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

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Abstract

We apply a range of techniques (thermal methods, microscopy, X-ray diffraction, IR spectroscopy) to characterize a drug (atenolol), several excipients (PVP=polyvinylpyrrolidone, MGST=magnesium stearate, Avicel©) and drug–excipients mixtures either as prepared, annealed, and exposed to moisture. We compare the data of the mixtures with those computed from a weighted average of similarly treated pure compounds to find evidence of drug properties modified by the interaction with the excipient. We find that thermal response is by far the most sensitive indicator of interaction while IR is the least sensitive one.

Avicel© has essentially no interaction with atenolol, while MGST modifies significantly only the thermal response of the drug in the MGST-rich mixtures. PVP interacts strongly with atenolol, and this interaction appears to be mediated by the substantial amount of hydration water the excipient brings in its mixtures with a water-free drug.

Keywords: atenolol, characterisation, compatiblity, DSC, FT-IR, Mg-stearate, microcrystalline cellulose, PVP, SEM, TG, XRPD

Introduction

Drug development is a very complex, costly, and time consuming process which makes concurrent use of many advanced technologies. Just one out of 5000 compounds analysed will end up in a commercial formulation. Development begins by selecting a pathology (disease selection) and the appropriate targets of the planned drug (target selection). The synthesis of new or modified classes of compounds follows (lead generation) which should selectively react, or affect, the molecular structures involved with the pathology. Many in-vitro and in-vivo tests are conducted with these potential drugs to evaluate efficacy, selectivity, pharmacokinetics-pharmacodynamics, optimal dosage, etc, with the goal of selecting the most promising candidates (lead selection). In the subsequent preformulation studies, the compatibility of the active ingredient(s) with several excipients is determined along with its (their) chemical stability, toxicity, details of

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bioavailability (absorption, distribution, excretion in experimental animals). The expensive and delicate phases of clinical trials follow.

To avoid wasting time with inappropriate drugs and dosage forms, it is very important to begin the clinical phases with formulations fully characterised from the physicochemical point of view [1–6]. While most excipients have no direct pharmacological action, they do perform either useful tasks (such as giving the product the proper physical/sensorial form) or damaging actions (such as speeding up degradation of the drug) [2]. In the case of products stored or administered in the solid form, it is essential to understand the role of water/moisture [3]. In fact, reaction with water may modify the properties of the active ingredient, and such a reaction may be facilitated by the excipient, which is often the vehicle of water into the formulation [4, 5]. For both liquid and solid products, an increase of temperature usually leads to faster degradation (oxidation, phase changes).

Two protocols of stability tests are currently in use for solid formulations [7–9]. In the long term test, the samples (1:1 mixtures of drug and excipient) are kept at 25°C (±2°C) and relative humidity (rh) of 60% (±5%) for at least one year and chromatographically analyzed every three months. In the accelerated test (lasting 6 months, or more), the storage conditions are 40°C (±2°C) and rh=75% (±5 %) [10].

Thermal methods have been mostly used for quick assessment of purity when chromatographic identification is not yet available. It is our opinion that these methods, coupled with other techniques (spectroscopy, X-rays scattering, microscopies) may be much better exploited through their systematic and concurrent use along with the standard tests. In fact, the standard tests are long, expensive, and far from exhaustive. We expect to achieve a better understanding of the basic properties of drug, excipient(s), and of their interactions by analyzing these compounds alone and mixed in different proportions under different conditions of temperature, humidity and storage time [11]. All these analyses may be performed in a relatively short time (compared with the standard tests) and with minimal amounts of active ingredient.

Here we will present such a systematic study for atenolol, a β-antagonist drug made in the ‘70’, used in hypertension, angina pectoris, and cardiac arrhythmia cases [12]. It comes as a white powder, nearly insoluble in water or organic solvents (acetone, chloroform) with a melting point of ~150°C. Its formula is given in Fig. 1.

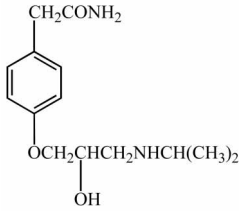

Fig. 1 Structural formula of atenolol

According to a 1995 thermal study [13], the commercial formulation of this drug (a pill with several commonly used excipients) does not present significant evidence of incompatibility since the DSC melting peak of the pure drug is seen also in the

mixture. On the other hand, a DSC investigation of binary mixtures atenolol:common excipient [14] has determined that this active principle is compatible with amid, compressible amid (Sta-Rx 1500), Primogel, Avicel© PH101, Ac-Di-Sol, magnesium stearate, Cl-polyvinylpirrolidone, calcium sulphate dihydrate, dicalcium sulphate, while it reacts with polyvinylpyrrolidone, stearic acid, lactose. Both of these studies have been limited to a single concentration of active ingredient in the mixtures and to a single scan rate.

As with indomethacin [15], we will study the active ingredient atenolol alone and in mixtures 20:80 and 80:20 with three common excipients: polyvinylpyrrolidone (PVP), magnesium stearate (MGST), and Avicel© (microcrystalline cellulose). We refer to a previous study [15] and to the literature for physicochemical characterisation of these excipients [16–21].

Experimental

Atenolol (batch 0901190, racemic mixture) has been kindly donated by Erregierre (Bergamo, Italy); the three commercial-grade excipients (PVP, MGST, Avicel©) have been provided by GlaxoSmithKline. All samples have been stored as received in air-tight plastic containers at rt and in the dark. About 3 g of binary drug:excipient mixtures (20:80 and 80:20) have been prepared by weighing the appropriate amount of the components and mixing them with a turbula (W. Bachofen, 96 rpm, 10 min). We will call 'untreated samples' the original compounds and their mixtures which have been stored in closed containers after being prepared as described above. To a fraction of each untreated sample we have applied one of the following treatments for variable time intervals (up to three months):

a) moisture conditioning at rt and rh>90%;

b) temperature conditioning in an open container at 70°C and rh<30%;

c) temperature/moisture conditioning in a closed container at 70°C.

The experimental techniques used are:

• scanning electron microscopy (SEM) with a Cambridge Stereoscan 200 with samples gold-sputtered under vacuum;

• thermal analyses (by a simultaneous DSC-TG apparatus – Polymer STA 625, Polymer Laboratories, UK) both in dry nitrogen and wet nitrogen (N_2 bubbled through water at rt) at two or more temperature scanning rates (2, 5 and 10 K min^{-1}) using open aluminium pans. The values of enthalpies and mass changes have an estimated uncertainty of less than 5%, which is our significance limit. All thermal data reported here result from an average of three or more repeated measurements;

• FT-IR by diffuse reflectance (DRIFT) in samples (3%) dispersed in anhydrous KBr (97%) (Nicolet FT-IR system with DRIFT collector by Spectra Tech – UK). Each 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 con-

tribution (a spectrum of dry KBr obtained with the same preparation protocol and acquisition parameters).

• X-rays powder diffraction (XRPD) (Bruker D 5000). The CuK_α radiation was obtained with a bent-graphite monochromator.

Results and discussion

We will present the characterisation of atenolol and its mixtures with the three excipients, which have been studied in the previous work [15]. As before, in the treated/untreated mixtures we search for deviations from the results which can be predicted from the response of treated/untreated components under the no interaction hypothesis.

Atenolol – PVP system

Atenolol

The untreated sample consists of irregularly shaped platelets joined in clusters 50÷100 μm in size (SEM pictures in Fig. 2). From the TG-DSC traces (Fig. 3) we see a small mass loss from rt to 60°C, associated with less than 0.5% of surface water, and an endothermic melting peak with onset temperature at 153.9°C and enthalpy of 127.9±2.9 J g^{-1} (average of 13 data with their standard deviation coming from measurements performed at different heating rates, and under different atmospheres).

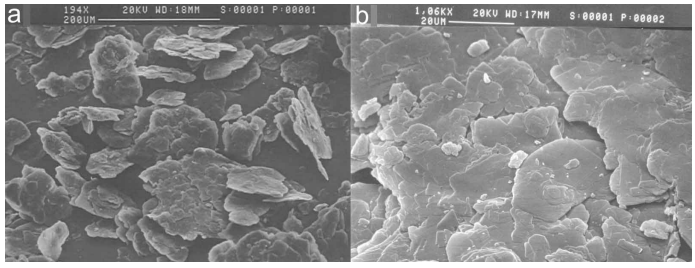

Fig. 2 SEM pictures of as received atenolol at different magnifications: a – 194×; b – 1060×

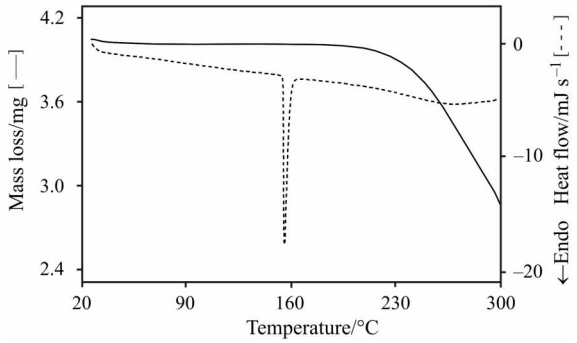

Fig. 3 Simultaneous TG (continuous curve) and DSC (dashed curve) plots of original atenolol in wet N_2 at 5 K min^{-1}

A sharp decrease in mass begins near 190°C, and signals the beginning of decomposition. Neither the onset temperature, nor the melting enthalpy are significantly affected by the atmosphere and the scan rate. The XRPD and DRIFT spectra will be discussed in connection with the corresponding patterns of treated samples.

Moisture treated samples (at rt and rh>90%, from 1 to 105 days) do not show significantly different onset temperatures and enthalpies of melting: in particular, the melting enthalpy and its standard deviation over all the runs with treated samples are 128.3±1.4 J g^{-1}. The morphology of the samples and the DRIFT spectra are not affected by treatment. Only the XRPD patterns present peaks which maintain the same position but progressively broaden as the treatment time increases (Fig. 4). A peak at 9.5° splits for weeks long treatment times. The main effect of months-long moisture treatment is a decrease of crystallinity.

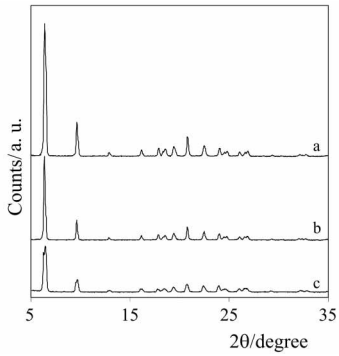

Fig. 4 XRPD spectra of a – original atenolol; b – atenolol moisture conditioned for 1 h; and c – for 3 months

The temperature treatment (at 70°C) in open or sealed containers for 40 days does not change the morphology of the samples. Onset temperature and enthalpy of melting are essentially unaffected. For example, the average value of the melting enthalpy for temperature-treated samples (129.8 J g^{-1}) differ by less than a standard deviation (2.9 J g^{-1}) from the corresponding value for untreated samples (127.9 J g^{-1}). Only the XRPD intensities decrease upon treatment, and the reduction is more noticeable in samples kept in open containers.

Polyvinylpyrrolidone (PVP)

We refer to a companion paper for characterisation of pure polyvinylpyrrolidone [15], and to selected papers [16, 17]. Its behavior is summarized in the following. Original PVP loses (endothermically) about 9 and 2% in mass of water below 100°C and around 150°C, respectively. Thermal analyses, SEM and XRPD all show that the compound is in a vitreous phase with glass transition near 200°C. It decomposes around 300°C. With just three hours of moisture conditioning the sample becomes a semi-solid slurry. But one hour is sufficient to substantially modify the SEM appearance: the spheroidal shells (balls) of the original sample are mostly broken, and col-

lapsed one within the other; the water lost below 100°C increases to 15.9%. DRIFT spectra and XRPD patterns remain the same.

Temperature conditioning (at 70°C for 40 days) reduces the mass by 4.5% in closed containers, and by 6.4% in open containers. SEM pictures shows balls partially collapsed and melted together. No DRIFT and XRPD effects are noted. Therefore, moisture and temperature conditioning appear to change the surface properties of PVP, but not its bulk properties.

At:PVP (20:80) mixtures

Figure 5a shows that, in the At:PVP (20:80) mixtures, the atenolol platelets are attached to deformed/collapsed PVP balls. Figure 6 shows the DSC traces of the pure compounds and of the mixture. The contribution of the ingredients are identifiable in the mixture, but the melting peak of atenolol is broader than in the pure compound and has shifted ~25°C to lower temperatures. The melting enthalpy of atenolol in the mixture is about 20% less than expected in the no interaction hypothesis at 5 K min^{-1}, and ~35% less than expected at 10 K min^{-1}. These differences are the same in dry and wet N_2. The DRIFT spectrum of the mixture is that expected by the no interaction hypothesis, but the XRPD reflections of atenolol in the mixture (well identifiable since PVP is amorphous) are much smaller than expected: the most intense reflection (at 2ϑ=6.5°) splits into two peaks (Fig. 7).

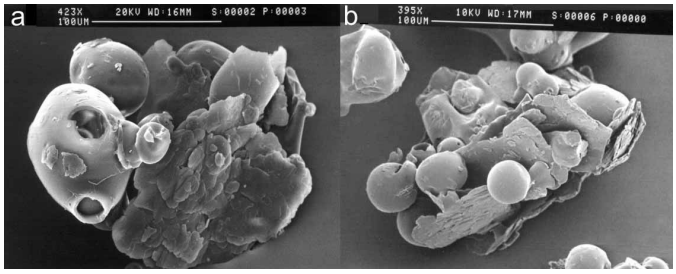

Fig. 5 SEM micrographs of a – At:PVP (20:80) mixture untreated and b – moisture treated for 1 h

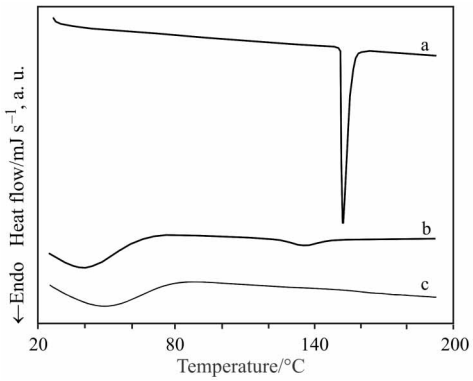

Fig. 6 DSC scans at 5 K min^{-1} in dry N_2 of a – atenolol; b – At:PVP (20:80) mixture; c – PVP. The feature below 80°C in b) and c) is due to dehydration of PVP

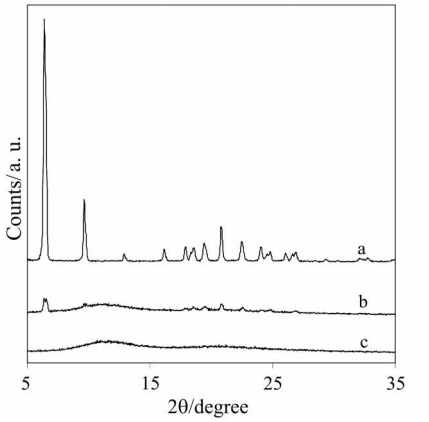

Fig. 7 Diffraction patterns of a – atenolol; b – At:PVP (20:80) mixture and c – PVP

SEM pictures show that moisture conditioning (for 1 h) favors a more intimate mixing of the constituents (Fig. 5b), with smaller PVP particles interleaved among atenolol platelets. Dehydration of PVP is now more spread-out, and partially overlapping the atenolol melting. Moisture conditioning does not change DRIFT spectrum; in the XRPD pattern of the mixture, the splitting of the 2ϑ=6.5° reflection of atenolol becomes more evident.

Temperature conditioning at 70°C for 40 days also causes a more intimate mixing of the components, which occasionally lose their characteristic shape, particularly for mixtures kept in closed containers. The atenolol melting enthalpy of thermally treated mixtures is 12.0 J g^{-1} in closed container and 15.4 J g^{-1} in open container, to be compared with the value of 25.6 J g^{-1} predicted by the no interaction hypothesis, and the value of 16.7 J g^{-1} of the untreated mixture at the same scanning rate (10 K min^{-1}). Figure 8 compares the XRPD patterns of pure atenolol, its 20:80 mixture, and pure

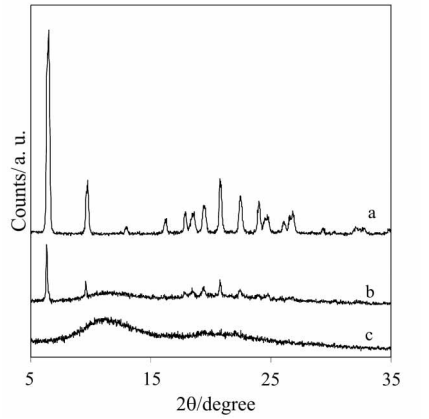

Fig. 8 Diffraction patterns of thermally treated (70°C for 40 days) samples in open pans: a – pure atenolol; b – At:PVP (20:80) mixture; c – pure PVP

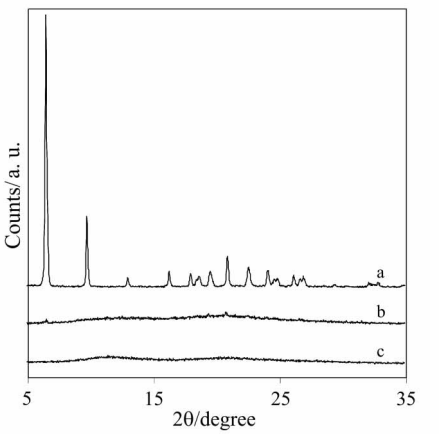

Fig. 9 Diffraction patterns of thermally treated (70°C for 40 days) samples in closed pans: a – pure atenolol; b – At:PVP (20:80) mixture; c – pure PVP

PVP which have been temperature conditioned for 40 days in open containers. Figure 9 shows the same set of spectra for samples annealed 40 days in closed containers. Peak intensities due to the drug decrease less in open containers while the mixture treated in a closed container has almost no reflections.

Summarizing, atenolol is substantially modified when mixed with PVP, although no changes of the DRIFT spectrum are observed. Hydration water of PVP certainly plays an important role in this interaction, which is enhanced by moisture treatment and temperature treatment in sealed container. On the other hand, annealing the mixture at 70°C in open container decreases the water content and causes a modest increase in the XRPD intensities, relative to the untreated mixture.

At:PVP (80:20) mixtures

The SEM pictures of the mixture show platelets of atenolol bonded together or attached to PVP shells. Figure 10 compares the DSC melting peak of atenolol in dry N_2 (a) with that of its 80:20 mixture (b); the pure PVP trace is also shown (c). We see here the beginning of the phenomenon which causes a substantially larger broadening and shifting of the atenolol melting in the PVP rich mixtures (Fig. 6). The main difference between (a) and (b) is the low temperature shoulder in the melting of the mixture since the melting enthalpy of the mixture is roughly as expected by the no interaction hypothesis (102.3 ± 2.3 J g^{-1}). In more detail, the melting enthalpy is within 1% of the expected value when the measurements are performed under dry N_2 and drops by ~10% and ~5% when the experiment is performed in wet nitrogen at 5 and at 10 K min^{-1}, respectively. No effects of mixing are noted in DRIFT spectra, nor in XRPD.

When the mixture is moisture-treated for 1 h, the PVP particles are no longer identifiable in SEM pictures and the clusters of atenolol platelets become larger than in the untreated sample. In dry N_2 at 10 K min^{-1}, the DSC peak is substantially reduced (to 90.1 ± 0.7 J g^{-1}) relative to the untreated mixture in the same experimental

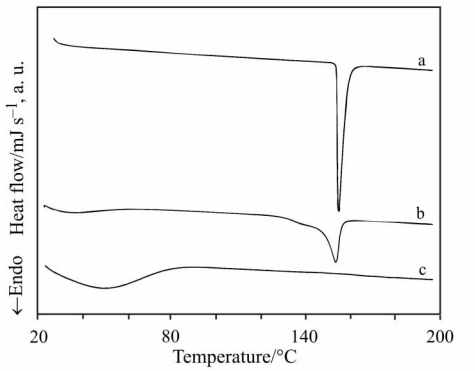

Fig. 10 Comparison of DSC responses at 5 K min^{-1} and dry nitrogen: a – pure atenolol; b – At:PVP (80:20) mixture; c – pure PVP

conditions. Furthermore, the low temperature feature is no longer apparent (Fig. 11). Another effect of moisture conditioning is the splitting of the two strong XRPD reflections occurring at 2ϑ=6.5 and 9.5° in the untreated sample (Figs 4 and 7).

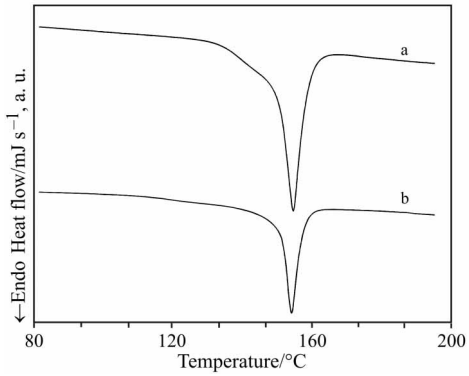

Fig. 11 Comparison of DSC responses in the melting region of a – untreated and b – moisture treated At:PVP (80:20) mixtures

SEM pictures of mixtures annealed in open and sealed pans at 70°C for 35 days are essentially the same as those of the untreated mixture. The melting enthalpy drops steadily with the annealing time, irrespective of the open/closed condition: it is about 92 J g^{-1} after two weeks, and 86 J g^{-1} (*vs*. the expected ~102 J g^{-1}) after 35 days. No other effects are noted in XRPD and DRIFT experiments.

The above suggests that the main cause of atenolol-PVP incompatibility is related with the moisture content of the excipient.

Atenolol – MGST system

Magnesium stearate (MGST)

The properties of magnesium stearate have been presented in detail elsewhere [15, 19, 20] and are summarized now. The untreated excipient is made of platelets

and grains of vastly different shapes and sizes. It contains about two molecules of water per unit formula (or 5.5% in mass) and dehydration occurs in two or more steps, depending upon the experimental conditions. Melting occurs near 120°C; endothermic phenomena at higher temperatures signal the presence of magnesium palmitate, or of high-melting polymorphs. A moisture-treated sample absorb about 1.1% in mass of surface water; this water causes the original grains to stick together in large blobs. The XRPD pattern is sharper in the moisture-conditioned than in the untreated sample; furthermore, this treatment causes the appearance of a peak at 2ϑ=19.5°, which is absent in the untreated sample.

Temperature conditioning at 70°C for days in open container causes the modifications of the DSC response illustrated in Fig. 12: relative to the untreated sample (a), one day (b) or three days (c) of annealing cause the disappearance of the dehydration peak below 80°C, although the sample still contains about 1.8% of water. After seven days of annealing (d) or more (e), we have a substantial growth of the melting peak near 140°C, which is attributed to formation of a pseudo-polymorph. As it is well known and may be partially seen in Fig. 12, melting and dehydration are partially overlapped. Therefore, for reasons of experimental accuracy, it is convenient to determine the total enthalpy change from 50 to 160°C. The overall enthalpy change of dehydration&melting decreases markedly during weeks long annealing (Table 1). In a closed container, water loss is a much slower process, with about 3% of water remaining after one week, and 1.9% after 2 weeks. The overall enthalpy change decreases less markedly than in an open container during annealing (Table 1).

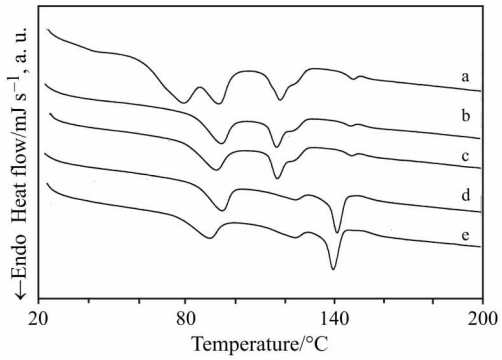

Fig. 12 DSC response of MGST in dry N_2 and 5 K min^{-1}: a – untreated sample; b – samples annealed at 70°C in open containers for 1 day; c – 3 days; d – 7 days; e – 14 days

Table 1 Dehydration and melting enthalpies *vs*. annealing time

	ΔH/J g^{-1}				
Time/days	0	1	3	7	14
Open Pan	253	153	153	114	80
Closed Pan		245	220	168	96

In summary, the drop of enthalpy change is accompanied by the growth, after a week-long annealing in either closed or open containers, of the melting peak associated with the pseudopolymorph. No major changes are caused by this transformation in the XRPD pattern, which displays broader peaks after three days of annealing in open containers.

At:MGST (20:80) mixtures

No obvious sign of interaction is evident from SEM pictures of the mixture.

The enthalpies from the DSC traces with the mixture are systematically lower than expected for atenolol and stearate melting. Furthermore, the last peak of the stearate is significantly broadened and shifted to lower temperatures relative to the pure compound. The differences between expected and measured enthalpies are of the order of 10% with a large dispersion; apparently, they depend upon the experimental conditions (atmosphere and scanning rate). DRIFT data agree with the no interaction hypothesis while several XRPD peaks of atenolol are missing in the mixture (Fig. 13).

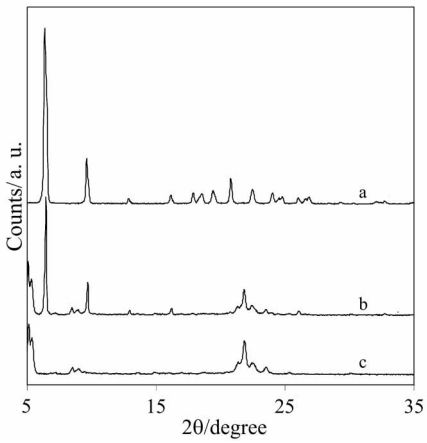

Fig. 13 XRPD spectra of a – atenolol; b – At:MGST (20:80) mixture and c – MGST

Moisture treatment of the mixture for 35 days favors aggregation among drug and excipient particles. However, thermal, DRIFT and XRPD data of treated and untreated mixtures are essentially the same, with no major change associated with either day-long or week-long moisture treatments. With moisture treated samples, we have a more uniform decrease of observed enthalpies relative to the expected values: in particular, all data for the atenolol melting peak in the moisture-treated mixture gives $\Delta H \approx 15.3 \pm 0.5$ J g^{-1}, to be compared with the expected value of 25.6 J g^{-1}.

The melting enthalpy of stearate and atenolol in the mixture annealed at 70°C for days (up to three) in open or closed containers are less than the values computed from data in thermally treated pure compounds. This decrease is similar to that noted above for the moisture treated mixture. No XRPD or DRIFT anomalies are noted.

At:MGST (80:20) mixtures

In the SEM pictures, there are many large and composite grains of atenolol with small particles of stearate on their surface. No major evidence of interaction emerges from the data (DSC, TG, XRPD, DRIFT) with untreated, moisture treated, and temperature-treated samples. The atenolol rich mixture presents essentially no sign of drug–excipient interaction, even with treated samples.

Atenolol – Avicel© system

Avicel©

The properties of the excipient may be summarized as follows [15–21]. The untreated Avicel© consists of aggregates of irregularly shaped grains. Adsorbed water (about 5%) is lost below 100°C apparently in a single, endothermic and spread-out process. No other thermal phenomena are observed before the beginning of decomposition, around 240°C. The XRPD pattern does not have sharp Braggs reflections, but few broad features between $15° < 2\vartheta < 25°$. Moisture treatment causes the water content of Avicel© to steadily increase to about 13% in 35 days. Annealing the sample for 35 days at 70°C reduces the water content to about 2.5% (2.2% when annealing in open container, 2.8% in closed container), with no consequences upon other properties.

At:Avicel© (20:80) mixtures

The characteristic grains of the drug and the excipient are easily identified, and apparently maintain the original shape with no tendency to form aggregates. The melting enthalpy of atenolol, measured in wet and dry N_2 at different scanning rates, is 23.9±0.9 J g^{-1} in the mixture, *vs*. the expected 25.6±0.6 J g^{-1}, a barely significant difference. No other qualitative signs of interaction are seen in XRPD or DRIFT data.

Moisture conditioning the mixture does not cause qualitative changes in SEM, DSC, XRPD and DRIFT data. Only the melting enthalpy of atenolol (a quantitative indicator) steadily decreases during the first two weeks of conditioning, and stabilizes at about 70% of the expected (no interaction) value afterwards.

Annealing for up to 35 days in open and closed containers causes only an appreciable (~10%) drop of the atenolol melting enthalpy, which is so reduced also by annealing times as short as one day. There may be a somehow larger effect with closed containers ($\Delta H \approx 22.9 \pm 1.1$ J g^{-1}) than in open pans ($\Delta H \approx 23.4 \pm 0.6$ J g^{-1}) but the difference is barely significant. No other evidence of interaction is seen in SEM, DRIFT or XRPD data.

At:Avicel© (80:20) mixtures

The only evidence of interaction in the untreated mixture is an average reduction of the atenolol melting enthalpy of 3% (with a substantial dispersion, possibly dependent upon experimental conditions). Moisture treatment somehow increases this reduction to about 4%, with no clear indication of a drop *vs*. time trend. Also temperature treatment (up to 35 days) has apparently no consequences: all temperature treated mixtures have, in the average, the same ~3% reduction of atenolol melting enthalpy shown by the untreated mixture.

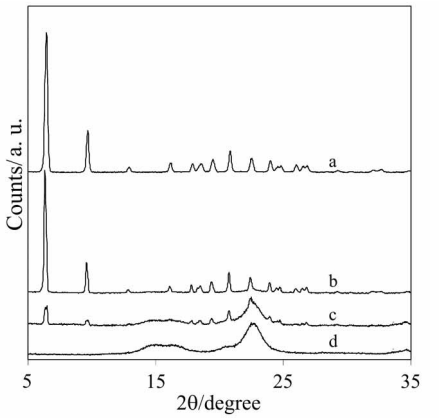

Fig. 14 XRPD patterns of samples moisture-treated for 35 days: a – atenolol; b – At:Avicel© (80:20) mixture; c – At:Avicel (20:80) mixture; d – Avicel

SEM, XRPD, and DRIFT evidence of drug excipient interaction is absent both in treated and untreated mixtures. Figure 14 shows XRPD patterns of pure compounds and their mixtures treated 35 days at >90% relative humidity. The patterns of these mixtures are well interpreted by the no interaction hypothesis.

Conclusions

It is worthwhile to summarize here the method which has been applied to this work. We have searched for differences between data of pure compounds (drug and excipients) and those of their mixtures. Of course, the reference data for the mixtures are appropriate weighted averages of the pure compounds data. These data are those we expect when no physical interactions between components occur (no interaction hypothesis). We explore these 'interaction indicators' as a function of concentration, moisture treatment, temperature treatment. Concentration is explored for two limiting compositions (drug rich and drug poor mixtures) irrespective of the typical concentration of the peculiar dosage form, the reason being that a high concentration of the excipient may show more clearly effects of interactions which are obscured in the drug rich mixtures. The moisture and thermal treatments with mixtures aim at detecting changes relative to pure compounds treated in the same way. That means, we search for additional effects just caused by mixing when combined with treatments.

The 'interaction indicators' are mostly qualitative in nature: for example, a XRPD pattern may show no change, mild changes (modified intensities), substantial changes (new peak positions or amorphization). Instead, enthalpies of melting are quantitative data since they may be expressed as a fractional change. We are not attempting a in depth interpretation of our results since our aim is simply that of scoring the level of interaction of a drug with different excipients.

According to the above, a rough outline of this work is as follows: interactions of atenolol are strong with PVP, mild with MGST, and nearly absent with Avicel©.

A more detailed summary is presented below, beginning with the two extreme cases of PVP and Avicel.

In the atenolol-PVP mixtures, substantial modifications are seen in the DSC response of atenolol as a consequence of an interaction drug–excipient which is enhanced, or mediated, by the hydration water of PVP. In fact, the indications of interaction are larger in the PVP-rich mixture, in the moisture treated mixtures, and in mixtures annealed (at 70°C) in closed containers, where relative humidity is expected to be higher than in open containers. Temperature conditioning has a sizable effect (upon the atenolol melting enthalpy) only after prolonged annealing in closed container: this effect is less than that induced by moisture conditioning which, in addition, appears to modify also the crystalline order of atenolol. The fact that DSC data in wet nitrogen reveal the interaction better than data in dry nitrogen is consistent with the emerging interpretation of a moisture-assisted mechanism of atenolol-PVP interaction.

There are no interactions with atenolol in his mixtures with microcrystalline cellulose (Avicel©), even if the excipient carries sizable amounts of 'absorbed water'. Indicators of interaction are mildly positive only in the case of Avicel©-rich mixtures, particularly if moisture-treated, or annealed in closed containers. All this points to a weak interaction, which again is mediated by the moisture content of the excipient.

The mixtures of atenolol with MGST have an intermediate behavior, with a complicated DSC response caused by the presence of both 'structural' and surface water in the excipient. A weak interaction is detected mainly in the thermal response of atenolol, which is significantly modified in the stearate-rich mixture (in particular, the moisture-treated ones). On the other hand, temperature treatment is of little consequence, presumably because of the dehydration which accompanies it.

Our data offer a rather clear indication about the excipients which are compatible with atenolol, and about the factors which enhance their interaction with the drug. Water moisture carried by the excipient appears to be a potentially important factor, while temperature and time play a role mostly by modifying the hydration conditions.

This study demonstrates that the DSC technique is by far the most sensitive technique in revealing effects of interaction, while DRIFT is the less sensitive one; SEM and XRPD gives qualitative indicators, (change or no change). Some quantitative effects upon the DSC response of the drug are revealed only in the excipient-rich mixtures, and appear to be related to moisture-driven mechanisms of interaction. Of course, these findings may be precious in defining a commercial formulation, and the precautions for storing it.

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