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Research paper

Compaction of lactose drug mixtures: Quantification of the extent of incompatibility by FT-Raman spectroscopy

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Abstract

It is well known that lactoses interact with drugs containing amino groups and undergo the Maillard reaction. Lactose monohydrate may also interact with moisture sensitive drugs and affect the stability of the drug. These interactions were analyzed using three model drugs – Thiaminchloride hydrochloride, Nicotinamide and Acetylsalicylic acid – which interact with spray-dried lactose or anhydrous lactose. FT-Raman spectroscopy was used for the first time to qualitatively and quantitatively analyze these excipient drug interactions in powders and tablets. Both lactoses undergo the Maillard reaction with Thiaminchloride hydrochloride. Nicotinamide did not react with the lactoses because the amide group is protected against the reaction with the lactoses. Only a transition from β- to α-lactose was noticed. The moisture sensitive drug Acetylsalicylic acid remained stable even when the tablets were stored under accelerated conditions (40 °C and 75% RH). The crystal water of lactose monohydrate (spray-dried lactose) had no influence on the drug stability but a transition from β- to α-lactose was noticed. In conclusion, FT-Raman spectroscopy is a fast and valuable tool for a quantitative determination of the extents of incompatibility in solid dosage forms.

Keywords: FT-Raman spectroscopy; Maillard; Moisture; Lactose; Thiaminchloride hydrochloride; Nicotinamide; Acetylsalicylic acid

1. Introduction

Interactions between drug and excipients play an important role during development of a new pharmaceutical formulation. This problem of chemical or physical interactions exists for all dosage forms including tablets.

Lactose is the most widely used excipient for tableting and used for formulation of various commercially available products. Unfortunately, lactose interacts with drugs containing amino groups to an extent. It is a fact that lactose is capable of non-enzymatic creation of pigments called Maillard browning. The Maillard reaction is named after Louis Maillard, who described the creation of brown pigments after reaction of amines and reducing disaccharides. Many investigations were performed dealing with the normal browning (without drug) of lactose and the browning in presence of amines [1]. Although it is often claimed that only primary amines are able to undergo Maillard reaction, it has been proven that nearly all primary and secondary amines can undergo this reaction [1] while tertiary amines do not [2].

The Maillard reaction in lactose tablets has been studied for several drugs: a visible colour change was found for tablets containing thiamine hydrochloride, benzocaine, sodium *p*-aminosalicylate, procaine hydrochloride, sulphaguanidine, chloroquine phosphate or ephedrine sulphate in combination with lactose [3]. The discoloration of tablets containing lactose and neomycin was found to be influenced by increasing pH, temperature and humidity. Interactions of dextroamphetamine and spray-dried lactose were influenced by increasing temperature and humidity [4]. The interaction between aminophylline and lactose

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has been studied using DSC and FT–IR spectroscopy [5]. More recently, an incompatibility in tablets was reported for lactose and lisinopril even at a very low concentration of lactose [6]. The Maillard reaction of fluoxetine hydrochloride with spray-dried lactose was found to be faster than with lactose monohydrate [1] and in this case the reaction was also accelerated by increasing temperature and humidity [1]. The effects of milling and compression on the solid-state Maillard reaction between metoclopramide hydrochloride and lactose have been investigated [7].

Another problem during tableting of spray-dried lactose could arise with moisture sensitive drugs. Spray-dried lactose consists of α-lactose monohydrate and contains about 15% (w/w) amorphous material. Even when it was described that the immobile water like hydrate water cannot be involved in hydrolysis processes [8], spray-dried lactose contains mobile water in its amorphous parts and can thus cause incompatibilities.

Only a few studies deal with the problem of moisture sensitivity and spray-dried lactose. In the presence of 10% (w/w) water, Acetylsalicylic acid was completely decomposed within 120 days at 50 °C [9,10]. The interaction of the moisture sensitive drugs Acetylsalicylic acid and niacinamide with lactose anhydrous and spray-dried lactose was most recently analyzed. Increasing temperature and humidity (mobile water) influenced stability. Because of the amorphous parts, spray-dried lactose is more hygroscopic than anhydrous lactose, which caused that drugs in anhydrous lactose were slightly more stable [11].

The objective of this study was to analyze the interactions of the two lactoses, spray-dried lactose and anhydrous lactose, in mixture with three model drugs – Thiaminchloride hydrochloride, Nicotinamide and Acetylsalicylic acid using FT-Raman spectroscopy. Thiaminchloride hydrochloride is expected to undergo Maillard reaction. The secondary amine in Nicotinamide is expected not to undergo the Maillard reaction since it contains a protected amide group. Acetylsalicylic acid is a moisture sensitive drug and is expected to remain stable even though spray-dried lactose contains mobile water [11]. The determined data should be helpful in understanding the behavior of both lactoses during formulation development. For the first time these interactions were analyzed by FT-Raman spectroscopy. Previous studies had used e.g. differential scanning calorimetry, HPLC, and capillary electrophoresis. The recent developments in FT-Raman spectroscopy enable a quantitative determination of these interactions, which is fast and precise.

1.1. Theoretical background: quantitative FT-Raman spectroscopy

Raman spectroscopy is a form of vibrational analysis. In the past, experimental difficulties tended to limit the use of Raman spectroscopy for vibrational analysis. However, with the advancement of Fourier transform techniques, instrumentation development, and laser improvements, the last 20 years has seen a renaissance of the Raman technique [12]. FT-Raman spectroscopy is used for qualitative (identification and structure determination) and quantitative analysis [13]. FT-Raman spectroscopy has many advantages. Sample preparation is not required in most instances. Thus, FT-Raman spectroscopy enables analysis of bulk or microscopic material in situ [14]. Furthermore, analysis of complex biological material is possible [15–17]. Góral and Zichy executed Raman spectroscopic assays for structure determination of important biological compounds like mono- and polysaccharides, nucleic acids and herbal ingredients [15]. More and more, FT-Raman spectroscopy is applied to solids due to a fast and accurate quantitative determination after a careful calibration.

In solid-state analysis, peak intensities or peak areas were determined for quantification after baseline correction. This method has been used in several studies [18–25]. Kontoyannis et al. developed a method for quantitative analysis of urine stones with the aid of FT-Raman spectroscopy. They used a dilution series and determined the Raman intensity of typical peaks of calcium oxalate monohydrate and calcium oxalate dihydrate from the measured Raman spectra [22]. Taylor and Langkilde found FT-Raman spectroscopy an appropriate method to analyze drugs and excipients in intact solid dosage forms. Phase transitions of anhydrous and monohydrate forms could be specially determined [23]. When chemometric methods based on Partial Least Squares (PLS) regression and multivariate calibration were developed for quantitative determination, a better accuracy of prediction became possible due to multivariate calibration. For multivariate calibration not only one data point but a complete spectral structure is used for calibration and modeling. Compared to univariate calibration characteristic peaks are dispensable. Thus, in recent years this technique has become popular [26–29], e.g. Taylor and Zografi determined crystallinity of Indomethacine with FT-Raman spectroscopy quantitatively with the use of PLS regression and multivariate calibration [26]. Further advances were achieved by principal component analysis by which only reduced spectral information is used for calibration [30–32], e.g. a quantitative analysis of polymorphic mixtures of ranitidine hydrochloride became possible. A most recent review highlights the advantages of FT-Raman spectroscopy in quantitative analysis for polymorphic forms [33].

2. Materials

Lactose anhydrous, namely Lactopress anhydrous® (LPAH or AH, Lot # 414008/S) and spray-dried lactose, namely Lactopress spray-dried® (LPSD or SD, Lot # 416027/S) were obtained from friesland foods DOMO (Borculo, The Netherlands). The spray-dried material contained at 60% and 75% RH $5.02 \pm 0.05\%$ water which is partially crystal water and partially sorbed water in the amorphous parts.

The materials were tableted in combination with three selected model drugs. The model drugs should be either moisture sensitive or drugs which undergo Maillard reaction with lactoses. The model drugs were Acetylsalicylic acid (Ass, Lot # 22684362, Caesar&Loretz GmbH, Hilden, Germany), Nicotinamide (Nico, Lot # 0306A046, Synopharm GmbH, Barsbüttel, Germany), and Thiaminchloride hydrochloride (Thia, Lot # 0303A202, Synopharm GmbH, Barsbüttel, Germany).

3. Methods

3.1. Apparent particle density

The apparent particle density ($\rho_{\text{app part}}$) of all materials was determined by using a Helium gaspycnometer (Micrometrics Accupyc 1330, Norcross, USA).

3.2. Preparation of mixtures

Mixtures of both spray-dried and anhydrous lactose with 25% (w/w) of the three model drugs were produced (LPSD + Ass (AssSD), LPAH + Ass (AssAH), LPSD +Nico (NicoSD), LPAH + Nico (NicoAH), LPSD + Thia (ThiaSD), LPAH + Thia (ThiaAH)). Tablet lubricant such as magnesium stearate was not used because the Maillard reaction can be influenced by this lubricant [34].

For quantitative determination of the extent of incompatibility a dilution series from 0% to 100% reaction and transition in steps of 10% was produced, respectively. For this purpose from non-converted powder and completely converted powder graded mixtures were produced. For all mixtures completely converted powders were produced at drastic conditions (60 °C and 70% RH). Completely converted powder means no further conversion was measurable. From these data the quantities of converted drug (mg g^{-1}) can be calculated.

All powders were mixed in a cubic mixer (Erweka GmbH, Heusenstamm, Germany) for 15 min at level 4. Before mixing in the cubic mixer all mixtures were passed through a 500 μm sieve to break down agglomerates of the powder.

3.3. Tableting

Tablets were produced on a calibrated, instrumented eccentric tableting machine (EK0/DMS, No. 1.0083.92, Korsch GmbH, Berlin, Germany) with 9 mm diameter flat faced punches at controlled temperature and humidity conditions in a climate room (21 ± 1 °C and 45 ± 2% RH). Elastic deformation of the punches and of the machine was corrected. Data acquisition was performed by a DMC-plus system (Hottinger Baldwin Meßtechnik, Darmstadt, Germany). Data were stored by BEAM-Software (AMS-Flöha, Germany).

The mass of each tablet was calculated using maximum relative density ($\rho_{\text{rel,max}}$) and manually weighed on a laboratory balance (Fa. Mettler-Toledo, Gießen, Germany).

$$\rho_{\text{rel,max}} = \frac{\text{mass [g]}}{\rho_{\text{app part}}\ [\text{g/cm}^3] \cdot \text{volume [cm}^3]}$$

The powder for each tablet was manually filled into the die and the 6 mixtures were tableted to $\rho_{\text{rel,max}}$ of 0.75, 0.85 and 0.95 with an accuracy of ±0.001. Nine tablets at each $\rho_{\text{rel,max}}$ were produced. The tablet height at maximum densification under load was held constant at 3.000 mm.

3.4. Storage conditions

Before tableting the excipients and drugs were stored under controlled temperature and humidity conditions in a climate room (21 ± 1 °C and 45 ± 2% RH) for equilibration.

The produced tablets were stored under various conditions:

- "normal conditions" (moderate climate): 21 °C and 45% RH (in a climate room);
- "stability test conditions" (subtropical climate): 30 °C and 60% RH (generated with a saturated salt solution of ammonium nitrate in a drying oven, WTB Binder Labortechnik GmbH, Tuttlingen, Germany);
- "accelerated conditions": 40 °C and 75% RH (generated with a saturated salt solution of sodium chloride in a drying oven, WTB Binder Labortechnik GmbH, Tuttlingen, Germany).

3.5. Characterization of the interaction of both the lactoses with the model drugs

3.5.1. Visual changes

Tablets stored under various conditions were controlled visually after the complete storing time.

3.5.2. FT-Raman spectroscopy

Materials and drugs were analyzed by FT-Raman spectroscopy to study the structural changes during browning or hydrolysis. The spectra were collected on a Bruker RFS 100/S FT-Raman spectrometer (Bruker GmbH, Karlsruhe, Germany) using a diode-pumped Nd:YAG with a operating wavelength of 1064 nm. Typical spectra were acquired with 200 scans and a laser power of 125 mW at the sample location. The interferograms were apodized with the Blackman–Harris four-term function and subjected to Fourier transformation to give spectra with a resolution of 4 cm^{-1}.

The powders (excipients and drugs) were analyzed in glass test tubes. Powder samples were placed in glass test tubes. The tablets were broken and the tablets were analyzed on a specially designed holder for tablet: the laser beam was focused on the fractured surface. This surface was deemed to be most appropriate to obtain a representative information on the tablet having in mind that the conversion is stronger at the outer surfaces of the tablet.

Spectra were analyzed by the software OPUS 4.2 and OPUS Quant 2.

3.5.3. Quantitative analysis of the extent of incompatibility by FT-Raman spectroscopy

With the aid of the dilution series spectra a method for quantitative analysis of the structural changes was developed and optimized. The method is based on multivariate calibration and described in Section 4.

In practice, Partial Least Squares (PLS) regression is the most established multivariate calibration method and the information of the spectra is compared with the corresponding concentration values. The extent of correlation between spectral data and concentration is of particular importance for quality analysis. To find a calibration function with the best correlation, the calibration model has to be validated. Two forms of validation are possible: cross validation (internal validation) or test-set validation (external validation). The main principle of both validation methods is to establish a calibration function and to check up this function with known samples. This comparison permits the calculation of the mean error of prediction which is a quantitative rate for the mean accuracy of prediction of the calibration model. The lower the mean error of prediction the better is the quality of the calibration model. The extent of correlation between spectral data and concentration is also described by the coefficient of determination, R^2, and values for R^2 should be higher than 90% for solid dosage form measurements. With the validated multivariate calibration model unknown samples can be determined and outliers can be identified automatically [35].

4. Results and discussion

4.1. Visual changes

Visual changes were determined after the whole storage time of the tablets: normal conditions (21 °C and 45% RH) after 112 days, stability test conditions (30 °C and 60% RH) after 102 days and accelerated conditions (40 °C and 75% RH) after 39 days. The higher temperature and humidity during storage were the more the visual changes were distinguishable. Tablets at normal conditions showed no visual changes. Tablets at stability test conditions showed the same visual changes as the tablets at accelerated conditions, but to a lesser extent. These visual changes are described in Table 1.

4.2. FT-Raman spectroscopy and quantitative analysis of the extent of incompatibility

Mixtures of Thiaminchloride hydrochloride with the lactoses underwent the Maillard reaction (Fig. 1). The Maillard reaction appears at aldehyde groups of open chained carbohydrates. A Schiff base is created, which is cyclizated to the corresponding *N*-glycosylamine [36]. In the presence of protons, as provided by Thiaminchloride hydrochloride, a reactive oxonium carbenium ion is formed from the lactose. The Thiaminchloride hydrochloride base is added at this ion and the *N*-glycosylamine is built. The

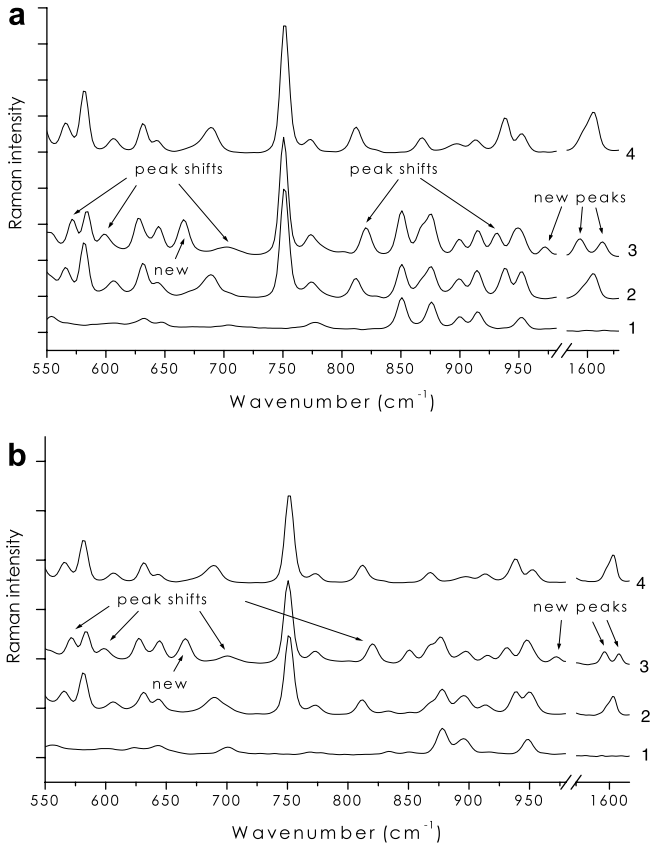

Fig. 1. Spectra of tablets of Thiaminchloride hydrochloride (Thia) and (a) spray-dried lactose (LPSD) or (b) anhydrous lactose (LPAH) with (1) LPSD or LPAH, (2) ThiaSD or ThiaAH after tableting, (3) ThiaSD or ThiaAH after complete Maillard reaction, and (4) Thia.

Table 1
Visual changes of tablets at stability test conditions and accelerated conditions

	Anhydrous lactose	Spray-dried lactose
Thiaminchloride hydrochloride	Bright beige coloured tablets changed to dark beige coloured tablets	White coloured tablets changed to bright beige coloured tablets
Nicotinamide	Bright beige coloured tablets changed to dark beige coloured blotched tablets, tablets expanded axially and radially because of water sorption	White coloured tablets changed to bright beige coloured blotched tablets
Acetylsalicylic acid	Bright beige coloured tablets changed to dark beige tablets, tablets expanded axially and radially because of water sorption	White coloured tablets changed to bright beige coloured tablets

N-glycosylamine undergoes the Amadori rearrangement to an amino ketone [1,37]. The configuration α (spray-dried lactose) and β (anhydrous lactose), respectively, for cyclic lactoses was irrelevant for the Maillard reaction because of the reaction of lactose in open chained form. Thus, nearly the same changes of spectra were noticed during storage for vibrations regarding Thiaminchloride hydrochloride, for example the new peak at 666 cm^{-1} and the peak shifts at 565 and 815 cm^{-1} (Fig. 1).

Fig. 2 shows the changes in spectra during storage for mixtures of the lactoses with Nicotinamide. It is visible that these mixtures do not undergo Maillard reaction even though Nicotinamide contains an amino group. The amino group of Nicotinamide is contained in an amide group. Amide groups are protected against reactive oxonium carbenium ions, so that they cannot undergo Maillard reaction. Thus, Nicotinamide remained stable during storage. A transition from β-lactose anhydrate (anhydrous lactose) to α-lactose monohydrate was noticed only in mixtures of Nicotinamide with anhydrous lactose. A new peak at 852 cm^{-1} appeared during storage (Fig. 2b). A plausible explanation for the transition is the absorption of water [1].

Similar observations were noticed for mixtures of Acetylsalicylic acid with the lactoses (Fig. 3). Acetylsalicylic acid is a moisture sensitive drug and remained stable even during storage at 75% RH. The crystal water of lactose monohydrate (spray-dried lactose) had no influence on the stability of Acetylsalicylic acid. A transition from β-lactose anhydrate (anhydrous lactose) to α-lactose monohydrate was noticed in mixture with anhydrous lactose. A new peak at 852 cm^{-1} increased during storage (Fig. 3b).

Changes in spectra were used to generate a calibration function with PLS regression and multivariate calibration. In all cases the calibration function with the best coefficient of determination and mean error of prediction was chosen, although different frequency ranges and preprocessings of spectra were used. Table 2 shows the parameters for calibration for all mixtures.

All calibration models were proven for their robustness by comparison of the values of the coefficient of determination and the mean error of prediction for cross validation and test-set validation. If there are nearly the same values for cross validation and test-set validation, the calibration model is robust [35]. The Maillard reaction and transition in tablets were determined quantitatively with the aid of the calibration model. The process of Maillard reaction and transition at different storage conditions is given in Figs. 4 and 6.

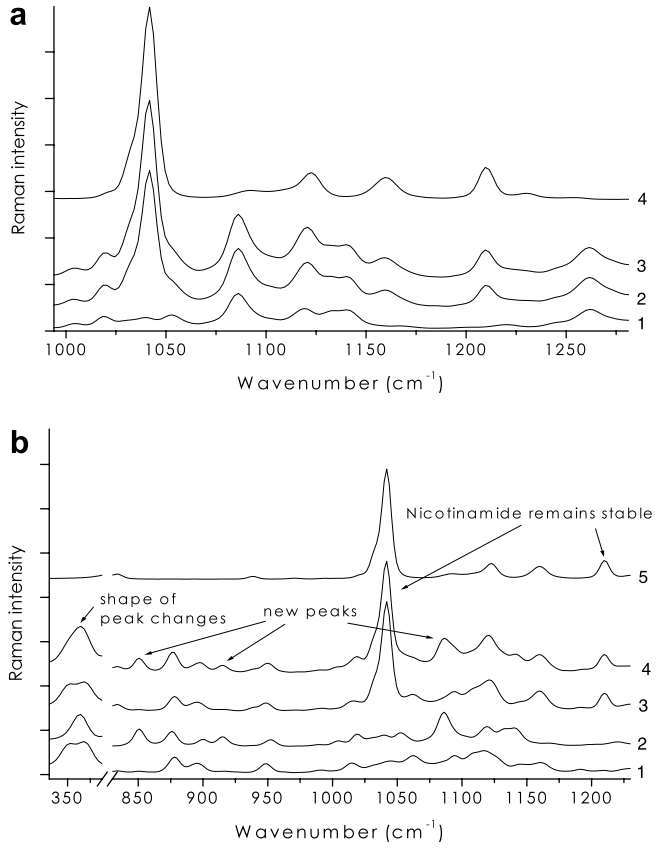

Fig. 2. Spectra of tablets of Nicotinamide (Nico) and (a) spray-dried lactose (LPSD) with (1) LPSD, (2) NicoSD after tableting, (3) NicoSD after storage, and (4) Nico, or (b) anhydrous lactose (LPAH) with (1) LPAH, (2) LPSD, (3) NicoAH after tableting, (4) NicoSD after storage, and (5) Nico.

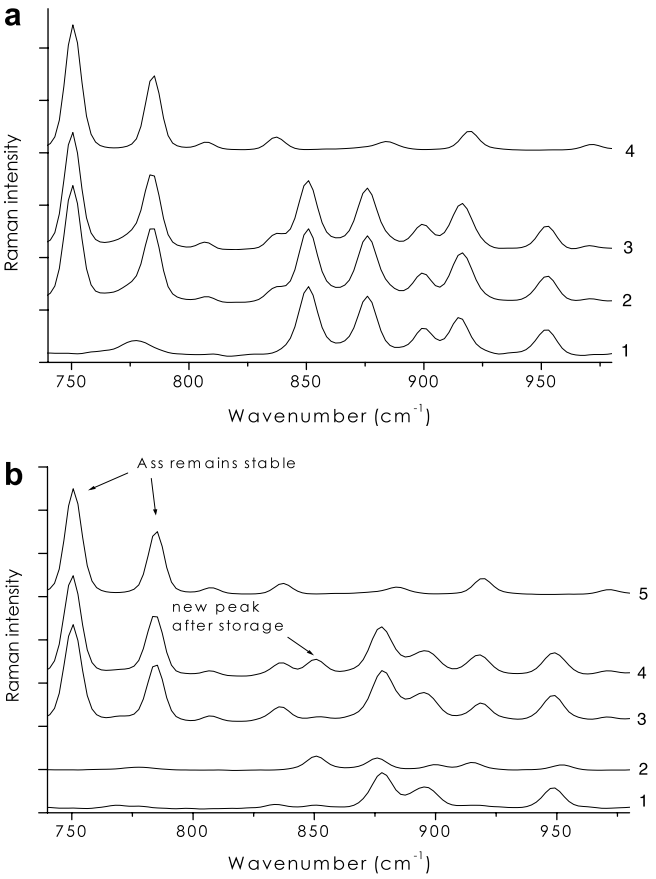

Fig. 3. Spectra of tablets of Acetylsalicylic acid (Ass) and (a) spray-dried lactose (LPSD) with (1) LPSD, (2) AssSD after tableting, (3) AssSD after storage, and (4) Ass, or (b) anhydrous lactose (LPAH) with (1) LPAH, (2) LPSD, (3) AssAH after tableting, (4) AssSD after storage, and (5) Ass.

Table 2
Calibration parameters of all mixtures

Mixture	Frequency ranges [cm^{-1}]	Preprocessing of spectra	Validation method	Coefficient of determination R^2	Mean error of prediction
ThiaSD	656–760	First derivation and vector normalization	Cross validation	99.12	3.02
ThiaAH	538–759	Vector normalization	Cross validation	99.12	3.00
NicoSD	*[a]				
NicoAH	826–957 2869–2991	Vector normalization	Cross validation	96.16	6.19
AssSD	*[a]				
AssAH	743–957	Vector normalization	Cross validation	98.56	3.81

[a] No calibration function was created, because there were no changes in spectra.

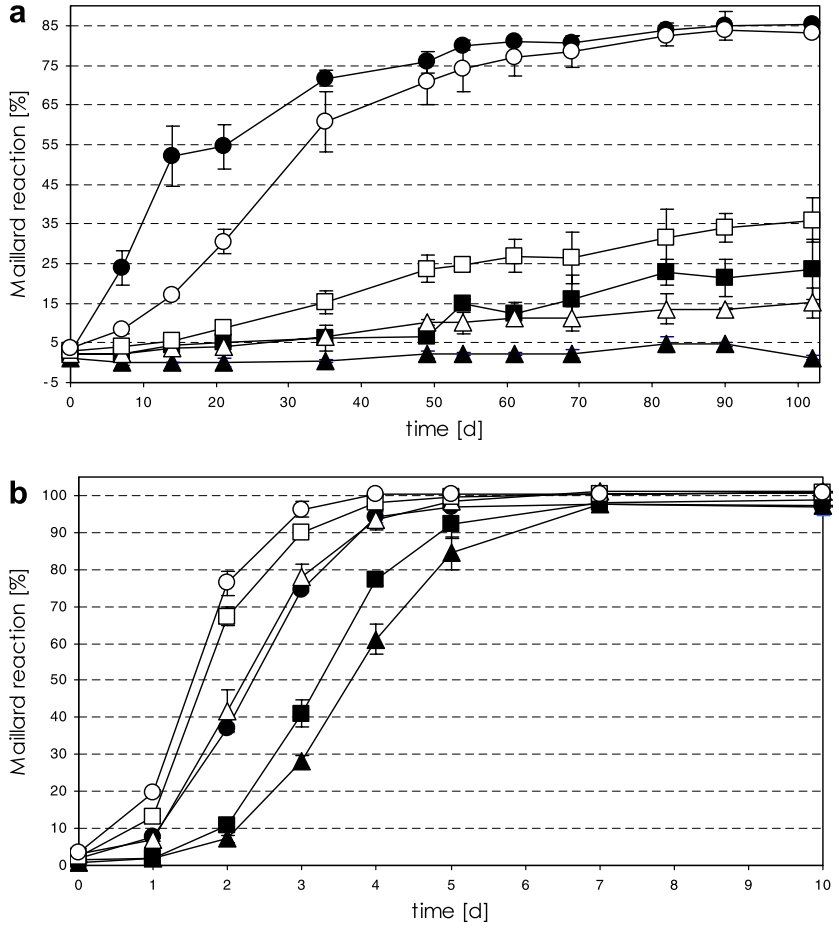

Fig. 4. Process of Maillard reaction (a) at stability test conditions (30 °C and 60% RH) and (b) at accelerated conditions (40 °C and 75% RH) for Thiaminchloride hydrochloride with spray-dried lactose (closed symbols) and anhydrous lactose (open symbols) at different $\rho_{rel,max}$ ▲, 0.75; ■, 0.85; ●, 0.95.

Tablets were stored at normal conditions 112 days. At normal storage conditions (21 °C and 45% RH) the Maillard reaction occurred to a very low extent. Mixtures of Thiaminchloride hydrochloride with spray-dried lactose showed a maximum conversion of 2% and mixtures of Thiaminchloride hydrochloride with anhydrous lactose showed a maximum conversion of 4%. Tablets at stability test conditions (30 °C and 60% RH) were stored for 102 days. The Maillard reaction was faster at these climate conditions than at normal storage conditions. The amount of conversion increased with increasing $\rho_{rel,max}$. The Maillard reaction needs some activation energy to get started. The pressure during tableting can serve as activation energy [38]. With increasing $\rho_{rel,max}$ the pressure during tableting increases and thus, the activation energy for the Maillard reaction increases also. An alternative explanation could be more contact surfaces between lactose and drug due to lower porosity in combination with higher absorption of

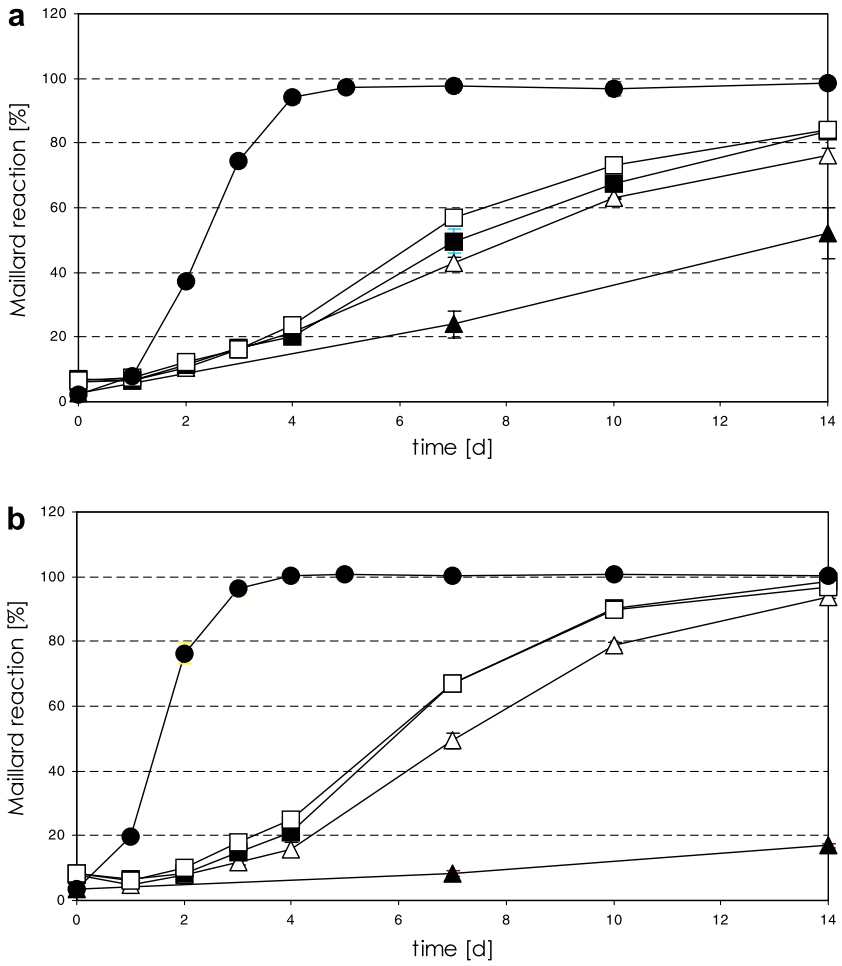

Fig. 5. Temperature dependent analysis of Maillard reaction of tablets of Thiaminchloride hydrochloride and (a) spray-dried lactose or (b) anhydrous lactose at ▲, 30 °C/60% RH; △, 36 °C/60% RH; ■, 38 °C/60% RH; □, 40 °C/60% RH; ●, 40 °C/75% RH (% total reaction).

capillary condensed water [39]. Both effects can be the reason for the increasing amount of conversion with increasing $\rho_{rel,max}$ (Fig. 4a).

The speed of the Maillard reaction increases strongly with increasing temperature and relative humidity. At stability test conditions the Maillard reaction is not completed after 102 days. In contrast the Maillard reaction needs only 7 days at accelerated conditions (40 °C and 75% RH) (Fig. 4b).

Fig. 4b shows a difference between the different $\rho_{rel,max}$ and a difference between the mixture with spray-dried lactose and anhydrous lactose. The Maillard reaction was faster with anhydrous lactose. A reason for this can be the higher hygroscopicity of anhydrous lactose [40]. Because of the higher hygroscopicity the reactive oxonium carbenium ion which is built from the lactose and which is needed for the Maillard reaction can be built more easily from anhydrous lactose. Since the Maillard reaction is dependent on temperature and humidity [34] the influence of temperature alone on the reaction is not clear. The temperature dependence was analyzed for tablets of $\rho_{rel,max}$ of 0.95 at a constant relative humidity RH of 60%. Fig. 5 shows the Maillard reaction at 30 ± 1, 36 ± 1, 38 ± 1 and 40 ± 1 °C at 60% RH compared to accelerated conditions (40 ± 1 °C and 75 ± 0.5% RH). The results exhibit that the Maillard reaction is faster at higher temperature, however relative humidity and relative humidity plus temperature, respectively, show a higher influence on reaction speed. This becomes visible by the enormous increase of reaction speed between stability test conditions (40 °C and 60% RH) and accelerated conditions (40 °C and 75% RH). At these high humidities capillary condensation as described by the GAB-model is strongly increased compared to normal conditions.

The transition of β-lactose anhydrate (anhydrous lactose) to α-lactose monohydrate was observed only at stability test conditions and accelerated conditions. Fig. 6 shows the process of transition for the mixtures containing anhydrous lactose with Nicotinamide and Acetylsalicylic acid, respectively.

It is visible that at the higher relative humidity the transition was faster because the transition of β-lactose anhydrate (anhydrous lactose) to α-lactose monohydrate is humidity dependent. Furthermore the transition is not

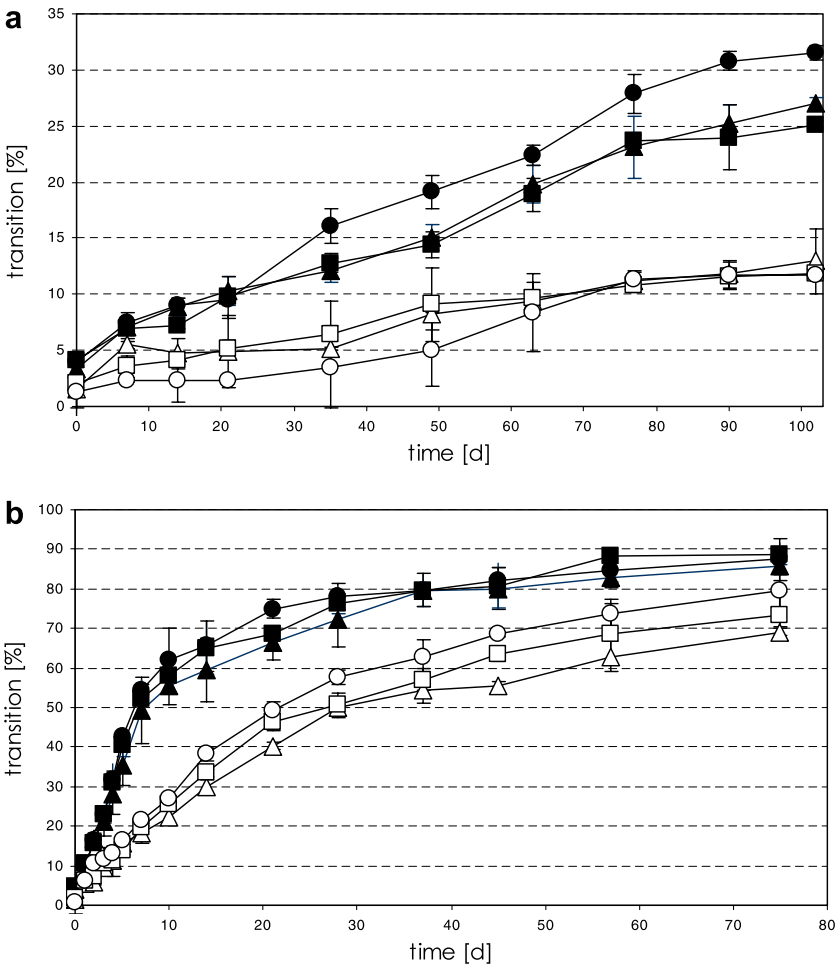

Fig. 6. Process of transition (a) at stability test conditions (30 °C and 60% RH) and (b) at accelerated conditions (40 °C and 75% RH) for Nicotinamide (closed symbols) and Acetylsalicylic acid (open symbols) at different $\rho_{rel,max}$ ▲, 0.75; ■, 0.85; ●, 0.95 of β-lactose anhydrate to α-lactose monohydrate.

dependent on $\rho_{rel,max}$ of the tablets, as visible in Fig. 6. The transition in tablets containing Nicotinamide was faster than in tablets containing Acetylsalicylic acid. A reason for this can be the higher hygroscopicity of Acetylsalicylic acid which protects the lactose against the moisture [41].

5. Conclusions

The interactions of the model drugs with both spray-dried lactose and anhydrous lactose were analyzed by FT-Raman spectroscopy. Maillard reaction was proved for mixtures of both lactoses with Thiaminchloride hydrochloride. The results indicate that the Maillard reaction needs activation energy and is dependent on both temperature and humidity. In mixtures of the lactoses with Nicotinamide and Acetylsalicylic acid a transition of β-lactose anhydrate (anhydrous lactose) to α-lactose monohydrate was proven. The transition is only dependent on humidity. Astonishingly, the moisture sensitive drug Acetylsalicylic acid stayed stable even during storage at 75% RH indicating that the mobile water of lactose monohydrate (spray-dried lactose) had no influence on the stability of Acetylsalicylic acid.

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