Journal of Thermal Analysis and Calorimetry, Vol. 73 (2003) 529–545

DRUG–EXCIPIENT COMPATIBILITY STUDIES BY PHYSICO-CHEMICAL TECHNIQUES
The case of indomethacin

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Abstract

This work exemplifies a general method of studying the drug–excipient interactions, with the aim of predicting rapidly and inexpensively the long term stability of their mixtures.

We study the physico-chemical properties of a drug (indomethacin) in the solid state and in different combinations with several excipients (PVP=polyvinylpyrrolidone, MGST=magnesium stearate, Avicel©). We compare the properties of pure compounds (untreated, or moisture/temperature conditioned) with those of binary mixtures drug:excipient which underwent the same treatment. The purpose is to find indications of interactions within the mixtures, which means a potential incompatibility of the excipient. Both morphological and thermal properties are sensitive to interactions which leave mostly unmodified the IR spectra and the X-rays patterns. In particular, we find that indomethacin does interact with PVP and MGST, but is certainly compatible with Avicel©.

Keywords: compatibility, drug, DSC, excipients, FT-IR, indomethacin, interaction, SEM, TGA, XRPD

Introduction

A drug, or active principle, is most often delivered to patient along with other chemical substances within a pharmaceutical formulation, which should comply with strict specifications, often prescribed by law. In order to be approved, a formulation should warrant well defined levels of stability, safety and efficacy. The desired level of stability is often difficult to achieve because the active principle may interact with the other substances of the formulation, the so called 'excipients' which do not have a specific pharmaceutical activity [1–4].

Sometimes, this interaction is fundamental for a proper functioning of the drug delivery system (e.g. to speed up dissolution, or controlling release). In most cases of mechanical drug–excipient mixtures in the solid state, however, we would like to predict possible negative effects of the interaction: faster degradation rate [5–7], chemical changes [8, 9], etc.

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1388–6150/2003/ $ 20.00
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Most often, the negative effects of the drug–excipient interaction in the solid state is mediated by water [2, 3, 6, 10–13] and enhanced by an increased temperature [2]. In fact, vapor released by the excipient may be absorbed/adsorbed by the drug, or water bonded to the excipient may promote a reaction at the excipient–drug interphase [13]. In the first case (vapor-mediated mechanism) the effects should be the more important the higher the concentration of the excipient is. In the second case, we often have partial solvation in the interphase area, and even traces of water may play a major role in degradation of water-soluble drugs through an increased mobility of drug–excipient which enhances their reactivity [13–16].

Owing to the length and complexity of the approval process, it is of paramount importance to address the drug–excipient compatibility issue from the early stages of preformulation. The standard 'fast stability test' involves storing binary drug–excipient mixtures under extreme temperature and humidity conditions, and periodically determining (over seven months) the drug concentration [7, 17, 18]. Possible pitfalls of this test is that concentration dependent effects are usually not identified, while some of the reactions observed at high temperature/humidity may not occur in normal storage.

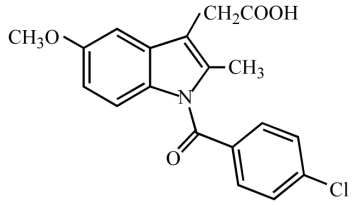
The general purpose of this paper is to develop a protocol of physicochemical characterisation which reliably predicts the outcome of standard stability/compatibility tests [19]. It envisions analysis of thermal [20], structural, morphological and spectroscopic data collected under a range of experimental conditions and treatments in the drug, the excipient, and their binary solid mixtures. For each treatment, the data for a mixture are compared with the 'superposition' of the responses of pure drug and pure excipient, which is expected under the 'no interaction hypothesis'. The outcome may be qualitative (existence of a significant difference or not) or may be quantified with numerical values, such as the change (in %) of the enthalpy of melting relative to the expectation.

Here we will systematically investigate the compatibility/stability problems of indomethacin form I [21–26], a non-steroidal anti-inflammatory drug with indolic structure with three different excipients:

1) polyvinylpyrrolidone (PVP), mostly used as a binder, particularly in wet processes;

2) magnesium stearate (MGST), $[CH_3(CH_2)_{16}COO]_2Mg$, working as a lubricant during compression [27–29];

3) microcrystalline cellulose (Avicel©), used as diluent, suspension or viscous medium [30, 31].



Scheme 1 Indomethacin: 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid

We have analyzed 80:20 and 20:80 drug:excipient mixtures, and applied a range of treatments, including months long annealing and moisture conditioning.

Experimental

Samples

Indomethacin form I (In) came from an industrial production batch (#MM011567) of Sigma-Tau (Milan, Italy). The commercial grade excipients were: PVP (average molecular mass 50000), magnesium stearate and microcrystalline cellulose (Avicel© PH102); they were provided by GlaxoSmithKline. All samples and their mixtures have been stored in closed plastic containers.

We prepared 80:20 and 20:80 mixtures (about 2 g) of indomethacin:excipient by mass. Mixing was performed by a turbula (W. A. Bachofen) at 96 rpm for 10 min.

For each system, we examined the pure samples 'as received' and the mixtures 'as made' ('untreated' samples); then, the same experiments were repeated with 'moisture conditioned' (protocol 1 below) or 'temperature treated' (protocols 2 and 3) samples as follows:

1) storage at room temperature (r.t.) and relative humidity (r.h.)>90% up to three months (or for a specified time), with samples in an open container with water on the bottom (moisture treatment);

2) storage in a stove at 70°C in open container up to three months;

3) storage in a stove at 70°C in a closed container up to three months, which is expected to reveal the combined effects of temperature and humidity with products containing bonded/adsorbed water.

Diagnostic tools

Scanning electron microscopy has been performed with a Cambridge Stereoscan 200 system with gold-sputtered samples. Simultaneous TG/DSC analyses from r.t. to 300°C have been performed with an apparatus by Polymer Laboratories (UK), mod. STA 625, using open aluminum pans. Each sample was examined both in dry and wet nitrogen (obtained by bubbling 45 mL min^{-1} of dry nitrogen in water at r.t.) with scanning rates of 2 and 5 K min^{-1}. The values of enthalpies and mass changes have an estimated uncertainty of less than 5%, which is our significance limit. All data reported here result from an average of three or more repeated measurements.

Standard TG traces in the r.t. – 200°C interval have been obtained with a TA2950 thermobalance (TA Instruments, USA) at 5 K min^{-1} in both dry and wet nitrogen flowing at 40 mL min^{-1}.

Diffuse reflectance FT-IR spectra (DRIFT) have been collected with a FT-IR system (Nicolet) equipped with a diffuse reflectance cell (DRIFT collector, Spectra Tech, UK). The sample had to be dispersed in about 500 mg of anhydrous KBr (97% in mass) by stirring, shaking and grinding the powders in an agate mortar until the desired grain size was attained. The sample was kept 20' or more in the cell and in dry

nitrogen before acquiring 256 scans, which were co-added to yield spectra in the 400–4000 cm^{-1} interval with a 2 cm^{-1} resolution. The spectra shown result from subtraction of the background contribution (a spectrum of dry KBr obtained with the same preparation protocol and acquisition parameters).

Powder X-ray diffraction patterns (XRPD) with $5°<2\theta<35°$ were obtained with a Bruker (Germany) D5005 diffractometer where the CuK_α radiation was obtained with a bent-graphite monochromator.

In the following, the data represented with their uncertainty are always in the format average±experimental standard deviation (not error of the mean). The other numeric data are quoted to the last (semi) significant digit.

Results

We begin with reference data about pure samples (untreated and treated) which will be compared with the corresponding data for 80:20 and 20:80 mixtures for the three systems.

Indomethacin

The untreated indomethacin form I powder consists of irregular particles (mostly slabs) ranging in size from few microns to about 10^2 microns. The TG/DSC traces show a single and sharp endothermic peak at ~160°C due to melting, with a corresponding enthalpy of 94.6±2.2 J g^{-1}. Mass loss begins near 200°C, which marks the beginning of decomposition.

The indomethacin sample conditioned at r.t. and r.h. >90% has essentially the same properties of the untreated sample, since only minor modifications are seen in the SEM images, in the DSC curves, XRPD patterns and DSC/TG runs. The DRIFT spectrum of the moisture-conditioned sample (4 months) shows only minor changes in the 3550–3400 and 3300–3100 cm^{-1} regions due to traces of adsorbed water (and to the exquisite sensitivity of the technique in detecting it). The indomethacin samples conditioned for three months at 70°C in open and sealed containers do not show important differences relative to the as received sample.

Polyvinylpyrrolidone (PVP)

The untreated sample is made of round and smooth particles (characteristic of a glass phase), up to 100 μm in diameter, with few holes on their surface. Some of these spheroid particles are broken, and have rough edges. The DSC-TG traces below 150°C (Fig. 1) display an initial mass loss from 8.4±0.2% in dry N_2 to 11.2±0.2% in wet N_2 (the uncertainty has been determined over a set of runs made with different scan rates). This mass loss is accompanied by a broad endothermic phenomenon over an ill-defined baseline which makes evaluation of the dehydration enthalpy quite uncertain. The sample readily dehydrates/rehydrates in dry/wet atmosphere, respectively, and its initial mass depends upon the moisture content of the atmosphere. Ap-

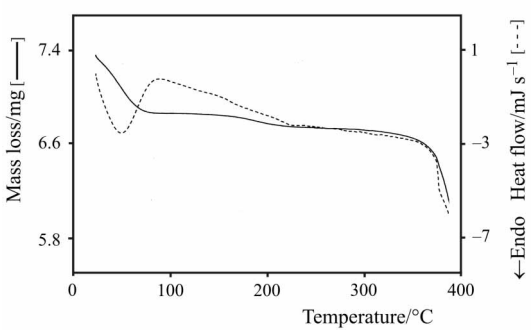


Fig. 1 TG-DSC traces of untreated PVP (dry nitrogen, 5 K min^{-1})

parently, dehydration is completed at 100°C in dry nitrogen, and at 120°C in wet N_2. However, a second mass loss stage (~2%) begins past 150°C and completes around 250°C. A sharp jump of the DSC baseline near 200°C is due to the glass transition of the amorphous polymer. Decomposition begins around 350°C. As expected for amorphous phases, the diffraction pattern does not have Bragg reflections.

After just 3 h in wet atmosphere and r.t. the PVP is transformed in a semi-solid mass. An hour exposure to r.h. >90% does not change the appearance of sample, but produces significantly modified SEM pictures (Fig. 2), and increases the water content to 16.1±0.6%, i.e., about two times that of the untreated sample in dry N_2. No significant changes are observed in the DRIFT spectrum and X-ray pattern. Therefore, one hour conditioning at r.h. >90% apparently just increases the water content of the sample, with little effects upon other physico-chemical properties. However, even a very short exposure to moisture deeply modifies the surface activity of the sample.

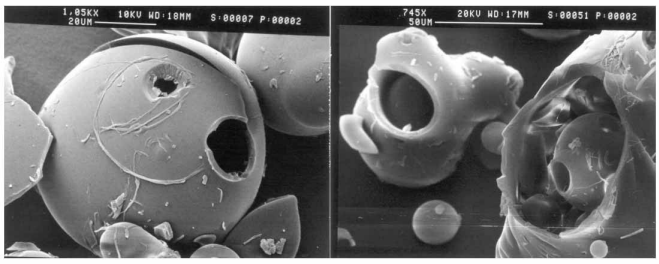


Fig. 2 SEM pictures of an untreated PVP sample (left) and a moisture-treated (3 h) one (right)

In 45 days of conditioning at 70°C in open or sealed container, the PVP grains partially lose their round shape, being mostly broken or even collapsed/joined together. The TG/DSC traces are similar to those of the untreated samples, with a reduced amount of hydration water (4.3±0.8 and 6.4±0.2% for the samples conditioned in open and closed container respectively). No other meaningful differences between untreated and temperature-conditioned PVP samples are observed either. Temperature conditioning apparently causes just a partial dehydration, with no other change in structural/thermal properties; however, the changes of morphology observed in SEM images again point to a substantial effect of the heat treatment upon surface reactivity.

Magnesium stearate (MGST)

The untreated magnesium stearate powder consists of thin and irregular flakes joined in clusters ~10^1 micron in size. Simultaneous TG/DSC scans in dry nitrogen (Fig. 3a) reveal several dehydration stages below 100°C. The first endothermic effect is due to release of a small amount of surface water. Around 60°C begins the first dehydration stage of structural water, which partially overlaps with a second stage at higher temperature. The overall mass loss due to surface water and to the first stage is ~3% while the amplitude of the second stage is ~1.5% of the initial mass. Melting of magnesium stearate begins at 110°C and produces an endothermic peak with a shoulder in the high temperature side which is caused by melting of magnesium palmitate. In fact, it is known that commercial lots of Mg stearate contain variable amounts of magnesium palmitate along with salts of other fatty acids [32–34]. The small endothermic peak above 140°C has been attributed [35] to melting of pseudopolymorphs of magnesium stearate and palmitate. Note the endothermic shift of the DSC baseline after the 140°C peak.

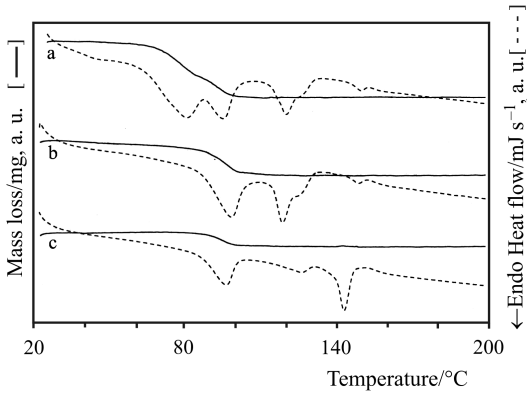


Fig. 3 Comparison of the TG-DSC traces (dry nitrogen, 5 K min^{-1}) of a – MGST untreated, b – kept 3 days and c – 7 days in an open container at 70°C

In wet nitrogen, and relative to the scan in dry N_2, the dehydration processes occur at higher temperatures and the first and second stages are better resolved. The DSC curves have markedly different shapes in dry and wet nitrogen mostly because, in wet nitrogen, the second dehydration stage and melting partially overlap. In wet nitrogen, the endothermic peak at 140°C is missing, but we still have the endothermic shift of the baseline near this temperature. Owing to the complexity and overlapping of the dehydration and melting phenomena, we opted to estimate the overall enthalpy change from 50 to 150°C and obtained ΔH_{tot}=253.4±2.9 J g^{-1} in dry atmosphere and ΔH_{tot}=253.2±3.4 J g^{-1} in wet atmosphere.

The sample was kept at r.t. and r.h. >95% for 45 days. Relative to the untreated sample, the only significant effect is shown by the TG/DSC data which reveal a marked increase of surface water, with essentially no differences in the enthalpy change above 50°C.

In open container, significant changes in the TG/DSC response are observed after one day or more of conditioning, while SEM data are not affected even by week-long annealing. In an open container, surface water and the first-stage hydration water are fully removed by three days of treatment (Fig. 3b). As a consequence, the overall enthalpy change becomes 153.4±0.4 J g^{-1}, with a ~40% reduction relative to the untreated sample. We observe also subtle changes in the melting behavior (e.g.; a better resolved palmitate peak) which become more important after a week-long annealing (Fig. 3c), in particular in the 110–150°C region of stearate and palmitate melting. For samples conditioned in a sealed container, the surface water is lost in less than a day but further changes in the DSC curve are seen only after three days when a new endothermic peak appears near 130°C, accompanied by a small (~8.5%) decrease of the overall enthalpy (Fig. 4). After a week, this peak has increased substantially, and the overall enthalpy has decreased also (by 22%) relative to the untreated sample.

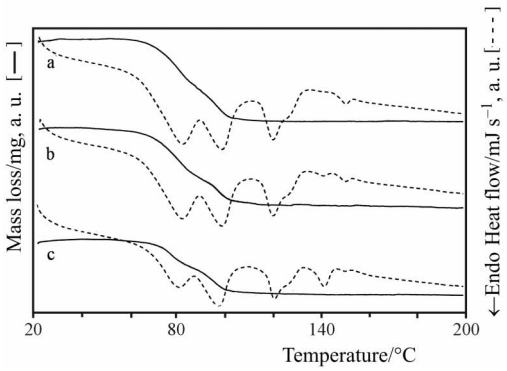


Fig. 4 Comparison of the TG-DSC traces (dry nitrogen, 5 K min^{-1}) of MGST kept a – 2 days, b – 3 days and c – 7 days in a sealed container at 70°C

DRIFT spectra of the temperature conditioned samples show some small changes (relative to the untreated sample) in the 1700–1400 and 3500–3100 cm^{-1} regions, which are certainly related with the loss of structural water. As concerns XRPD measurements, only the pattern of the sample conditioned in open container shows some minor differences of relative intensities with respect to those of the untreated sample. It may be concluded that thermal treatments affect the properties of MGST by releasing some structural water and, eventually, leading to some minor structural change. Treatments for more than three days cause noticeable decomposition.

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The untreated powder is made of particles of irregular shape and size forming clusters of about 100 μm. The samples are fully dehydrated at 120°C (in dry N_2) and at 160°C (in wet N_2); the water content ranges from 4 to 6% in mass since a substantial water intake occurs even for a brief exposure to moisture at r.t. An important endothermic

effect is associated with dehydration (Fig. 5). There is no evidence of melting. Decomposition begins above 200°C. Absence of Bragg diffraction peaks confirms that the sample is amorphous.

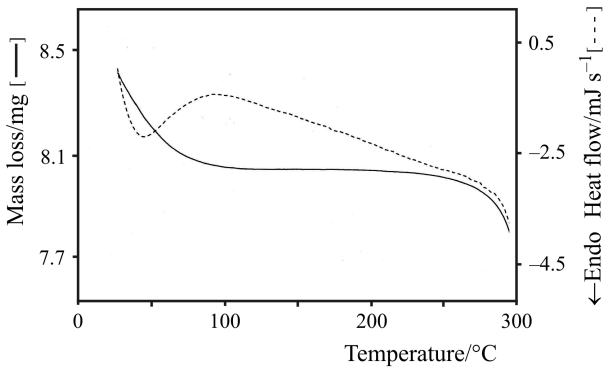

Fig. 5 TG-DSC traces of untreated Avicel© (dry nitrogen, 5 K min^{-1})

SEM, DRIFT and XRPD data are qualitatively the same for untreated sample and samples moisture conditioned (r.h. >90%, r.t.) for as long as 45 days. The water content has been determined as a function of the conditioning time with TG runs at 5 K min^{-1} in dry N_2; it goes from 4% in the untreated sample to 8% after a day, 10% in a week, 14% in 5 weeks.

Samples kept 35 days at 70°C in open or closed containers turned from white to light yellow. However, no significant changes were observed in SEM, DRIFT and XRPD data, relative to untreated samples. After 35 days, water content was 2 and 3% for samples in open and closed containers, respectively.

In:PVP (20:80) mixtures

SEM micrographs of the untreated mixture show the indomethacin crystals (Fig. 6a) well attached to, and sometimes incorporated into, the PVP spheroidal shells, which are deformed relative to pure PVP (Fig. 6b). In the thermal analyses (Fig. 7) the main 'interaction' effect is the DSC melting peak of indomethacin, which is now much broader than in the pure drug, and begins near 135 rather than 160°C. Furthermore, in

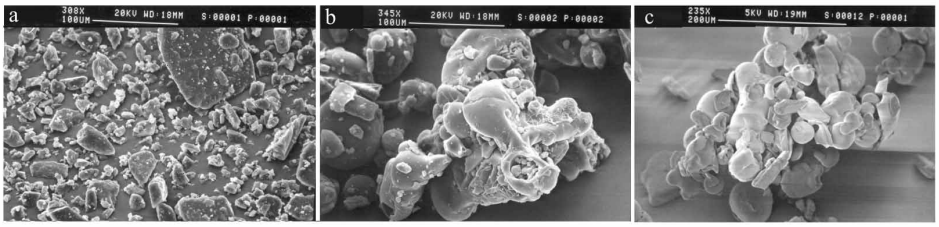

Fig. 6 SEM pictures of a – untreated indomethacin, b – untreated In:PVP (20:80) mixture and of the same mixture annealed c – 45 days in a sealed container at 70°C

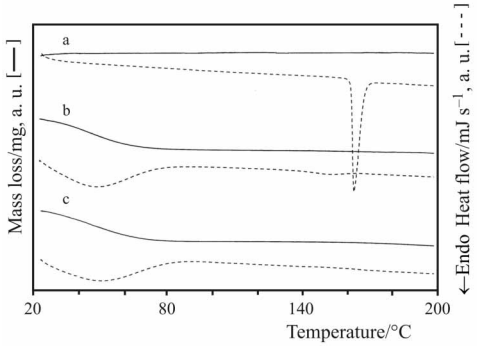

Fig. 7 Comparison of the DSC traces of b – In:PVP (20:80) mixture, with those of a – pure indomethacin and c – pure PVP

different experimental conditions (wet or dry N_2, rates of 2 or 5 K min^{-1}) the melting enthalpy of indomethacin falls into the 8.2–9.8 J g^{-1} range, i.e., about half its expected value of 19 J g^{-1}. The runs in wet N_2 and low scan rate (2 K min^{-1}) yield the lowest enthalpy values. Water loss below 150°C is about 1% higher than expected due to the PVP content of the mixture: 7.6% in dry N_2 (*vs*. an expected 6.7%), 9.7% in wet N_2 (*vs*. an expected 8.9%). Above 150°C, the mass loss is apparently due to decomposition of indomethacin and final dehydration of PVP. On the other hand, both DRIFT and X-ray patterns are well explained in terms of weighted superposition of the patterns of the pure substances.

It may seem strange that substantial changes of morphology and melting behavior occur in this mixture, relative to the pure components, with no detectable modifications of molecular conformations and crystal structure. In particular, differential calorimetry appears to be especially sensitive to physico-chemical changes occurring upon mixing, and presumably involving the indomethacin-PVP interphase. Such a phenomenon is quite reasonable, because crystal melting begins at the surface and is mediated by long range interactions.

As for the PVP, the mixture has been moisture conditioned (at r.h. >90%) for one hour. Following this treatment, no difference relative to the untreated mixture is seen by SEM, DSC, DRIFT and X-rays. Predictably, this treatment changes only the water content.

The thermal treatment at 70°C in open and closed containers has been carried out for 45 days. Relative to the untreated mixture, the SEM micrographs of the mixture treated in the open container show a more pronounced deformation of the PVP spheroidal particles, which have more holes and now mostly incorporate the indomethacin crystals. The treatment in the sealed container leads to a full collapse of the PVP spheres into smooth and rounded particles with indomethacin crystals attached to them in clusters ~10^2 μm in size (Fig. 6c). Furthermore, this sample has turned from white to light yellow in about 20 days of thermal treatment. Another noteworthy change is the slight decrease of the indomethacin melting enthalpy as the conditioning time increases. However, as for the untreated mixture, the melting enthalpy of the thermally treated samples remains about half the enthalpy predicted

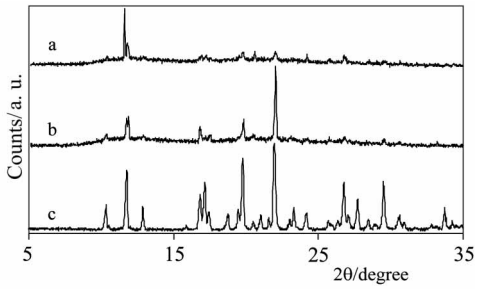

Fig. 8 XRPD of c – indomethacin and In:PVP (20:80) mixtures treated (45 days at 70°C) in b – open container and a – closed container

by the no interaction hypothesis. Finally, the DRIFT spectrum is not modified while the diffraction patterns reveal substantial modifications. Figure 8 compares the normalized XRPD patterns of indomethacin (c) and those of the mixtures thermally treated in open (b) and sealed containers (a). In Fig. 8b, several reflections (2θ=17, 27, 29.5°) have much reduced relative intensities while others have disappeared altogether; the peak at 12° has splitted in two. In Fig. 8a (mixture treated in a sealed container) many peaks have disappeared while the most intense reflection now occurs at 2θ=11.5°. We call attention to the fact that DSC and XRPD phenomena are somehow 'independent'; DSC detects signs of interaction already in the untreated mixture (not seen by XRPD), but it is apparently insensitive to the structural modifications revealed by XRPD and caused by the thermal treatment.

In:PVP (80:20) mixtures

The SEM picture of the untreated mixture reveals a majority of large, unmodified indomethacin particles. The PVP particles are mostly deformed, relative to pure PVP; they are attached to, or incorporate, the small indomethacin crystals (Fig. 9a). Melting of indomethacin now begins at 140°C (rather than at 160°C, as in the pure sample) and its decomposition starts with melting, as for the 20:80 mixture. Relative to the pure sample, the melting enthalpy decreases by ~14 and ~20% at 5 and 2 K min^{-1}, respectively, inde-

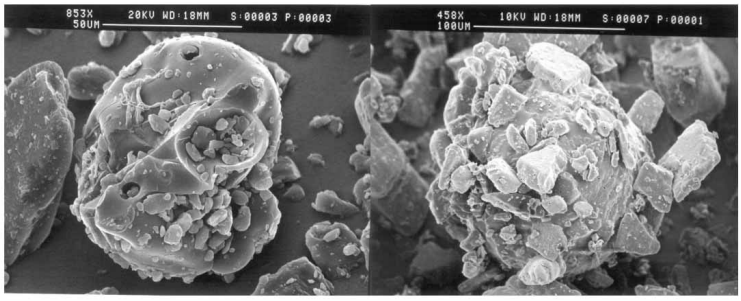

Fig. 9 SEM pictures of In:PVP (80:20) mixture untreated (left) and moisture treated (right)

pendently of the atmosphere (dry or wet). The PVP dehydration is smaller than expected in dry atmosphere (1.2 *vs*. 1.7%) and larger in wet atmosphere (3.1 *vs*. 2.2%), as if PVP surface area increased upon mixing, thus causing faster water exchange processes. No significant changes, relative to the no interaction hypothesis, is seen in DRIFT and XRPD plots.

As for pure PVP, moisture conditioning was limited to just one hour. The mixture exposed to r.h. >90% has PVP spheres with wrinkled surfaces, tightly attached to indomethacin crystals (Fig. 9b). The main changes of the DSC curve are a melting peak which now begins near 130, i.e., 10°C before the untreated mixture and a reduced melting enthalpy (relative to the untreated mixture). Few XRPD peaks (at 2θ=10.5 and 17°) have substantially reduced relative intensities or have disappeared; others are modified relative to those of pure indomethacin and/or the mixture untreated.

The thermal treatments at 70°C in open and sealed containers has been carried out for 45 days. Apparently, they do not change the morphology, the DSC curve, the DRIFT spectrum and the XRPD pattern of the untreated mixture. It seems that the thermal conditioning does not affect the PVP-indomethacin interaction in the PVP-poor mixtures.

In:MGST (20:80) mixtures

The SEM pictures show that the characteristic flakes of the stearate are either clustered together, or attached to indomethacin crystals (Fig. 10).

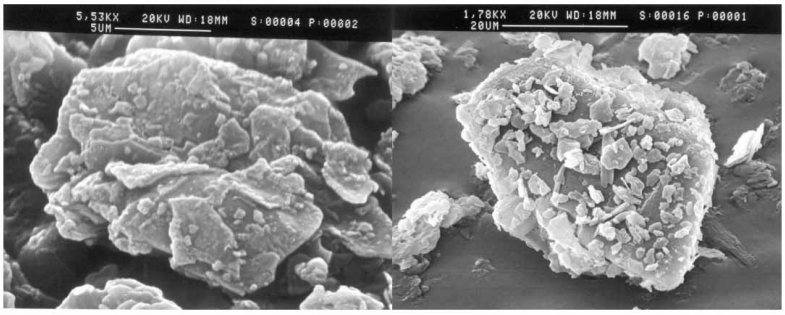

Fig. 10 SEM pictures of untreated samples: MGST (left) and In:MGST (20:80) mixture (right)

Below 130°C, the features of the DSC curve are essentially those expected from dehydration and melting of the stearate. Figure 11 shows a simultaneous TG/DSC run in dry N_2 at 5 K min^{-1}; the 160°C melting peak of pure indomethacin has been replaced by a broad endothermic feature in the 130–160°C interval; decomposition now begins at 170°C, while it occurred above 180°C and 200°C in pure indomethacin and MGST, respectively. At lower scan rates (2 K min^{-1}) decomposition in dry N_2 starts at lower temperatures (~160°C). The results in wet atmosphere are very similar, except for a substantial overlapping of the last dehydration stages and further reduction of the temperature for the onset of decomposition: 160°C at 5 K min^{-1} and 150°C at 2 K min^{-1}.

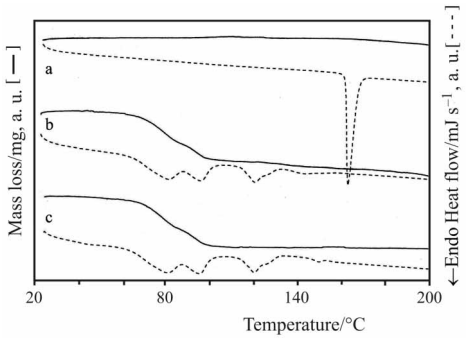

Fig. 11 Comparison of the TG-DSC traces (dry nitrogen, 5 K min^{-1}) of b – In:MGST (20:80) mixture with those of a – pure indomethacin and c – pure MGST

Both in dry and wet atmosphere, the thermal effects attributable to MGST and indomethacin can be integrated separately. The total enthalpy attributable to MGST is always substantially smaller than predicted in the no interaction hypothesis by 6–19%, with the larger decrement occurring at 2 K min^{-1} with dry N_2. The same happens to the indomethacin melting enthalpy, which shows the larger decrement (39%) at 5 K min^{-1} with wet N_2. The DRIFT spectra and XRPD patterns of the mixture are those predicted by the no interaction hypothesis.

The SEM, DRIFT, and XRPD data for samples kept 45 days at r.t. and r.h. >90% are very similar to the corresponding data of pure samples: in particular, SEM confirms that moisture favors clustering of the MGST flakes. Also the DSC/TG curves are qualitatively comparable with those taken under the same conditions in the untreated mixture. However, both the total enthalpy changes attributable to MGST and indomethacin are further reduced by moisture-conditioning, relative to the values expected in the no interaction hypothesis: by ~20% for MGST (*vs*. 10.5% in the untreated mixture) and 44% for indomethacin (*vs*. 30% in the untreated mixture).

Three days of annealing at 70°C in open or closed containers do not change the morphology of the mixture, the DRIFT spectrum, or the XRPD pattern. Only the total enthalpies are well below the expect ones, but their values are comparable with those observed in the untreated mixture. Therefore, annealing at 70°C does not significantly enhance the interaction between indomethacin and MGST.

In:MGST (80:20) mixtures

The SEM picture (Fig. 12a) shows indomethacin crystals mostly covered by MGST flakes. The DSC curves obtained at different scanning rates and in wet/dry N_2 display a sharp endothermic peak, beginning between 100 and 110°C, immediately followed by a broad feature ending near 160°C, mostly assigned to indomethacin melting. Figure 13 shows a TG/DSC scan performed at 5 K min^{-1} in dry N_2; here, decomposition begins near 150°C, substantially below the onset temperatures of decomposition of the constituents. However, the overall enthalpy changes are essentially those predicted in the no interaction hypothesis. Also the total mass change coincides (within experimental error) with that expected in the no interaction hypothesis.

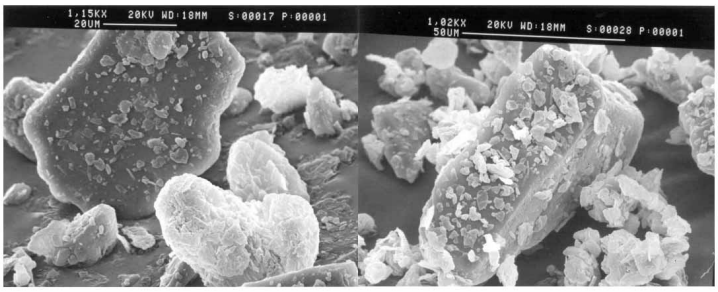

Fig. 12 SEM pictures of In:MGST (80:20) mixtures: untreated (left) and kept 2 days in a sealed container at 70°C (right)

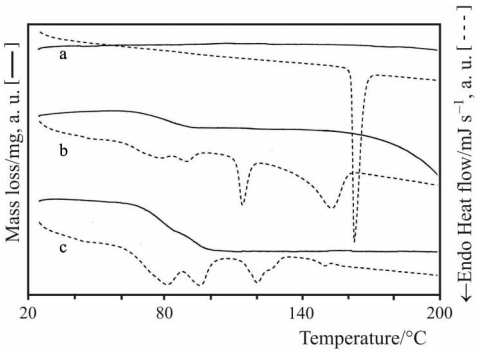

Fig. 13 Comparison of TG-DSC traces of b – In:MGST (80:20) mixture with those of a – pure indomethacin and c – pure MGST

Both DRIFT spectra and XRPD patterns of the mixture are well accounted by the zero interaction hypothesis.

SEM, DRIFT and XRPD data of samples kept at r.t. and r.h. >90% for 45 days are not significantly different from the corresponding data of untreated mixture. The main effect of exposure to moisture is a 17% reduction (in average) of the overall enthalpy change.

A three-day treatment in open container at 70°C does not change the morphology (relative to the untreated mixture) but after two days in a sealed container the MGST flakes are less clustered together and sticking more to the indomethacin crystals (Fig. 12b). Thermal treatments from one to three days in open/closed container do not change the TG/DSC curves, the DRIFT spectra, or the XRPD patterns.

In:Avicel© (20:80) mixtures

SEM, TG/DSC, DRIFT and XRPD data are mostly well explained by the no interaction hypothesis. In particular, the SEM picture of the powder shows clusters of Avicel grains (Fig. 14, left) and of indomethacin flakes mostly well separated (Fig. 14, right).

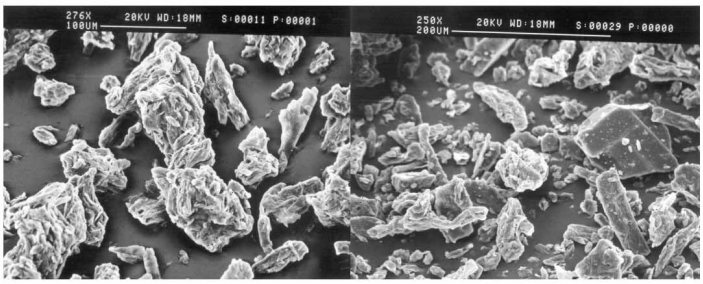

Fig. 14 SEM pictures of untreated samples: pure Avicel© (left) and In:Avicel© (20:80) mixture (right)

After 35 days in wet atmosphere, the only data that have changed are the TG/DSC data related with the water content of Avicel, which increased its mass by nearly 10%. The DSC melting peak of indomethacin maintains the expected shape but its associated enthalpy is somehow smaller (by few percent) than expected after correcting for the presence of about 10% extra water in the mixture.

In 35 days at 70°C all mixture acquired a shade of yellow, with the samples in open containers taking a lighter color. All data are consistent with data of the temperature conditioned components and the no interaction hypothesis.

In:Avicel© (80:20) mixtures

All data are consistent with the no interaction hypothesis. Again, all data with samples kept 35 days at r.t. and r.h. >90% are fully compatible with the no interaction hypothesis. Annealing the mixture for 35 days at 70°C in open or closed containers does not cause any evidence of drug–excipient interaction.

Discussion

It is instructive to compare the different 'sensitivities' to treatments and to drug–excipient interactions of the techniques applied. The morphology always suggests that some sort of interaction occurs in the mixtures, and is quite sensitive to treatments. Unfortunately, SEM provides a very qualitative indicator because the long range structure is determined by many and largely unknown mechanisms. Differences in the hydration/dehydration behavior revealed by TG in samples with PVP probably just reflect different morphologies, grain size and interphases. On the other hand, DSC provides a very quantitative and sensitive indicator of interaction with the temperatures and enthalpies of indomethacin melting. We may suggest that the changes of these parameters are determined by 'interactions over medium range distances' at the drug-excipient interphase. Quite surprisingly, XRPD detects only changes produced in the mixtures by moisture or temperature treatments. This means that a new or modified crystal structure becomes energetically possible upon mixing, but transition to the new form has a very slow kinetics, which needs rate enhancing factors, such as temperature or hydration, to take place. We recall that sharp

Bragg reflections require crystals of at least 10^2 lattice spaces in size. Finally, DRIFT is sensitive only to the short range molecular arrangements which, in our case, remain essentially the same in all forms.

A first conclusion is that an important interaction occurs between indomethacin and PVP upon simple mechanical mixing. Since such an interaction is mostly revealed by the indomethacin melting, it is quite understandable that the effect appears more clearly in the 20:80 indomethacin:PVP untreated mixture. A kinetic factor certainly plays a role, because the melting peak is more modified at low scan rates and in wet atmosphere. In particular, the kinetics may be that of transformation to new indomethacin polymorphs, as suggested by the XRPD results with treated mixtures. We may safely say that the interaction brings about a substantial increase of the surface free energy of indomethacin; melting at the interphase occurs at lower temperatures, and with less enthalpy intake, relative to ordinary melting and explains the modified melting peaks.

Treatments with moisture have no consequences for indomethacin, but have dramatic effects upon PVP, which essentially solvates in few hours when r.h >90%. In the mixtures, moisture enhances the interaction with the drug in the PVP poor mixture (apparently through an expanded interphase), but not in the PVP rich one, where interaction is already strong, and not limited by PVP availability.

No indomethacin-MGST interaction is revealed by DRIFT and XRPD data with the mixtures, while some effects are shown by SEM. On the other hand, indomethacin in the mixtures begins melting around 110°C (when MGST has just melted) rather than at 160°C, probably as a result of an interaction with the excipient in the liquid phase, which also substantially decreases the melting enthalpy of indomethacin. Accordingly, the shifting and broadening of the original indomethacin melting peak is qualitatively the same in the 80:20 and 20:80 mixtures.

From the stearate point of view, the interaction decreases the onset of melting by 10°C in the indomethacin rich mixture (but not in the 20:80 mixture).

It is quite surprising that, in the 80:20 mixture, the overall enthalpy change (due to melting and dehydration) is essentially that predicted in the no interaction hypothesis; on the other hand, this change is somehow smaller than expected in 20:80 mixture.

No significant changes are associated with moisture and temperature treatments of the mixture (relative to the treated components). Therefore, we have mainly qualitative indicators of interaction (new features of the DSC/TG curves observed in the mixtures) rather than quantitative indicators (e.g., the overall enthalpy).

Avicel© and indomethacin appears to be fully compatible, in the sense that no significant evidence of interaction has been found in the untreated and treated mixtures. However, in most formulation, the hygroscopic nature of the excipient should be taken into account.

Conclusions

We begin with remarks about the method applied to this study. We applied several techniques in the search of ‘anomalies’ in the physical properties of drug–excipient

mixtures, relative to properties of the individual components. The study has been performed with drug-poor and drug-rich mixtures, under different experimental conditions, with untreated samples and with samples exposed to moisture or annealed. We obtain qualitative information about the drug–excipient interaction just by listing which techniques are sensitive to it, and which treatments or parameters (e.g. composition, temperature scan rate) favor it. In the case considered, the enthalpy of melting of indomethacin is a quantitative indicator of interaction: a decrease of this enthalpy, and reduced melting temperatures, are taken as indication of a potential incompatibility between drug and excipient, since the drug becomes less likely to maintain its properties a long time or under extreme conditions.

In more detail, the combined TG/DSC analysis has proven much more sensitive than DRIFT and XRPD, and more specific than SEM, in detecting changes of properties essentially arising at the drug–excipient interphase. By analyzing how the enthalpy of melting of indomethacin changes with the composition of mixture, with the experimental conditions and with the treatments we achieve a fairly complete picture of what enhances, or hinders, this interaction. In the mixtures In:MGST (20:80) and In:PVP (80:20) this melting enthalpy is primarily a function of the temperature rate, while the atmosphere of the run (wet or dry) has little influence. This means that the interaction proceeds from the interphase with a temperature activated rate. In the In:PVP (20:80) mixture, the moisture of the measuring atmosphere has a major effect, and concurs with temperature and time in modifying the basic properties of the drug.

Several observations provide evidence of how complex the interplay among different factors is. The In:PVP (80:20) mixture and both the mixtures In:MGST treated one month or more with moisture have an indomethacin phase substantially more affected than the corresponding untreated mixtures. With a hydrophobic drug and a hygroscopic excipient, the hydration of the excipient, along with its high concentration, helps achieving a characteristic threshold of interaction, even at r.t. In our cases, temperatures below 70°C appear to have little or no effect upon this threshold, which explains why thermal treatments have very little effects upon the mixtures. Of course, these results helps planning standard compatibility tests. They may be compared with DSC data of the In:MGST (1:1) and In:Avicel© (1:1) systems, performed only in dry N_2, closed containers, and with a 10 K min^{-1} heating rate.

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