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Impact of process variables on the micromeritic and physicochemical properties of spray dried microparticles- Part II. Physicochemical characterisation of spray dried materials.

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Abstract

In this work we investigated the residual organic solvent content and physicochemical properties of spray dried chlorothiazide sodium (CTZNa) and potassium (CTZK) salts. The powders were characterised by thermal, X-ray diffraction, infrared and dynamic vapour sorption (DVS) analyses. Solvent levels were investigated by Karl-Fischer titration and gas chromatography.

Spray drying from water, methanol (MeOH) and mixes of methanol and butyl acetate (BA) resulted in amorphous microparticles. The glass transition temperatures of CTZNa and CTZK were ~192 °C and ~159 °C respectively. These materials retained their amorphous nature when stored at 25 °C in dry conditions for at least 6 months with no chemical decomposition observed. DVS determined critical relative humidity of recrystallisation of CTZNa and CTZK to be 57% RH and 58% RH, respectively.

Inlet temperature dependant oxidation of MeOH to formaldehyde was observed; the formaldehyde was seen to deposit within the amorphous matrix of spray dried product. Spray drying in the open blowing mode coupled with secondary drying resulted in a three-fold reduction in residual BA (below pharmacopoeial permitted daily exposure limit) compared to spray drying in the closed mode. Experiments showed recirculation of recovered drying gas increases the risk of deposition of residual solvents in the spray dried product.

Keywords: spray drying, amorphous, organic solvent, oxidation, critical relative humidity, recrystallisation, residual solvent level, secondary drying, permitted daily exposure.

1. Introduction

Spray drying is a technique whereby solid particles are formed by atomisation of a liquid feed and evaporation of the solvent from the resulting droplets by suspending them in a hot gas. It is a one step, continuous process with a high degree of reproducibility, which makes spray drying a unique and important unit operation used in pharmaceutical technology¹. Spray drying often results in the production of amorphous or partially amorphous phases². To assess the degree of amorphisation and characterise amorphous phases of the product, powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) are in common use³. As amorphous materials, due to their molecular structure tend to retain solvent/water vapours, residual solvent or moisture content may be assessed quantitatively by the use of thermogravimetric analysis (TGA) and quantitative analysis of water (moisture) content often involves application of Karl-Fischer titrimetry. Appropriate methods to assess chemical integrity of the compound post spray drying include e.g. infrared spectroscopy⁴.

The use of organic solvents in spray drying has increased considerably due to the fact that this process is utilised commercially to process active pharmaceutical ingredients (APIs) that are poorly soluble in water, an approach aimed to improve the apparent solubility of drugs⁵. The use of organic solvents may have serious regulatory implications regarding the residual solvent contents and physicochemical stability of processed APIs, as it is known that amorphous materials tend to retain more residual solvents due to their disordered nature compared to crystalline non-solvated substances, where only surface adsorption is possible^{6, 7}. It is known that amorphous phases due to the high Gibbs free energy are thermodynamically unstable and prone to crystallisation. The main factors affecting stability of an amorphous form are temperature⁸ and the presence of residual solvent or atmospheric moisture⁹. Solvent content in amorphous materials is relevant in estimation of their physical stability as the glass transition temperature (T_g) of such materials can be sufficiently decreased to cause spontaneous nucleation at the storage temperature due to high

plasticization effects of solvents¹⁰. Therefore to ensure a low residual solvent content in spray dried materials, secondary drying processes may be employed to decrease the solvent level to the required limits either to fulfil the regulatory obligations or to ensure adequate physical stability.

Residual solvent content in a spray drying process is determined by the heat and mass balance depending on the configuration and size of the instrument, process parameters and liquid formulation characteristics. One of the key process parameters controlling the levels of residual solvent is the relative saturation of the solvent at spray dryer outlet conditions, which depends on the molecular weights of the solvent and gas, the absolute pressure in the spray dryer chamber and the equilibrium vapour pressure of the spray solvent evaluated at the outlet temperature¹¹. Additionally, for spray dryers operating in a closed (recycle) mode, the relative solvent vapour saturation at the inlet of the dryer must also be considered¹¹. In a well designed spray drying process the minimum outlet temperature is determined by both the T_g of the formulation and the relative solvent saturation at the outlet, as insufficient drying may result in material build-up on the inner walls of the instrument and on the other hand the outlet temperature should be kept below T_g¹².

Recently, a method to test physical stability of an amorphous form in isothermal conditions of changing atmospheric humidity dynamic by vapour sorption (DVS) was developed. It measures the onset relative humidity for a glass transition and crystallization processes in amorphous or partially amorphous materials, a useful parameter describing stability of solid state forms⁹

Despite a number of theoretical studies on evaporation in spray drying very little experimental data has been published on the residual solvent levels in spray dried APIs^{6, 13}. This report therefore aims at investigating the solid-state physicochemical transformations of two model hydrophilic compounds, chlorothiazide sodium (CTZNa)¹⁴ and potassium (CTZK)¹⁵ upon spray drying and their subsequent characterisation in terms of residual solvent content and physical

stability. The micromeritic characterisation of CTZK and CTZNa spray dried from water, methanol (MeOH) and MeOH/ butyl acetate (BA) mixtures was described in Part I of this paper¹⁶.

2. Materials and methods

2.1. Materials

Materials used in experiments were chlorothiazide (CTZ), potassium bromide (KBr, FT-IR grade) and PurpaldTM (Sigma Ireland), sodium hydroxide (NaOH, Riedel de Haën Germany), potassium hydroxide (KOH, Merck Germany). Solvents and other reagents: deionised water (Purite Prestige Analyst HP, Purite Limited, UK), ethanol (Corcoran Chemicals, Ireland), methanol (MeOH) (Sigma, Ireland), n-propanol and ethyl acetate (Lab Scan, Ireland), butyl acetate (BA) (Merck, Germany), Hydranal-Composite and hydrochloric acid 32% (Riedel de Haën, Germany), Apollo Scientific Limited, UK), acetonitrile (Fischer Scientific, Ireland), sodium dihydrogen phosphate (Sigma-Aldrich, Ireland) and phosphorus pentoxide desiccant (Fluka, Ireland).

2.2. Methods

2.2.1. Salts preparation and spray drying

Chlorothiazide sodium (CTZNa DH) and potassium (CTZK DH) dihydrate and anhydrous CTZNa were obtained as described before^{14, 15}. Production of anhydrous CTZK and the complete range of spray drying and additional drying (AD) conditions were reported in Part I of this paper¹⁶.

Figure 1 illustrates the nitrogen flow upon spray drying in closed and open mode.

Part II is focused on characterisation of samples listed in Table 1.

2.2.3. Physicochemical characterisation

Differential scanning calorimetry (DSC) and thermogravimetric (TGA) analyses were performed using a Mettler Toledo DSC 821^e and Mettler TG 50 module. Three measurements were carried out in vented aluminium pans, at a heating/cooling rate of 10 °C/min, under nitrogen purge¹⁵. A PerkinElmer (USA), Diamond DSC unit with HyperDSC was implemented to modulated

temperature DSC analysis (StepScanTM)¹⁷. Samples placed in vented aluminium pans were heated at 5°C/min and 2 °C steps. Between each of the dynamic steps a 1 minute isothermal step was applied. The area algorithm was applied to calculate the specific heat of glass transition from the enthalpy flow. A baseline run was performed for each sample to minimise sample holder mass error. Presented results are the average of triplicate analyses. To perform Karl-Fischer analysis 0.5 g of CTZNa or CTZK sample (n=3) was dissolved in pre-titrated 50 ml of methanol. As Karl-Fischer reaction is not stoichiometric in alkaline solutions (Scholz, 1987), the pH was adjusted with 50 µl of 32% hydrochloric acid. Metrohm 841 Titrando was used for titration and the unit was calibrated with 20 µl of water. The results were averaged. Infrared spectra were recorded in duplicate on a Nicolet Magna IR 560 E.S.P. spectrophotometer equipped with MCT/A detector. A spectral range of 650-4000 cm⁻¹, resolution 2 cm⁻¹ and accumulation of 64 scans were used. A KBr disk method was used with a 0.5-1% sample loading. KBr disks were prepared by direct compression under 8 bar pressure for 1 minute (Healy et al., 2008). The sample preparation did not affect the spectra as confirmed with an attenuated total reflectance (ATR) spectrometer Perkin Elmer Spectrum One (data not shown). Powder XRD (PXRD) analysis was conducted as described in part one of this manuscript¹⁶.

2.2.4. Dynamic vapour sorption (DVS)

Vapour sorption experiments were performed on a DVS Advantage-1 automated gravimetric vapour sorption analyzer (Surface Measurement Systems Ltd., London, UK). The DVS-1 measures the uptake and loss of water vapour gravimetrically with a mass resolution of ± 0.1 µg. The temperature was maintained constant at 25.0 ± 0.1°C. A mass of around 10 mg of amorphous powder was loaded into a sample net basket and placed in the system. The samples were equilibrated at 0% of relative humidity (RH) until a dry, reference mass was recorded. The samples were exposed to the sorption programmes ranging from 0 to 90% RH at the following %RH rate

changes: 2.5% RH per hour (2.5 Δ RH%/h), 5% RH per hour (5 Δ RH%/h) and 10% RH per hour (10 Δ RH%/h). An isotherm was calculated from the complete sorption profile¹⁴. The amount of sorbed water was expressed as a percentage of the dry mass. Recrystallisation of the material was indicated by the points of inflection. %RH of recrystallisation were then plotted versus Δ RH%/h and linearly extrapolated to 0 Δ RH%/h⁹. Presented values are the average of three measurements.

2.2.5. Aldehyde detection

Purpald[®] (4-amino-3-hydrazino-5-mercapto-1,2,4-triazole) was used as a reagent for the selective detection of aldehydes¹⁸. A 10 mg of powder (n=2) was added to approximately 20 mg of Purpald[®] dissolved in 2 ml of 1M NaOH. The mixture was aerated and the colour noted after a few minutes. The change of colour from yellow to purple indicates the presence of aldehyde in the tested solution. The samples were compared against a reference solution containing dissolved Purpald reagent and CTZNa anhydrous material (negative control).

2.2.6. Stability studies

Amorphous, spray dried samples of CTZNa (#1) and CTZK (#2) were subjected to stability studies in desiccated conditions over phosphorus pentoxide at 25 °C in a Gallencamp economy incubator with fan, size 1 (Weiss-Gallencamp, UK). Samples were characterised on monthly basis using PXRD, DSC and HPLC assay.

2.2.7. High pressure liquid chromatography (HPLC)

Chemical stability of CTZNa and CTZK was determined with high pressure liquid chromatography (HPLC)¹⁹. The HPLC system used was a Shimadzu HPLC Class VP series with a LC-10AT VP pump, autosampler SIL-10AD VP and SCL-10AVP system controller. The mobile phase was filtered through a 0.45 μ m membrane filter (Gelman Supor-450, USA). The analytical column used

was a Waters SpherisorbTM ODS2 column (250 mm length, internal diameter 4.6 mm, particle size 5 μ m). UV detection was carried out at a wavelength of 260 nm and the injection volume was 10 μ l. Separation of degradation products was carried out isocratically at ambient temperatures with a flow rate of 1 ml/min. The mobile phase consisted of 0.1M NaH₂PO₄ phosphate buffer/acetonitrile 10:1 (v/v) brought to the pH of 3.0 \pm 0.1 with phosphoric acid. Under these conditions the retention times of chlorothiazide (CTZ) and the main degradation product of CTZ were \sim 12 and \sim 10 min, respectively. Presented values are the average of three measurements.

2.2.8. Gas chromatography with flame ionisation detector GC-FID

A GC-FID PerkinElmer Clarus 500 with auto sampler and Supelco SPB-GC column (60 m x 0.25 mm x 0.5 μ m, 35% phenyl 65% dimethyl polysiloxane filling) were used to detect the residual content of MeOH and BA²⁰ in the spray dried CTZNa and CTZK. Helium at 8 psi pressure was used as a carrier gas. The oven temperature was 50 °C and the detector temperature was set to 325 °C. Both solvents were assayed based on individual calibration curves with internal standards included (ethyl acetate for BA and n-propanol for MeOH). The injection volume was 1.0 μ l and the retention times were as follows: MeOH: 3 min 57 s, n-propanol: 4 min 34 s, BA: 12 min 50 s and ethyl acetate: 5 min 00 s of the total of 20 min method length. Samples were prepared by dissolving between 100 mg and 500 mg of the tested powder in 10 ml of water, depending on the expected residual solvent content. Solubility of BA and ethyl acetate was reported to be 0.7 g/100 ml and 8.3 g/100 ml, respectively²¹, and are well above the expected concentrations of the solvents in water. Presented values are the average of three measurements.

2.2.9. Statistical analysis

Statistical analysis for the specific surface area (n=3), median particle size (n=3) and true density (n=3) data was carried out using the Minitab software. The Kruskal-Wallis test was carried

out at a significance level of 0.05, with a p-value of less than 0.05 indicating that the observed difference between the means was statistically significant.

3. Results and discussion

3.1. Physicochemical properties of spray dried samples.

CTZNa and CTZK samples after spray drying regardless of solvent used were PXRD amorphous, Fig.1. The results of thermal analyses: DSC and TGA (Fig. 2 and 3) indicated the presence of residual solvents in spray dried materials. DSC confirmed that spray dried CTZNa was amorphous. StepScanTM analysis detected that the Tg of amorphous CTZNa was 191.8 ± 0.5 °C (change of the specific heat at the Tg (ΔC_p) 0.21 ± 0.04 J/g). DSC analysis of spray dried CTZK (#2) confirmed the Tg of the material to be at 159.0 ± 0.4 °C (ΔC_p 0.23 ± 0.06 J/g).

FTIR spectra of CTZNa dihydrate (Fig. 4a), CTZNa anhydrous (Fig. 4b) and the amorphous material spray dried from water (#1) did not show significant changes in the fingerprint region except for smoothing and slight broadening of peaks of the amorphous material. Similar changes were observed for the hydrated and anhydrous CTZK (Fig. 5a, b) as well as the amorphous material spray dried from water (#2).

Considering previous studies on crystal forms of CTZNa¹⁴ and CTZK¹⁵, the production of amorphous forms of CTZNa and CTZK salts on spray drying can be ascribed to two factors. The first aspect is related to the fast, highly-energetic process of solvent evaporation in spray drying. The evaporation is fast enough to prevent crystal nucleation after the concentration of solid in drying droplets reaches supersaturation. Spray drying was previously reported as an effective method for the production of amorphous drugs². The second aspect is related to the hydrated nature of both solids^{14, 15}. CTZNa and CTZK need molecules of a solvent (water or ethanol) in order to develop the crystal lattice. Due to the rapid solvent evaporation or excluding water from the system

using alternative solvents and/or anhydrous salt forms during spray drying, the contact of water with the precipitating API is strongly limited.

3.2. Physicochemical stability of spray dried samples

The amorphous nature of materials (by DSC and XRD) and chemical stability (by HPLC) was maintained for at least 6 months under the conditions of the stability studies (data not shown).

Dynamic vapour sorption studies (Fig. 6) were performed to assess the physical stability of the amorphous salts compared to the stability of the previously reported crystalline forms^{14, 15}. The critical relative humidity of recrystallisation ($RH_{\text{cryst } 0}$) of the amorphous materials in isothermal conditions at 25 °C was determined. The $RH_{\text{cryst } 0}$ describes the limit of the highest environmental humidity, below which an amorphous material will not recrystallise under storage or processing conditions⁹. The $RH_{\text{cryst } 0}$ for CTZNa was determined to be 56.6% RH ($R^2= 0.997$) and for CTZK the value was established to be 58.2% RH ($R^2= 0.999$). As the method used was time limited, resulting in no time for sample mass equilibration at a particular humidity, consequently water uptake was incomplete at the given conditions, as $\Delta m/\Delta t$ was greater than 0.002 mg/h at each measured time point. The experiment was therefore repeated under time independent conditions, i.e. waiting every 10% RH in the 0-90% RH range until sample mass had reached a mass equilibrium and water sorption was complete ($\Delta m/\Delta t \leq 0.002$ mg/h with the initial sample mass m_0 of 10 mg). This resulted in recrystallisation (represented as an inflection in the graph) of CTZNa in the range of 40-50% RH, earlier than determined by the time dependent method. For CTZK the inflection was not recorded, indicating perhaps that the water sorption event overlapped with recrystallisation. These results show that recrystallisation of an amorphous material is not only related to the rate of RH% changes over time but also to the time of equilibration of the material under given RH conditions.

3.3. Residual solvent content

3.3.1. Residual methanol, butyl acetate and water

Assessment of the residual solvent content by GC-FID and KF was performed for the samples presenting the largest specific surface area (T_{BET}) at given feed concentration and drying mode¹⁶. The results showed that the CTZNa (#12) and CTZK (#18) powders collected after spray drying in the closed mode from 2% w/v solutions contained $1.27 \pm 0.05\%$ w/w MeOH and $4.98 \pm 0.81\%$ w/w BA and $0.85 \pm 0.08\%$ w/w MeOH and $4.55 \pm 0.55\%$ w/w BA, respectively. Spray drying of the equivalent systems (CTZNa #19, CTZK #20) in the open blowing mode reduced the level of MeOH in CTZNa and CTZK to a concentration below the detection level (for CTZNa: $0.19 \pm 0.02\%$ w/w and for CTZK: $0.19 \pm 0.01\%$ w/w) and of BA to $2.4 \pm 0.1\%$ w/w and $1.9 \pm 0.3\%$ w/w, respectively. A further reduction in the organic solvent content in the spray dried batches was obtained by additional drying. The final contents of the organic solvents were as follows: MeOH was below the limit of detection and BA was 9200 ± 0 ppm and 10200 ± 1500 ppm for CTZNa (#19*) and CTZK (#20*), respectively. The limits of detection for BA were for CTZNa: 1900 ± 200 ppm and for CTZK: 1900 ± 100 ppm.

The European Pharmacopeia lists permitted daily exposures (PDE) of the residual organic solvents and the limit is 30 mg/day (or 3000 ppm) for MeOH and 50 mg/day (5000 ppm) for BA²⁰. Maximal daily dose of CTZ is 1500 mg which is equivalent to 1616.31 mg of anhydrous CTZNa or 1698.33 mg of anhydrous CTZK. Therefore the maximal daily exposure to BA for CTZNa is ~ 15 mg/day and for CTZK is ~ 17 mg/day and is for both salts approximately 3 times below the PDE.

The experiments showed that the open blowing mode was more efficient in reducing residual BA content and resulted in a 2-fold decrease in BA content compared to the closed configuration. The combination of the open blowing mode and secondary drying appeared to be the most efficient and resulted in a 3-fold reduction of the residual BA content in comparison to the sample spray dried in the closed mode.

KF titrimetry of the spray dried samples indicated that a lower residual water content was attained by processing in the closed mode (batches #12 and #18) compared to the open mode configuration (samples #19 and #20). The highest levels of residual water were measured after secondary drying (samples #19* and #20*) (Table 2). These results concur with the spray drying mode used as moisture levels are limited when operating in the closed mode due to the use of dehumidifier and dry nitrogen. Changing the configuration to the open mode increases the exposure to environmental humidity of air. This is even more marked with the additional drying process as the incubator uses air with relative humidity of 30 - 50%.

3.3.2 Solvent oxidation

The DSC scan (Fig. 2g) of sample #10 (spray dried from 100% MeOH in inlet temp. 100 °C) indicated three small endothermal events ($\sim 216.5\text{-}227.9$ °C, $\sim 230.3\text{-}239.8$ °C and $\sim 249.0\text{-}255.4$ °C) in the temperature range from 210 °C to 260 °C. This sample (Fig. 3g) displayed a two-stage mass loss of $6.6\pm 0.2\%$ and $22.2\pm 0.3\%$ by TGA. The DSC endotherms corresponded to the second mass loss recorded by TGA, most likely attributed to the solvent captured in the amorphous powder matrix. Additional drying of the material in the TGA instrument by heating up to 250 °C removed the captured solvent and DSC analysis of this additionally dried material (Fig. 2h) did not record the previously visible endotherms. This suggests that the changes in CTZNa observed by DSC were caused by a volatile substance and a high temperature was needed to remove this contaminant. FTIR spectrum of CTZNa freshly spray dried from MeOH clearly indicated the differences (Fig. 4e). A few absorption bands appeared at $2870\text{-}3000$ cm^{-1} suggesting the presence of CH aliphatic groups. A sharp and intense peak emerged at around 1740 cm^{-1} indicative of a compound with a C=O group and a weak band at $1050\text{-}1100$ cm^{-1} implied the existence of MeOH residues. FTIR of the CTZNa methanolic sample dried at 250 °C showed the absence of the extra absorption peaks.

As the sample was processed from 100% MeOH, it was considered that the captured MeOH was oxidised to methanal (formaldehyde) during spray drying and that this contaminant was captured in the CTZNa powder. In support of this theory are weak FTIR peaks at 2850-2870 cm^{-1} which can be assigned to aldehydic C-H stretching modes. The aldehyde test with Purpald[®] reagent confirmed the presence of an aldehyde in sample #10 and its disappearance after additional drying in the TGA instrument. TGA analysis allowed the molar ratio of CTZNa to formaldehyde in the adduct to be determined as 1:2. The $22.2 \pm 0.3\%$ mass loss recorded by TGA corresponded well with the theoretical content of 21.6% w/w of formaldehyde in sample #10. The exact mechanism of this phenomenon is not known, however it depends on the inlet temperature of the process as the material obtained at the inlet of 80 °C was identical with that spray dried from water i.e. had no traces of formaldehyde. It was further observed that formaldehyde evaporated within 72 hours when the sample was left at ambient conditions, thus the nature of the CTZNa/aldehyde adduct was metastable.

Studies on hydrolysis of benzothiadiazines^{22, 23} indicated a possibility of opening the heterocyclic ring of hydrochlorothiazide (HCTZ) with the release of formaldehyde, convertible to methanediol in an aqueous environment. Even though spray drying of sample #10 was not performed in an aqueous environment, the sample was tested for chemical decomposition. HPLC analyses showed no significant decomposition of CTZNa spray dried from MeOH ($p > 0.05$) in comparison to the starting material.

4. Conclusions

Spray drying was an effective method for producing amorphous powders of chlorothiazide sodium and potassium salts (CTZNa and CTZK). Thermal analyses confirmed T_g of CTZNa and CTZK to be ~192 °C and 159 °C, respectively.

Physical stability testing showed that these spray dried materials retained their amorphous character when stored at 25 °C in dry conditions for at least 6 months with no chemical decomposition observed. Dynamic vapour sorption experiments determined time dependent critical relative humidity of recrystallisation of CTZNa and CTZK to be 57% RH and 58% RH, respectively.

Inlet temperature dependant oxidation of MeOH to formaldehyde was observed, the formaldehyde was seen to deposit within the amorphous matrix of spray dried product. Levels of MeOH and BA were seen to decrease below pharmacopoeial permitted daily exposure limits when spray drying in the open blowing mode coupled with secondary drying was used. A three-fold reduction in residual BA in the open mode configuration compared to spray drying in the closed mode was achieved. Experiments showed recirculation of recovered drying gas increases the risk of deposition of residual non-aqueous solvents in the spray dried product.

Acknowledgements

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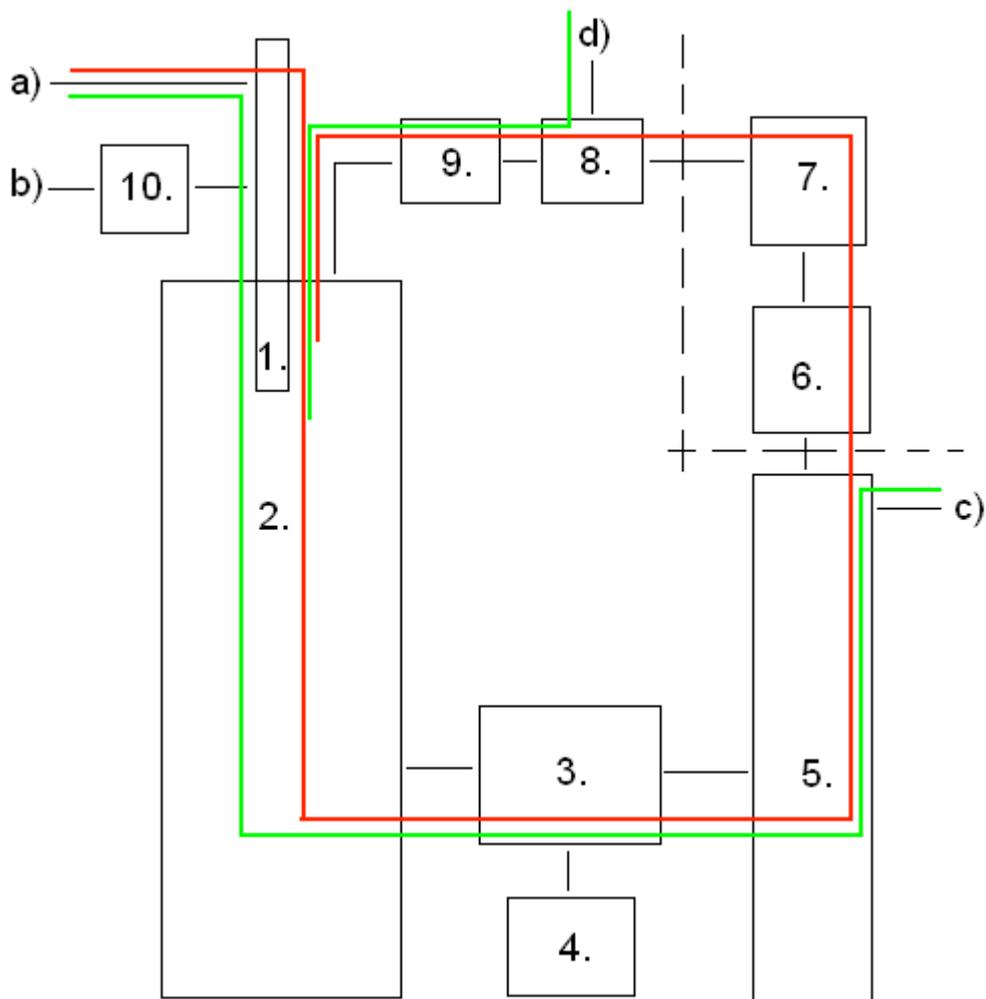


Fig. 1. Simplified scheme of gas flow in spray dryer. Green line- open blowing mode, red line- closed mode. 1. Nozzle, 2. Drying chamber, 3. Cyclone, 4. Collecting vessel, 5. Filter, 6. Inert Loop, 7. Dehumidifier, 8. Aspirator, 9. Heater, 10. Feed pump. a) Atomising gas supply (nitrogen) in open and closed mode, b) Feed supply, c) Gas exhaust in open mode, d) Drying gas (nitrogen) supply in open mode.

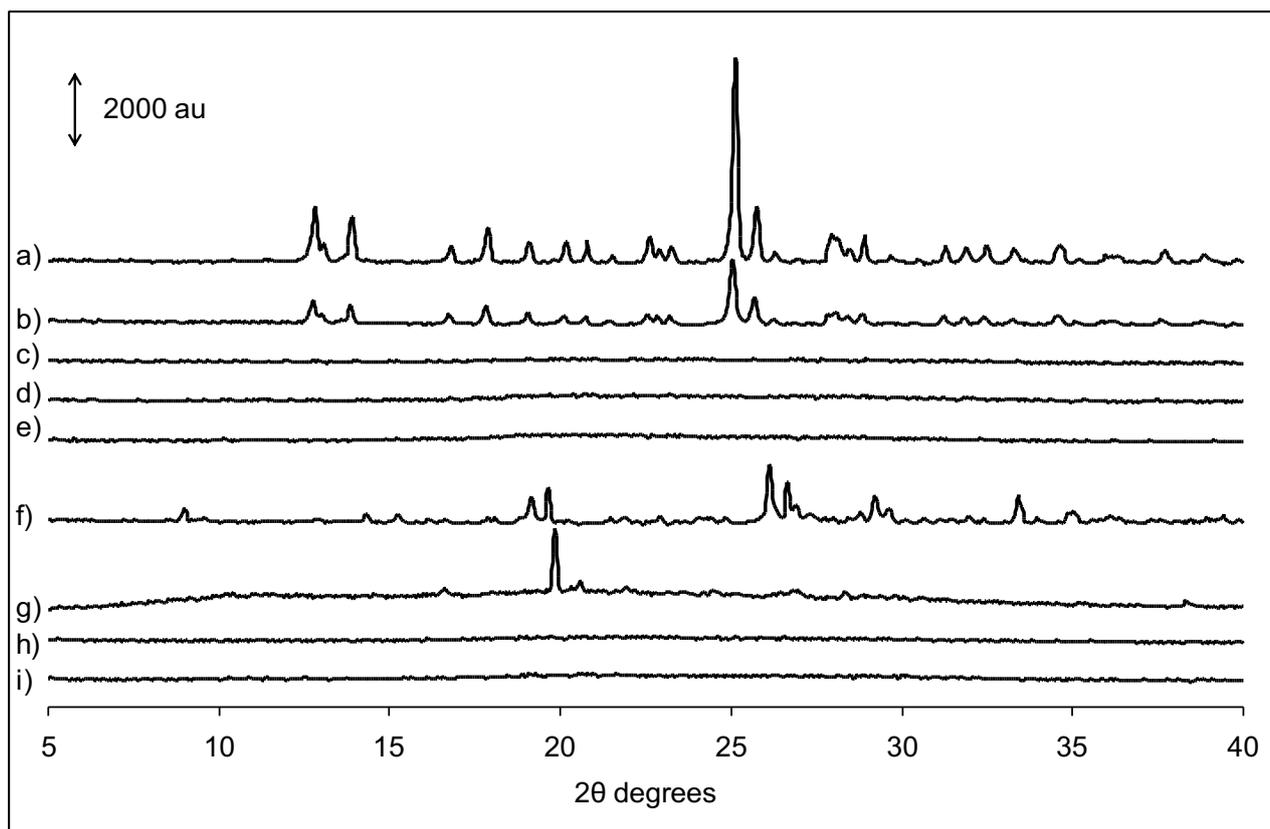


Fig. 1. PXRD patterns of: a) CTZNa dihydrate, b) CTZNa anhydrous, c) CTZNa spray dried from water (#1), d) CTZNa spray dried from MeOH/BA mixture (6:4 v/v solvent ratio) (#6), e) CTZNa spray dried from methanol (#10), f) CTZK dihydrate, g) CTZK anhydrous, h) CTZK spray dried from water (#2), i) CTZK spray dried from MeOH/BA mixture (6:4 v/v solvent ratio) (#11).

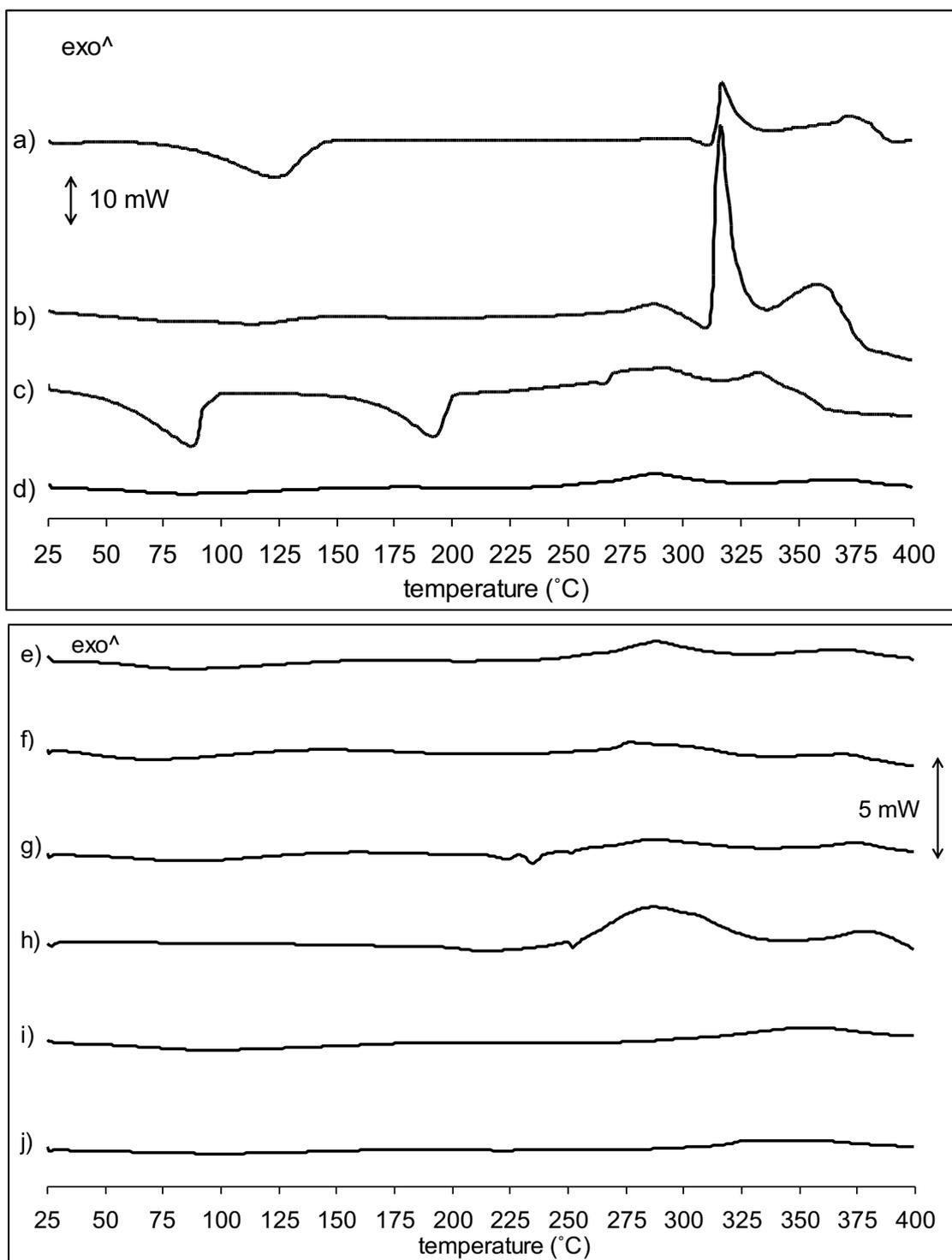


Fig. 2. DSC of: a) CTZNa dihydrate, b) CTZNa anhydrous, c) CTZK dihydrate, d) CTZK anhydrous, e) CTZNa (#1) spray dried from water, f) CTZNa (#6) spray dried (CM) from MeOH/BA (6:4 v/v solvent ratio), g) CTZNa spray dried from methanol (#10), h) CTZNa spray dried from methanol (#10) and dried (25-250-25 °C at 10 °C/min by TGA), i) CTZK spray dried from water (#2), j) CTZK spray dried (CM) from MeOH/BA (6:4 v/v solvent ratio) (#11).

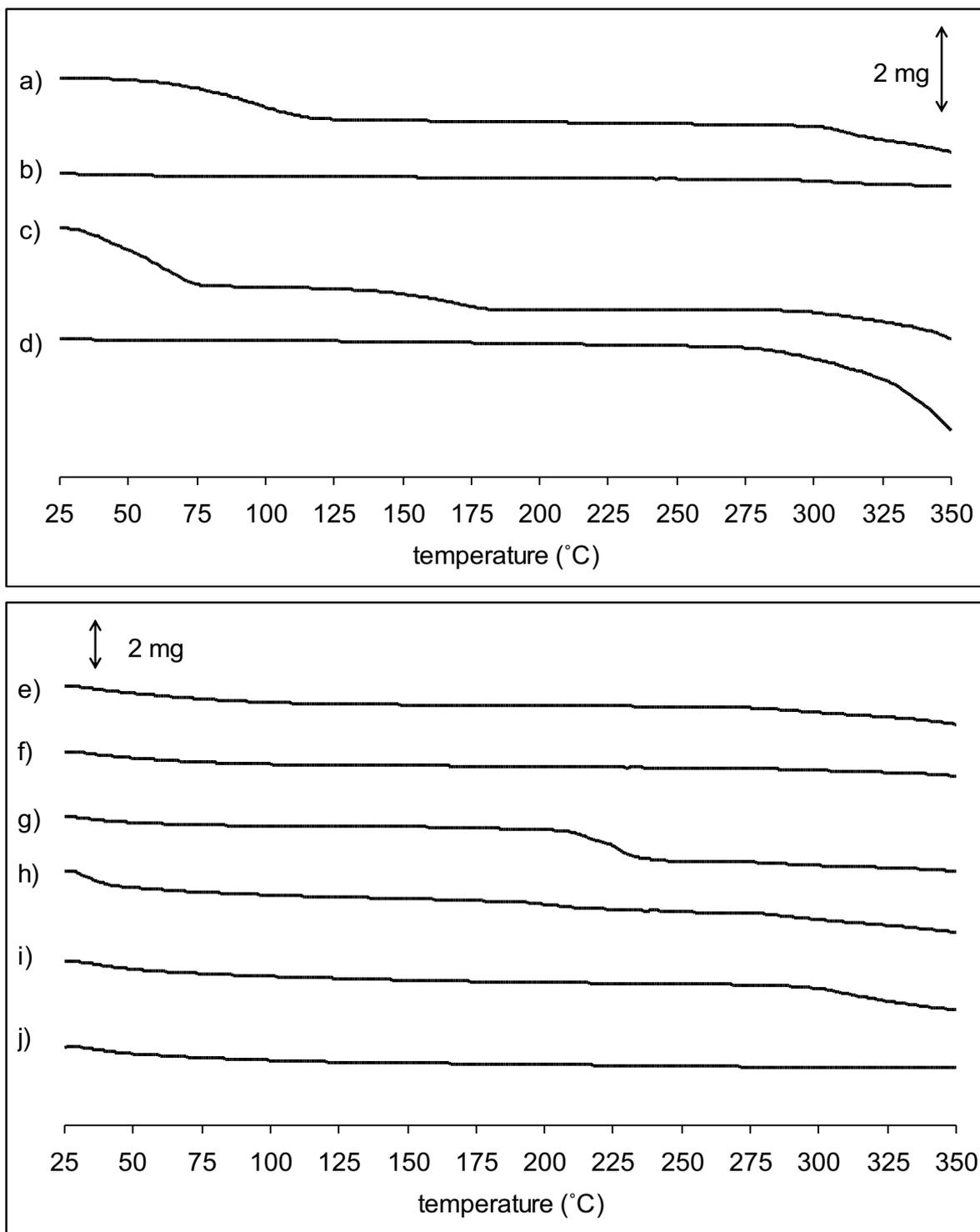


Fig. 3. TGA of: a) CTZNa dihydrate, b) CTZNa anhydrous, c) CTZK dihydrate, d) CTZK anhydrous, e) CTZNa (#1) spray dried from water, f) CTZNa (#6) spray dried from MeOH/BA (6:4 v/v solvent ratio), g) CTZNa (#10) spray dried from methanol, h) CTZNa (#10) spray dried from methanol, secondary dried (25-250-25 °C at 10 °C/min by TGA), i) CTZK (#2) spray dried from water, j) CTZK (#11) spray dried from MeOH/BA (6:4 v/v solvent ratio).

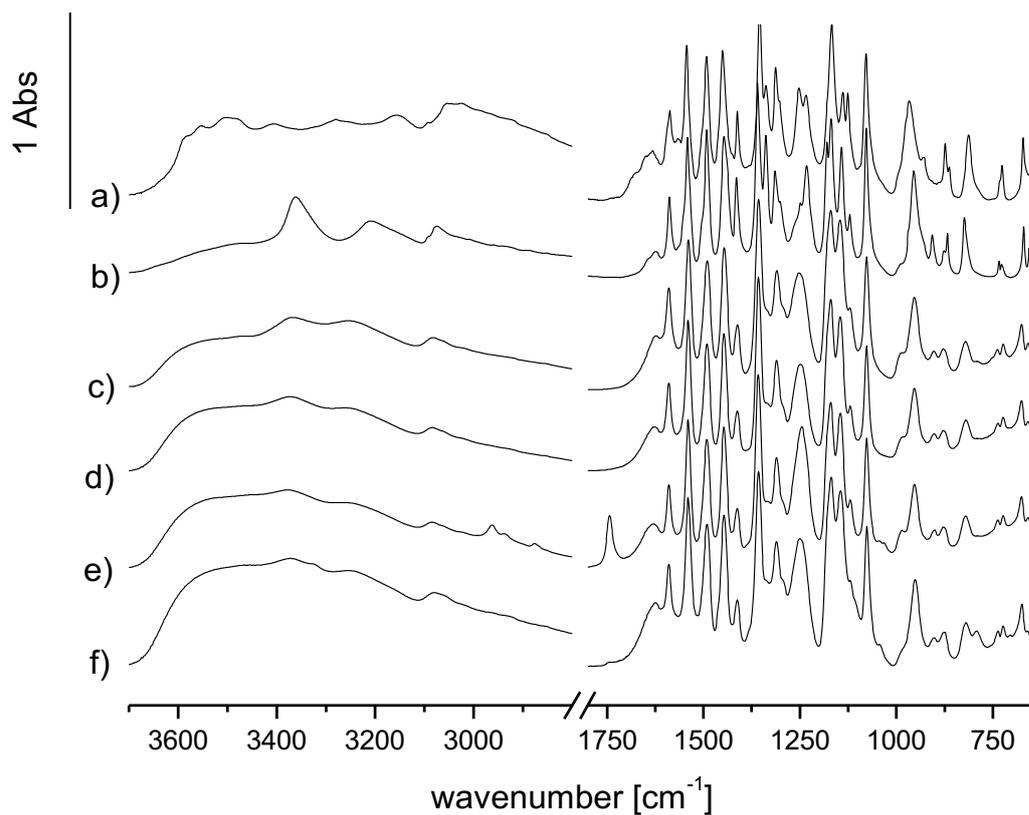


Fig. 4. FTIR spectra of CTZNa: a) dihydrate, b) anhydrous, c) spray dried from water (#1), d) spray dried from MeOH/BA (6:4 v/v solvent ratio) (#6), e) spray dried from methanol (#10), f) sample #10 after drying to 250 °C in the TG analyser.

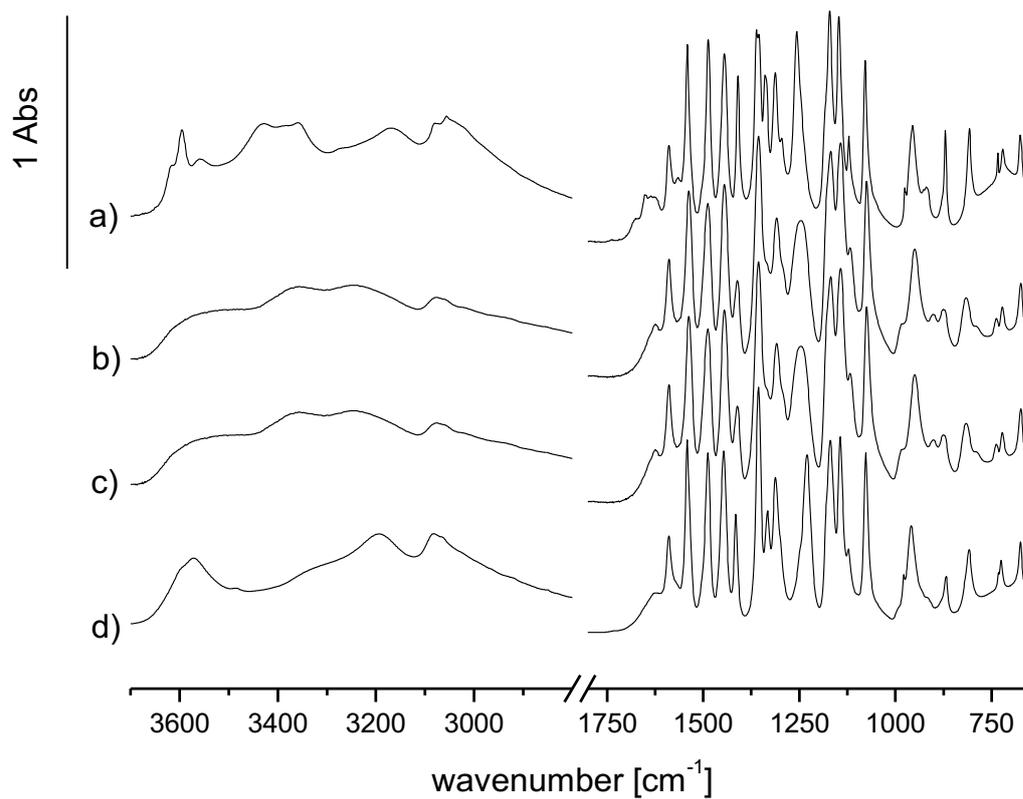
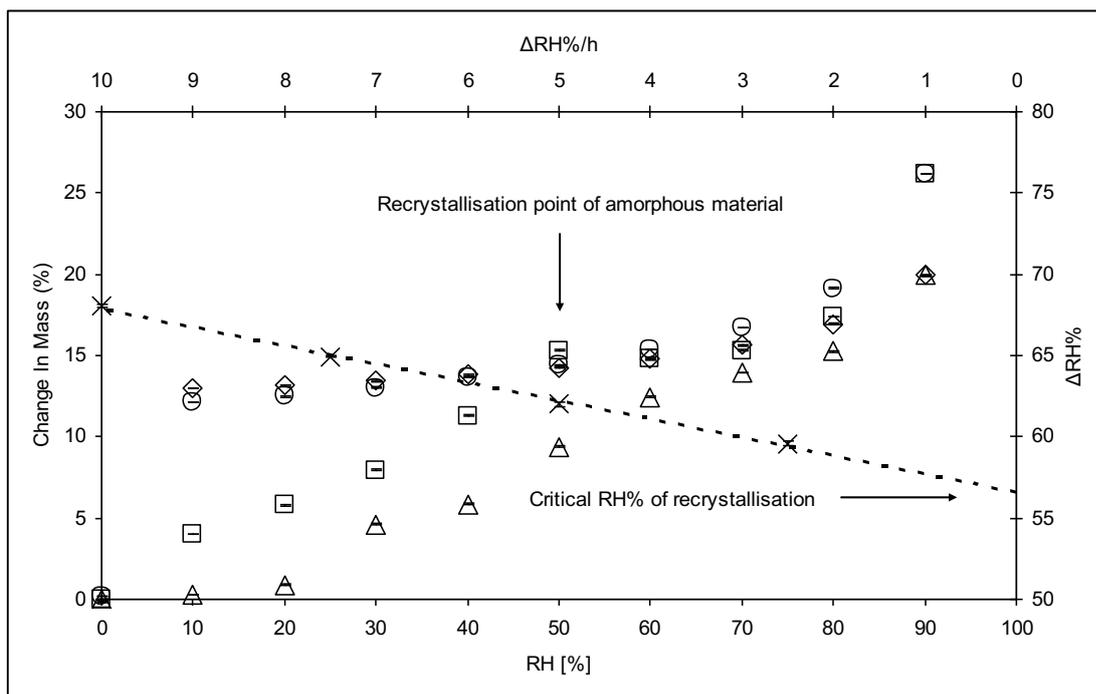
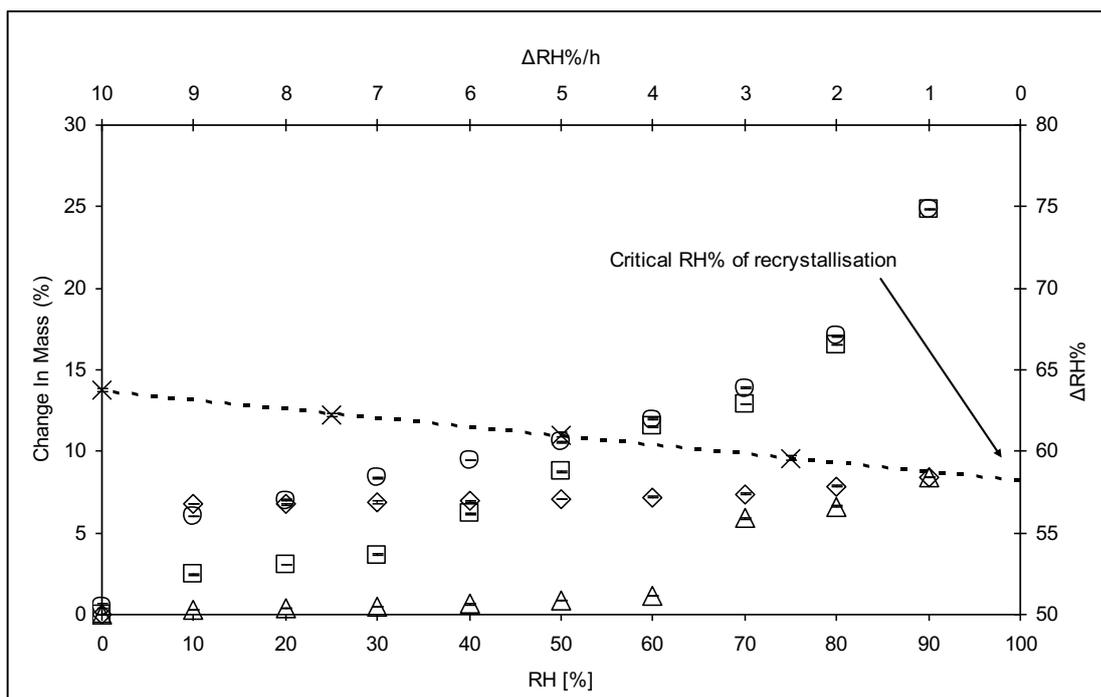


Fig. 5. FTIR spectra of CTZK: a) dihydrate, b) anhydrous, c) spray dried from water (#2), d) spray dried from MeOH/BA (3:2 v/v solvent ratio) (#9).



I



II

Fig. 6. DVS analysis of: I CTZNa, II CTZK, RH [%]- relative humidity, $\Delta RH\%$ -relative humidity of recrystallisation corresponding to $\Delta RH\%/h$ -rate of change of relative humidity per hour. The \diamond and Δ - crystalline material (anhydrous CTZNa and monohydrate of CTZK), the \circ and \square -amorphous material (#1, #2), the \square and Δ - sorption, the \circ and \diamond -desorption, dotted - $f(\Delta RH\%$ of recrystallisation) $\Delta RH\%$ /hour. Error bars correspond to standard deviations.

Table 1. Spray drying conditions for CTZNa and CTZK samples. C_{MeOH} is the concentration of methanol (MeOH) in the MeOH/butyl acetate (BA) solvent mixture. Sample numbers are consistent with Part I of this paper¹⁶.

Sample (No #)	Solvent system	C_{MeOH} (%v/v)	Feed conc. (% w/v)	Inlet temp (°C)	Outlet temp (°C)	Mode*
#1. CTZNa	Water	-	2.0	160	99	OM-S
#2. CTZK	Water	-	2.0	160	101	OM-S
#6. CTZNa	MeOH/BA	60	0.5	120	98	CM
#9. CTZNa	MeOH/BA	90	0.5	120	99	CM
#10. CTZNa	MeOH	100	0.5	80,100	75,87	CM
#11. CTZK	MeOH/BA	60	0.5	120	97	CM
#12. CTZNa	MeOH/BA	30	2.0	120	98	CM
#18. CTZK	MeOH/BA	30	2.0	120	98	CM
#19. CTZNa	MeOH/BA	30	2.0	120	99	OM-B
#20. CTZK	MeOH/BA	30	2.0	120	99	OM-B

* OM-S – open, suction mode, OM-B – open, blowing mode, CM- closed mode.

Table 2. Residual solvent content of the samples with the largest specific surface area (T_{BET}) at given feed concentration¹⁶.

Sample	TGA mass loss	BA content by GC-FID [%]	MeOH content by GC-FID [%]	Water content by KF [%]
#12	8.6±0.4	4.98±0.81	1.27±0.05	2.81±0.18
#19	7.6±0.2	2.4±0.10	<0.19±0.02	4.00±0.19
#19* after AD	6.4±0.3	0.92±0.00	<0.19±0.02	5.15±0.11
#18	8.0±0.4	4.55±0.55	0.85±0.08	3.50±0.08
#20	7.1±0.2	1.9±0.30	<0.19±0.01	4.46±0.07
#20* after AD	6.5±0.3	1.02±0.15	<0.19±0.01	5.21±0.17