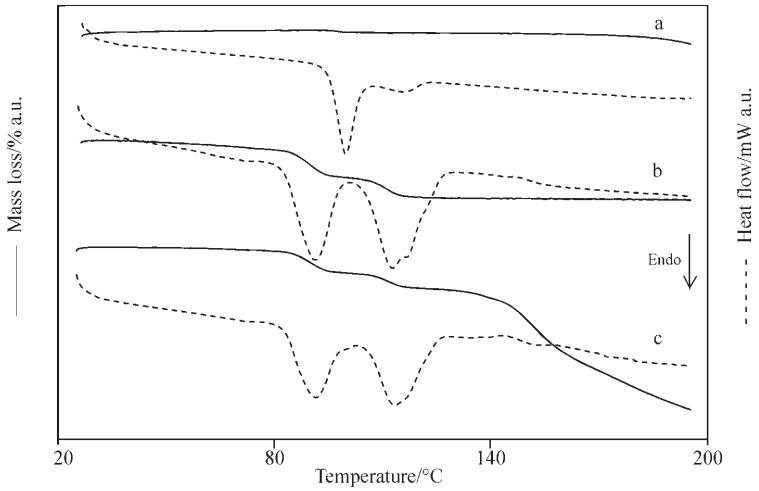


Fig. 4 TG/DSC traces recorded in wet nitrogen at 5 K min^{-1} on a – A1, b – E16, c – physical mixture A1:E16 20:80 (mass ratio)

E16 stored 3 days at RH>90% shows a dehydration enthalpy increase of 14% (a further dehydration step with mass change of about 0.6% shows up at temperature below 65°C, Fig. 5a). No further change in dehydration enthalpy occurs by storing up to 35 days. The mixture stored 35 days at RH>90% shows the expected additional dehydration step (Fig. 5b) and yields an experimental ΔH_{tot} different of about 10% from that expected for an additive behaviour (calculated with reference to the pure components stored in the same conditions). As the accuracy of our measurements is around 4%, a ΔH_{tot} difference of 10% with respect to an additive behavior can be considered a positive interaction indicator. It has, however, to be noted that, on the contrary, XRPD, FT-IR and SEM do not suggest interaction.

The decomposition of A1 in the mixtures (no matter which treatment they underwent) lies some 20°C below that in pure A1. However we thought it wiser not to consider this effect as a qualitative indicator of interaction as it could well be due to the presence of a liquid phase (indeed E16 melts at about 120°C).

The annealing of the mixture at 65°C causes the disappearance of the melting peak of A1 (Fig. 5c) and the value of ΔH_{tot} (TG/DSC scan performed in wet nitrogen at 2 K min^{-1}) corresponds to that expected as if the mixture only contained E16.* Thus the annealing at 65°C has caused drug-excipient interaction.

We note that STA results obtained on the mixtures stored at RH>90% (interaction evidence) are somewhat different from those obtained on the physical mixture scanned under wet nitrogen (possible but not reliable interaction evidence). It is likely this is due to a quite slow interaction kinetics, which takes 35 days at RH>90% to give a 10% differ-

* Remember that A1 shows no change after the same treatment.

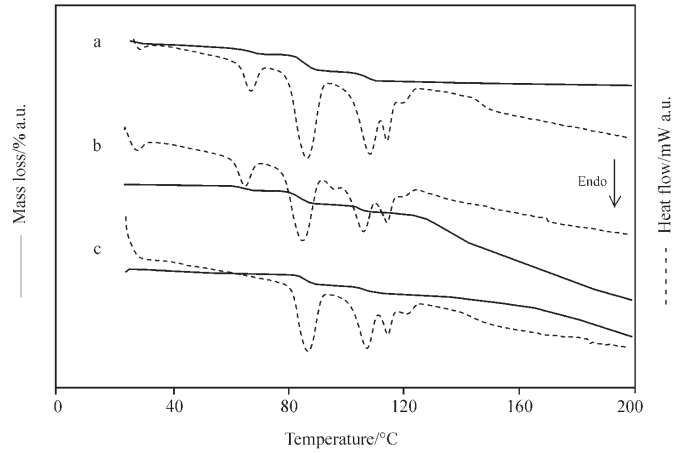


Fig. 5 TG/DSC traces recorded in wet nitrogen at 2 K min^{-1} on samples stored 35 days at RH>90%: a – E16, b – mixture A1:E16 20:80 (mass ratio) and on c – mixture A1:E16 20:80 (mass ratio) annealed at 65°C for 6 days

ence between the experimental and expected values of ΔH_{tot}. Another point of interest is the disagreement between the general indication of STA (probable or sure interaction) and that from XRPD, FT-IR, SEM (no interaction). This suggests that quantitative interaction indicators are more sensitive than qualitative ones.

A1:E16=80:20 (mass/mass)

In the case of the mixture with high drug content (A1:E16=80:20), the thermal effects of the pure components are still present in the physical mixture: however, dehydration of E16 and decomposition of A1 occur at a lower temperature than in the pure components. These temperature shifts of thermal events can be considered qualitative indicators of interaction. The mean value of the total enthalpy change is 93.0±3.5 J g^{-1} in dry nitrogen and 109±3.0 J g^{-1} in wet nitrogen while the value expected in case of additive behaviour is 98.6 J g^{-1}. The difference between the ΔH value obtained under wet nitrogen and the expected one is well beyond the experimental error and can be considered a reliable interaction indicator. On the contrary, XRPD and FT-IR spectra of the mixture are just the sum of those of the pure components and they do not provide us with positive qualitative indicators.

The mixture stored 35 days at RH>90% yields a ΔH_{tot} (in wet nitrogen at 2 K min^{-1}) which differs by about 28% from that expected for an additive behaviour. On the contrary, both SEM and FT-IR analyses do not show evidences of interaction between the components.

The annealing at 65°C of the mixture 80:20 results in the disappearance of melting peak of A1.

We note that a composition effect is apparent also in this system. However, such an effect seems to have opposite direction with respect to that discussed for the A1:E8

system. As concerns the effects produced by the annealing at 65°C, we believe they can be traced back to water vapour released from the sample and entrapped into the vial (and to the increase of reaction rate with temperature).

Tricyclic β-lactam: α-lactose monohydrate (A1-E17)

A1:E17=20:80 (mass/mass)

TG/DSC traces of the physical mixture 20:80 (curves c) recorded at 5 K min^{-1} in dry nitrogen, and in wet nitrogen are reported respectively in Figs 6 and 7 along with those of pure components (curves a and b). As it can be seen, they correspond to the superimposition of the traces of the pure components, as expected in case of no interaction. The following thermal events are present:

– melting of A1 at about 90°C;

– a mass loss of about 4% at 135°C, associated with an endothermic peak with a left shoulder due to the E17 dehydration;

– an endothermic-exothermic effect at about 170°C due to melting (endothermic peak) of anhydrous unstable α-lactose (obtained together with the stable anhydrous form from dehydration of the hydrate crystals) and crystallization (exothermal effect) of the β:α lactose compound (1:1 molar). This effect is more evident in dry nitrogen (Fig. 6) than in wet nitrogen (Fig. 7) meaning that anhydrous unstable α-lactose preferentially forms in dry nitrogen than by high water partial pressure [16];

– an endothermic effect at about 208°C due to melting and decomposition of lactose.

The total enthalpy change, of A1 melting and E17 dehydration (153.37±5.81 J g^{-1}), does not significantly differ from the expected value (147.87 J g^{-1}), meaning no interac-

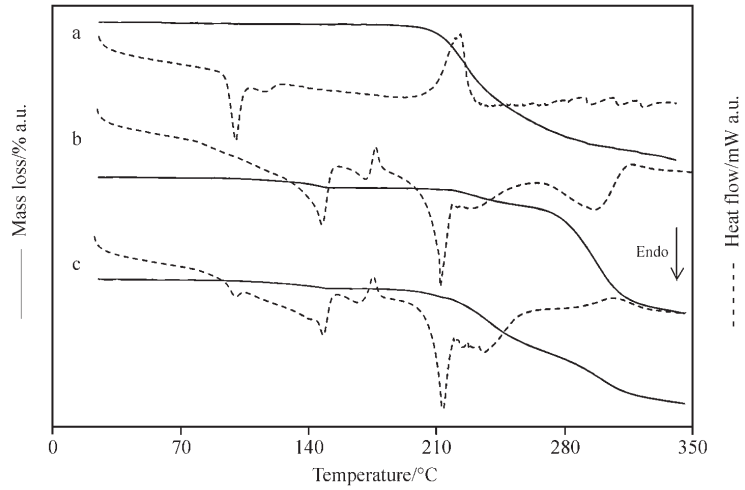


Fig. 6 TG/DSC traces recorded in dry nitrogen at 5 K min^{-1} on a – A1, b – E17, c – physical mixture A1-E17 20:80 (mass ratio)

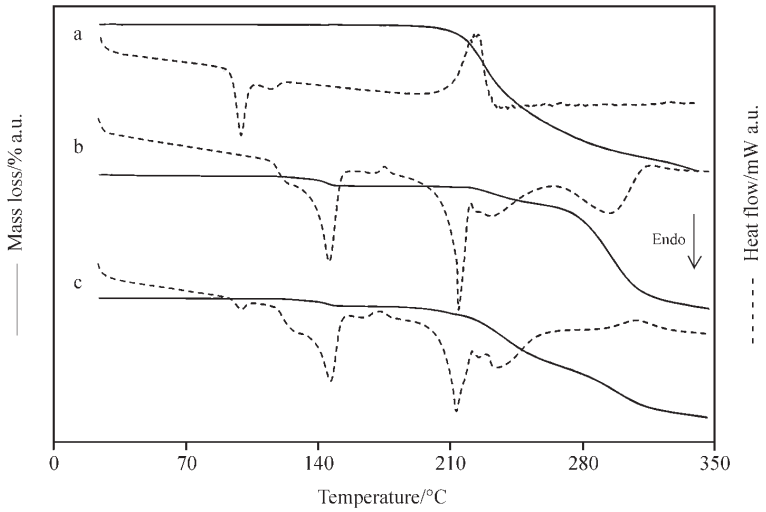


Fig. 7 TG/DSC traces recorded in wet nitrogen at 5 K min^{-1} on a – A1, b – E17, c – physical mixture A1-E17 20:80 (mass ratio)

tion occurs. This is true for measurements performed both in dry and in wet nitrogen. The thermal results well agree with the FT-IR and XRPD diffraction ones: neither of these techniques put into evidence indicators of interaction.

Thermal traces (wet nitrogen, 2 K min^{-1}) of the excipient stored at RH>90% show a new stage of dehydration below 50°C (due to surface water), a decrease of the dehydration enthalpy (due to structural water) and a diminished (less intense) exothermal effect. All these effects increase with the storage duration (Table 2). The thermal curves (wet nitrogen, 2 K min^{-1}) of mixture stored at RH>90% show qualitative changes related to the excipient only (when stored in the same conditions). On the contrary the total enthalpy changes are always significantly higher than those expected (Table 3), suggesting that storing at RH>90% promotes interaction.

Table 2 Changes of thermal parameters of E17 as a function of the storage time at RH>90% (r.t. open vial). Δm_{ads} is the mass loss due to 'surface' water; Δm_l is the mass loss due to 'structural' water; ΔH_l is the dehydration enthalpy change ('structural' water)

Storage time/days	Δm_{ads}/%	Δm_l/%	ΔH_l/J g^{-1}
0	0.02	4.93	175.1
3	0.69	4.89	173.1
7	0.72	4.88	156.9
13	2.91	4.78	155.0
30	9.72	4.64	141.2

Table 3 Total enthalpy changes of the system A1:E17 20:80 (mass/mass) as a function of the storage time at RH>90%. The expected value (reported for comparison) has been calculated by considering the mean value of the dehydration enthalpies of E17 stored at RH>90% (Table 1)

Storage time/days	ΔH_{tot}/J g^{-1}
3	158.2
7	171.6
13	151.4
Mean value ±s. d.	160.4±8.4 (5.2%)
Expected value	138.1

Figure 8 shows a wet conditioned (35 days) mixture where the crystals of the drug are adherent to the excipient particles, as a probable consequence of changed superficial properties of E17. Neither qualitative nor quantitative indicators of interaction could be pointed out, by all techniques, in the case of mixture annealed at 65°C in closed vials. This suggests that temperature alone (T=65°C) does not constitute a critical parameter and that interaction is promoted by the joined effects of temperature and water vapour. Taking into account that α-lactose looses water only at T>130°C, the amount of water vapour in the closed container is very low and no interaction occurs as a consequence of the annealing.

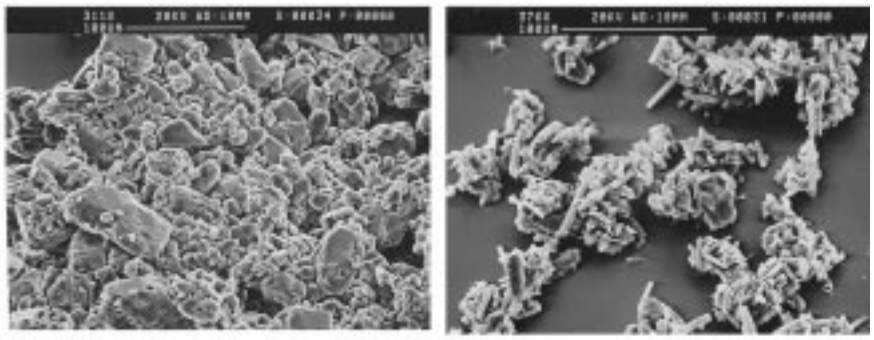


Fig. 8 SEM micrographs of samples stored 35 days at RH>90%, room temperature: a – E17, b – mixture A1:E17 20:80 (mass ratio)

We note, last, that opposite indications have been obtained from thermal measurements for mixtures stored at RH>90% (sure interaction evidence) and physical mixtures scanned under wet nitrogen (no interaction evidence). Again, this is probably due to a too low interaction kinetics.

A1:E17=80:20 (mass/mass)

The thermal effects of the pure components are still present in the relevant curves of the physical mixture. However the mean value of total enthalpy change fairly agrees in case of measurements performed in dry nitrogen (88.6 J g^{-1}) with the expected one (85.1 J g^{-1}) while it differs of at least 20% when wet nitrogen is the purging gas. Such a difference represents a quantitative indicator of interaction. On the contrary, an additive behaviour is deduced by all the other techniques.

The thermal traces of the mixture stored at RH>90% give values of total enthalpy change appreciably different from the expected one (Table 4), showing that interaction occurs as a consequence of storing at high RH.

Table 4 Total enthalpy changes of the system A1:E17 80:20 (mass/mass) as a function of the storage time at RH>90%. The expected value (reported for comparison) has been calculated by considering the mean value of the dehydration enthalpies of E17 stored at RH>90% (Table 1)

Storage time/days	ΔH_{tot}/J g^{-1}
3	102.4
7	106.2
13	98.3
Mean value±s. d.	102.3±3.2 (3.1%)
Expected value	82.7

It has to be noted that the interaction indicators from thermal measurements are now positive both for the physical mixture scanned under wet nitrogen and for the mixture stored at RH>90%. The comparison with the previous case shows once again the relevance of the system composition in compatibility studies.

As in the previous case, no interaction evidence has been obtained on mixtures annealed at 65°C in closed vials. This confirms a hypothesis on the role of water vapour in the interaction.

Conclusions

Among the techniques employed in this work the thermoanalytical ones proved to be the most suitable to point out possible interactions between the components. This is true provided that the proper experimental parameters are selected and the quantitative results are duly considered in the interpretation of the results. In particular, performing the measurements under wet nitrogen allowed to find quantitative indicators of interaction already from the analysis of the physical mixture not previously treated under stress conditions. Moreover, the analysis of the stressed systems has confirmed the predictive value of such indicators. The idea to study two different compositions (instead of the mostly studied 50:50 mass ratio) turned out to be particularly advantageous allowing to evidence the dependence of interaction on system composition.

Work is in progress in order to test the predictive ability of the proposed method with other drug-excipient systems.

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