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Microwave-induced *in situ* drug amorphization using a mixture of polyethylene glycol and polyvinylpyrrolidone

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Abstract

The use of a mixture of polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) was investigated for microwave-induced *in situ* amorphization of celecoxib (CCX) inside compacts. Such amorphization requires the presence of a dipolar excipient in the formulation to ensure heating of the compact by absorption of the microwaves. Previously, the hygroscopic nature of PVP was exploited for this purpose. By exposing PVP-based compacts for set time intervals at defined relative humidity, controlled water sorption into the compacts was achieved. In the present study, PEG was proposed as the microwave absorbing excipient instead of water, to avoid the water sorption step. However, it was found that PEG alone melted upon exposure to microwave radiation and caused the compact to deform. Furthermore, CCX was found to recrystallize upon cooling in PEG-based formulations. Hence, a mixture of PEG and PVP was used, where the presence of PVP preserved the physical shape of the compact, and the physical state of the amorphous solid dispersion. To study the impact of the polymer mixture, different compact compositions of CCX, PEG and PVP were prepared. When exposing the compacts to microwave radiation, it was found that the PEG:PVP ratio was critical for *in situ* amorphization and that complete amorphization was only achieved above a certain temperature threshold.

Keywords

In situ amorphization, microwave irradiation, polyethylene glycol, ternary phase diagram, drug loading, amorphous solid dispersion, transmission Raman spectroscopy.

1. Introduction:

The formation of the amorphous form of a drug is a promising approach to overcome a poor solubility and a slow dissolution rate, which is often associated with the crystalline state of a drug.[1,2] However, due to the thermodynamically instability of the amorphous from, recrystallization occurs over time[3] and hence, formulation approaches such as co-amorphization, loading onto mesoporous silica or formulation as an amorphous solid dispersion (ASD) are generally necessary to stabilize the amorphous form.[4-7] ASDs are mostly produced by solvent evaporation (e.g. spray-drying) or melt-quenching (e.g. hot-melt-extrusion) techniques.[6,8,9] In an ASD, the drug is molecularly dispersed in a polymeric carrier such as hydroxypropyl methylcellulose acetate succinate, polyvinylpyrrolidone (PVP) or polyethylene glycol (PEG).[9-12] ASDs are usually physically stable at relatively low drug loadings (up to ~20-30 wt%), however, the hygroscopicity of hydrophilic polymers can still cause phase separation and recrystallization at timescales within the shelf life of the drug product, as the sorption of water can lead to a mobility increase of the ASD.[3,4,6,13] Besides the shelf life stability problem, the manufacturing of an ASD can be difficult due to e.g. the poor flow properties of the ASD.[14] Furthermore, manufacturing of an ASD requires additional processing steps related to the formation of the ASD compared to direct compaction, i.e. higher costs are associated with the manufacturing.[14]

In situ amorphization is a recently introduced concept, which potentially can overcome the manufacturing and stability issues associated with ASDs.[15] Using *in situ* amorphization, the ASD is formed within the final dosage form, e.g. a compact, either as a final manufacturing step or immediately prior to administration.[16,17] The use of *in situ* amorphization allows for processing of a physical mixture, consisting of a crystalline drug and polymer, which enables the use of direct compaction. Presently, *in situ* amorphization has been described by: *(i)* immersion in water, *(ii)* heating using a convection oven and *(iii)* exposure to microwave radiation.[16-25] Of these approaches, only (*iii)* has successfully been utilized to prepare a completely amorphous ASD.[22,23,25] Recently, the preparation of completely amorphous ASDs after exposure to microwave radiation at 2.45 GHz was presented. Here, compacts containing physical mixtures of 30 wt% celecoxib (CCX) and PVP were stored under humid conditions to gain 20-30 wt% of sorbed water. The compacts were subsequently exposed to microwave radiation for 10 min to achieve a

completely amorphous ASD. In these compacts, the sorbed water acted as a plasticizer and enabling excipient absorbing the microwave radiation and producing heat.[22]

Microwaves range from the frequencies 0.03 GHz to 300 GHz of the electromagnetic spectrum,[26] with a typical household microwave operating at a fixed frequency of 2.45 GHz. During the exposure of a material to microwave radiation, the response of the material is determined by its dielectric properties, i.e. its ability to absorb microwave radiation.[27] Molecular dipoles couple to microwave radiation and heat is generated by their resulting oscillations[28], which means the approach is only limited suitable for thermolabile drugs, as high temperatures are reached during exposure to microwave radiation. Since many drugs and polymers, such as PVP, either have weak dipoles or not sufficient molecular mobility, their impact on the *in situ* amorphization is usually negligible.[29] Therefore, the addition of a suitable (enabling) excipient is necessary. Previously, water and glycerol have been used as enabling excipients for *in situ* amorphization.[22,23] However, it is desirable to keep the complexity of the formulation low and avoid additional excipients where possible.

During *in situ* amorphization, it is suggested that the amorphization follows a dissolution process of the drug into the polymeric network at temperatures above the glass transition temperature (T_g) of the polymer.[16,22] Due to the high T_g of polymers used for *in situ* amorphization so far, it has been necessary to lower the T_g of the polymers to a temperature that can be reached during exposure to microwave radiation using a suitable plasticizer, such as e.g. sorbed water or glycerol, which are also dielectric enabling excipients.[16,18,19,22] Nevertheless, sorbed water inside compacts can be impractical, as it requires long conditioning periods prior to exposure to microwave radiation and can, potentially, also lead to the hydrolysis of the drug.[3,30] In order to avoid the use of sorbed water when preparing compacts for *in situ* amorphization, it was suggested to include an enabling polymeric excipient.

In this study, the polymer PEG was introduced as an enabling excipient for *in situ* amorphization. PEG is available in a large range of molecular weight grades. Common to all grades is that they are semi-crystalline polymers that exhibit a T_g far below 0 ºC.[31] In addition, they all exhibit an onset of melting below 65 ºC.[32] At temperatures below its melting point (T_m), PEG only absorbs microwave radiation to a small extent. However, at

temperatures above its T_m the absorption of microwave radiation increases strongly[33,34] as its mobility increases, which allows it to couple its dipoles more effectively to the alternating electromagnetic field.[35] PEG has previously been used to obtain an ASD from physical mixtures upon microwave radiation.[36] Furthermore, PEG is known to form monotectic mixtures (special case of a eutectic mixture) with drugs that are miscible with PEG. In case of the formation of a monotectic mixture, the T_m of a compound (here: drug) is suppressed to the T_m of another compound (here: PEG), i.e. in the present study both solid phases will melt at the T_m of PEG. By the formation of a monotectic mixture, PEG holds the potential of dissolving drugs at the T_m of the respective grade of PEG, i.e. at lower temperatures than other polymer excipients, such as Soluplus® and PVP, which were used in previous publications describing *in situ* amorphization.[37,38] Based on this, the use of PEG is expected to allow for a faster onset and rate of amorphization. Hence, the inclusion of a polymeric enabling excipient of sufficient mobility, and with suitable dipole moment, which can form a monotectic mixture and an ASD with the drug, is a promising strategy for *in situ* amorphization using microwave radiation.[36]

However, above the T_m of PEG, the compacts will greatly deform as the viscosity of PEG decreases. Additionally, the recrystallization tendency of PEG was high upon cooling, which can be followed by the recrystallization of the drug, i.e. phase separation occurs.

To *(i)* minimize the deformation of the compacts and *(ii)* increase the physical stability of the obtained ASD, PVP was incorporated into the compact formulation in a step-wise fashion. To study the mechanism of *in situ* amorphization using an enabling polymeric excipient, the aim of this study was two-fold: Firstly, to identify a PEG:PVP ratio, which would *(i)* allow for sufficient dielectric heating by the polymer PEG to achieve complete amorphization of the drug, *(ii)* stabilize the physical shape of the compacts and ensure physical stability of the obtained ASD upon cooling, and *(iii)* achieve complete amorphization for a drug load of 30 wt% or 50 wt% CCX after a maximum of 600 s of exposure to microwave radiation. Secondly, two different grades of PEG, 2000 and 3000, were tested, to study the influence of the polymer on the rate of amorphization of the drug.

2. Methods and materials:

2.1. Materials:

Celecoxib (CCX, M_w = 381.37 g/mol) and magnesium stearate (MgSt, M_w = 591.27 g/mol) were purchased from Fagron Nordic A/S (Copenhagen, Denmark). Polyethylene glycol (PEG) 2000 (M_w = 2000 g/mol) and PEG 3000 (M_w = 3000 g/mol) were a kind gift from Merck KGaA (Darmstadt, Germany). PEG 4000 (M_w = 4000 g/mol) was purchased from Honeywell Fluka (Vallensbæk, Denmark). Kollidon® 17PF (PVP, M_w = 7000-11000 g/mol) was kindly gifted by BASF (Ludwigshafen, Germany). Silica gel was purchased from Sigma-Aldrich A/S (St. Louis, MO, USA). All chemicals were used as received.

2.2. Thermal analysis:

Thermal analysis was performed using a Discovery differential scanning calorimeter (DSC) from TA Instruments Inc. (New Castle, DE, USA). The experiments were performed under a nitrogen gas purge of 50 mL/min and conducted as single runs (n = 1). The results were analyzed using the TRIOS software (version 4.1.1) from TA Instruments Inc. (New Castle, DE, USA). The T_m were determined as the onset of melting for PEG 2000, PEG 3000, CCX-PEG, CCX-PVP and PVP-PEG, and as the temperature of the maximum peak height of the melting endotherm for the CCX-PEG and CCX-PEG-PVP mixtures (where the dissolution rate is highest), whilst the T_g were determined at half height of the transition. In the experiments described below (Section 2.2.1. – 2.2.4.), samples of 3-5 mg were placed into Tzero aluminium pans with hermetic lids. The lids were perforated for mixtures containing PVP to allow for water evaporation.

2.2.1. Binary PVP-PEG mixtures:

To evaluate the solubility of PVP in PEG, physical mixtures, of 100 mg each, were prepared by mortar and pestle containing 10-90 wt% PVP and PEG 2000 or PEG 3000 in 10 wt% increments. A modulated heating scan was applied from 0 °C to 180 °C at a heating ramp of 3 °C/min with a modulation amplitude of 1 °C every 50 s.

2.2.2. Binary CCX-PEG mixtures:

To evaluate the solubility of CCX in PEG, physical mixtures of 100 mg, containing 10-90 wt% CCX and PEG 2000 or PEG 3000 in 10 wt% increments, were prepared using mortar and pestle. These mixtures were analyzed using a heating rate of 10 °C/min from 0 °C to 180 °C without modulation.

2.2.3. Binary CCX-PVP mixtures:

To determine the melting-point depression for CCX in PVP, 100 mg physical mixtures containing 10-90 wt% CCX in PVP in increments of 10 wt% were prepared by mortar and pestle. A modulated heating run was applied from 20 °C to 190 °C at a rate of 3 °C/min with an amplitude of 1 °C every 50 sec.

2.2.4. Ternary CCX-PEG-PVP mixtures:

To obtain the data points for ternary contour plots of CCX, PEG, and PVP physical mixtures, containing CCX, PEG 2000 or PEG 3000 and PVP (see Table 1) were analyzed using the modulated DSC method as described in Section 2.2.1.

2.2.5. Pure PEG 2000 and PEG 3000:

To characterize the pure substances, samples of PEG 2000 and PEG 3000 were measured by DSC at a heating rate of 10 °C/min from 20 °C to 100 °C and their respective T_m were determined.

2.3. Compact preparation:

Physical mixtures, containing either 30 wt% or 50 wt% CCX, PEG 2000 or PEG 3000, PVP and 1 wt% magnesium stearate (lubricant), were prepared by mortar and pestle. The composition of the physical mixtures can be found in Table 1. Following preparation, 100 ± 2 mg of each physical mixture was compacted into flat-faced cylindrical compacts with a diameter of 6 mm using an instrumented single punch tablet press GTP-1 from Gamlen Instruments (Nottingham, UK) fitted with a 500 kg load cell (CT6-500-022) at a compression pressure of 35 MPa. The compacts were stored over dried silica at ambient temperature until use to avoid water sorption.

2.4. *In situ* amorphization:

The compacts were exposed to microwave radiation to induce *in situ* amorphization using a household-microwave oven, NN-DF383BGPG from Panasonic (Hamburg, Germany). Due to the presence of hotspots caused by standing waves in multimode cavities, such as the microwave oven used, the compacts were placed on the same hotspot (which was larger than the compact) in each experiment to ensure uniformity and reproducibility. To reduce passive heating of the compacts from the bottom plate of the microwave oven, each compact was placed on a polypropylene watch glass with only minor contact areas to

the bottom plate of the microwave oven. The watch glass was then placed in the location of the selected hotspot. Polypropylene is microwave transparent and therefore reduces any effects due to additional heating of the compacts from microwave radiation.

Due to their small volume, the compacts absorb only a small proportion of the microwave radiation. In order to avoid damaging the microwave oven, a beaker filled with 500 mL of distilled water and glass beads, sealed inside a Quick Clean™ microwave steam bag from Medela AG (Baar, Switzerland), was placed in the microwave oven to absorb the residual microwave radiation. The steam bag contained the steam created by the water upon exposure to microwave radiation for approx. 5 min. The steam was then released through a small opening of the steam bag towards the microwave oven door, where a paper was located to absorb (most of) the steam. Nevertheless, another beaker (150 mL) was placed upside down over the polypropylene watch glass with the compact, to protect the compact from the increasing humidity inside the microwave chamber during exposure to microwave radiation. (The increasing humidity is caused by evaporation of water from the beaker in the microwave steam bag.) Due to the increasing humidity in the microwave oven from the steam, it cannot be excluded that convective heat transfer was possible from the (hot) air to the compact (passive heating). It was not possible to completely exclude the contribution of convective heat transfer to the heating upon exposure to microwave radiation.

The surface temperature of the compact was monitored every second during exposure to microwave radiation, with a resolution of 0.1 °C, using a fiber optic temperature probe OTG-A from OpSens Solutions (Québec, Canada). The generated signal was transferred using a Pico-M signal conductor and further analyzed using the Softsense Software from OpSens Solutions (Québec, Canada). Each compact was exposed to microwave radiation for 120 s, 240 s, 360 s, 480 s or 600 s at a power output of 1000 W. Each experiment was conducted in triplicate (n = 3).

2.5. Quantification of amorphous content of celecoxib:

Transmission Raman spectroscopy was used as an *in-line*, non-destructive measurement to quantify the degree of amorphization of CCX before and after exposure to microwave radiation. Prior to transmission Raman spectroscopy analysis, the compacts were allowed to cool down to room temperature, i.e. the analysis was performed 1-2 min after exposure

to microwave radiation. The quantification was performed using a Kaiser RXN1 Microprobe from Kaiser Optical Systems (Ann Arbor, MI, USA) equipped with a PhAT-probe (Pharmaceutical Area Testing). The setup was described in detail by Hempel *et.al.* (2020).[22] In short, the compacts were placed on an excitation fiber with a power output at the fiber of 200 mW connected to an AD127NT diffuser from Thorlabs Inc. (Newton, NJ, USA). Using the PhAT-probe, the inelastically scattered light was collected at a distance of 20 mm using a 5x objective. The total acquisition time was 20 s, which is equal to an average of 5 measurements with an exposure time of 4 s each. The wavelength of the excitation laser was 785 nm. The Raman spectra were recorded in the range of 150 cm^{-1} to 1900 cm^{-1} at a resolution of 5 cm^{-1}. Dark frames were subtracted from each measurement and the analysis was conducted using a partial-least-squares regression (PLS) model from a calibration space described by Edinger *et al.* (2018).[19] The PLS model was obtained from the spectral region from 705 cm^{-1} to 845 cm^{-1}, which shows distinguishable features of crystalline and amorphous CCX. The PLS model, which was initially only designed for compacts containing CCX and PVP, was validated for the additional excipients PEG 2000 and PEG 3000 (section S1 in Supplementary Material (SM)). Based on the results in Figure S1a and Figure S1b, the PLS model was applicable for compacts containing PEG next to CCX and PVP, as only CCX is active in the chosen spectral region. Pre-processing of the data was performed using Savitzky-Golay (SG) smoothing and standard normal variate transformation (SNV). The data pre-processing was performed using the PLS toolbox 8.1.1 from Eigenvector Research Inc. (Manson, WA, USA) in MatLab from MathWorks (Natick, MA, USA).

3. Results and discussion:

During exposure to microwave radiation compacts with CCX and PEG 2000 or PEG 3000 will melt due to the formation of a monotectic mixture at temperatures above the T_m of the polymers, and recrystallize upon cooling. Hence, the incorporation of a polymer that can stabilize the physical shape of the compacts and the amorphous state of the drug, such as PVP, was required to produce a shape- and physically stable ASD. In order to determine the solubility of CCX in the polymers PEG and PVP, as well as the necessary temperature to obtain an ASD upon exposure to microwave radiation, thermal analysis was performed. For this, ternary mixtures of CCX, PEG 2000 or PEG 3000 and PVP as well as binary

mixtures of CCX:PEG, PVP:PEG and CCX:PVP, were analyzed and ternary phase diagrams were plotted.

The temperature threshold as determined by thermal analysis, i.e. the T_m of the mixture, was linked to the measured surface temperature of the compact that was obtained during exposure to microwave radiation. This approach allowed for the determination of an optimal ratio between CCX:PEG:PVP for *in situ* amorphization. The ratio between PEG and PVP was considered critical. For example, insufficient amounts of PEG will result in inefficient heating and insufficient amounts of PVP will result in deformed compacts that are limited by their high drug recrystallization tendency.

3.1. The determination of the solubility of CCX in the polymer mixtures and the temperature threshold for *in situ* drug amorphization:

3.1.1. Binary systems of CCX in PEG 2000 and PEG 3000:

The solubility of CCX in PEG 300 (liquid at room temperature, i.e. 20 °C) was recently determined to be approximately around 40 wt%.[39] It was suggested that the solubility in molten PEG 2000 and PEG 3000 is comparable to the reported value for liquid PEG 300, as the drug-polymer solubility is only influenced by the molecular weight of the polymer to a minor extent. For example, the independence of the drug-polymer solubility on the polymer grade has previously been described for drug-PVP systems.[40] Figure S2 shows the phase diagrams for CCX in PEG 2000 and PEG 3000 as determined by thermal analysis. It can be seen that a monotectic behavior is present and the solubility limit is reached at a weight ratio of 40:60, CCX to PEG (2000 or 3000). Figure S3 shows the thermograms of mixtures for a weight ratio of 40:60 and 50:50, CCX to PEG 2000 and PEG 3000, respectively. These data confirmed that the solubility limit was exceeded at a 50:50 wt% as an additional endothermic event can be observed at higher temperatures. The temperature for the onset of melting in a mixture of 40:60 CCX to PEG (2000 or 3000) was slightly lower compared to the pure compound PEG 2000 and PEG 3000, indicating the formation of a monotectic (Figure S2a and b).

Due to a decrease in viscosity, and the resulting increase in molecular mobility,[32,41,42] the dissolution rate of CCX in PEG 2000 and PEG 3000 increases at temperatures above the T_m of the PEGs. This means that the dissolution of CCX into the polymers takes place *(i)* relatively more slowly in the amorphous domains of the polymer at temperatures above the

T_g of PEG but below T_m of PEG, and *(ii)* at a higher dissolution rate above the T_m of PEG. Temperatures exceeding T_g are required for the dissolution process as the translational motions required for diffusion and subsequent molecular mixing between drug and polymer in the solid-state are not possible at lower temperatures. The T_g of PEGs with low molecular weights are reported to be below -70 °C (e.g. PEG 4000 has a reported T_g of -76.6 °C),[43] whilst with decreasing molecular weight, the T_g is usually lower.[31] The T_m of PEG 2000 and PEG 3000 were found to be at 50.3 °C and 57.5 °C, respectively (Figure S4).

The monotectic behavior of CCX-PEG was confirmed by exposing compacts containing only 30 wt% CCX and 69 wt% PEG 2000 or PEG 3000, or 50 wt% CCX and 49 wt% PEG 2000 or PEG 3000 without the addition of PVP to microwave radiation (Table 1). As predicted, the compacts deformed/liquefied (Figure S5a-b). The compacts containing only CCX and PEG 2000 or PEG 3000 were at first completely liquid. However, upon cooling to room temperature PEG and CCX recrystallized quickly into separate phases.

3.1.2. Binary systems of PVP in PEG 2000 and PEG 3000:

Mixtures of PEG and PVP are commonly used to prepare ASDs.[12,44] It is hypothesized that small amounts of PVP can sterically hinder the recrystallization upon cooling, both of CCX and PEG, as it also dissolves in the PEG melt, which allows for the formation of larger amorphous domains inside the compacts, which in turn will stabilize the ASD.[45]

PVP can dissolve into the PEG melt until the solubility limit is reached. It has been reported that the solubility of PVP and PEG in each other depends on the molecular weight of both polymers and their respective ratio.[46,47] Hence, the solubility of PVP in PEG 2000 and PEG 3000 was determined.

The solubility for PVP : PEG 2000 and PVP : PEG 3000 was determined using binary mixtures of the polymers (phase diagram Figure S6). PVP dissolved into the molten PEG 3000 at the T_m of PEG 3000 until a 50:50 wt% mixture was reached. At higher concentrations of PVP, a T_g for a PVP polymer-rich phase was observed at temperatures above the T_g of the mixed polymer phase (Note: the T_g of PVP is lowered with increasing amount of PEG), indicating complete solubility between PVP and PEG 3000 for mixtures within the range of ratios of 0:100 to 50:50 wt%. For PEG 2000, the solubility of PVP in PEG 2000 was higher, i.e. up to 90 wt% PVP could be dissolved in PEG 2000. At higher

concentrations of PVP, a separate T_g that was indicative of a PVP polymer-rich phase was detected. Overall, it was found that PVP has a higher solubility in PEG 2000 compared to PEG 3000.

The solubility limit of PVP in PEG 2000 is not reached in the compact compositions investigated (Table 1). In the compacts containing PEG 3000, the maximum amount of PVP was 59 wt% to 10 wt% PEG 3000 (85:15 wt% PVP to PEG 3000, Table 1), hence not all PVP was able to dissolve into the PEG 3000 melt at the highest PVP content.

3.1.3. Binary system of CCX in PVP:

CCX has a solubility of around 40 wt% in PVP at room temperature and this was found to be independent of the molecular weight of the PVP.[48] Therefore, the drug could potentially also dissolve into the pure PVP-rich phase above the T_g of PVP. The T_g of PVP (Lit.: 138 ºC[49]) corrected by the water content in the mixtures (Table S1 and S2), was detected at around 100 ºC. It has previously been suggested that no considerable dissolution of CCX into the pure polymer phase of PVP can take place until a temperature of T_g + 20 °C has been reached, as only above this temperature the viscosity is sufficiently low to allow for dissolution in a time-frame relevant for *in situ* amorphization, i.e. ≤ 20 min.[50] As this temperature (i.e. 120 °C) is far above the T_m of PEG it is highly unlikely that a dissolution process of the drug into pure PVP is taking place as described for previous studies in the field of *in situ* amorphization.[16,19,22] Furthermore, in a recent publication, a lower M_w of PVP, i.e. PVP12, was used for *in situ* amorphization utilizing microwave radiation. [22,25] As the T_g of PVP12 is lower than of PVP used in this study, i.e. PVP17, it was observed that drug dissolution of CCX into PVP12 was possible at temperatures below 100 °C. To avoid drug dissolution into the PVP, and thereby only evaluate PVP's function as a stabilizer with respect to the physical form, PVP17 was chosen for the present study. Based on this consideration, both the model drug CCX and the polymer PVP17 of the present system are expected to predominantly dissolve into the molten PEG.

3.1.4. Ternary systems of CCX in PVP-PEG 2000 and PVP-PEG 3000 blends:

Figure 1a shows the ternary phase diagram for CCX, PEG 2000 and PVP and Figure 1b shows the ternary phase diagram for CCX, PEG 3000 and PVP. For the ternary phase diagram, the temperature of the last endothermic event (T_m or T_g) was determined as this is considered equivalent to the minimum temperature needed to achieve complete

amorphization upon exposure to microwave radiation. The compact compositions used for *in situ* amorphization are marked in the ternary phase diagram as black dots (Figure 1). Following the bottom-axis (celecoxib content) at a drug load of 30 wt% and 50 wt%, the compositions were chosen by increments of 10 wt% PEG 2000 or PEG 3000 (see also Table 1). The drug load of 30 wt% was chosen, as this represents the recently reported highest drug load achieved using CCX and PVP by *in situ* amorphization. The drug load of 50 wt% was chosen to represent a drug load above the solubility limit of CCX in molten PEG and PVP at room temperature, respectively (both were approximately 40 wt%). As temperatures above room temperature are reached during exposure to microwave radiation, higher drug loadings were considered possible.

3.2. The role of the amorphous polymer PVP in the compacts:

PVP is an amorphous polymer, which does not liquefy under the applied conditions. PVP was incorporated into the compacts *(i)* in order to stabilise the physical shape and to decrease the softening of the formulation and the subsequent deformation of the compacts upon exposure to microwave radiation; and *(ii)* as an amorphous stabilizer for the obtained ASD to prevent recrystallization of CCX upon cooling to room temperature.[51,52]

In order to identify a suitable ratio of PVP:PEG 2000 and PVP:PEG 3000, which would *(i)* allow for sufficient dielectric heating by the polymeric enabling excipient PEG, *(ii)* stabilize the physical shape of the compacts and the obtained ASD upon cooling by the polymer PVP and *(iii)* achieve complete amorphization for a drug load of 30 wt% or 50 wt% CCX after latest 600 s of exposure to microwave radiation, the amount of PVP was increased by 10 wt% steps, with the remaining PEG content being at least 10 wt% (Table 1), while the physical stability and the degree of CCX amorphization of the compacts were studied. A maximum exposure time of 600 s was chosen, as this was the exposure time needed to obtain a complete amorphous ASD of 30 wt% CCX and PVP using water as an enabling excipient.[22]

With the addition of low amounts of PVP (9 wt%), i.e. for the compacts 30 wt% CCX, 60 wt% PEG 2000 or PEG 3000 and 50 wt% CCX, 40 wt% PEG 2000 or PEG 3000 (Table 1), no sufficient physical stabilization was obtained, resulting in a recrystallization of PEG and CCX upon cooling as revealed by XRPD. Diffractograms of the compacts without PVP and with low amounts of PVP, after exposure to 600 s of microwave radiation, indicate

complete amorphization only in some cases, as CCX recrystallized before, during or following the measurement (Figure S7). The initially transparent visual appearance of the compacts (Figure S5) supports that the compacts were initially completely amorphous as a melt, meaning CCX was completely dissolved in the molten PEG. However, CCX and PEG showed a high tendency to recrystallize in the compacts (Figure S7). Most likely this is a result of the high tendency of PEG to recrystallize upon cooling to room temperature.[45,53] The recrystallization of PEG subsequently resulted in the recrystallization of CCX since it could only stay amorphous in the remaining amorphous areas of the semicrystalline PEG polymer.

The quantification of the amorphous content after exposure to microwave radiation using transmission Raman spectroscopy could not be conducted on molten transparent compacts (directly after exposure to microwave radiation), i.e. compacts containing only the PEG and not a polymer mixture of PEG and PVP due to the insufficient laser scattering from the transparent compacts.

It was found that a minimum of 19 wt% PVP was necessary to obtain compacts that did not deform to a high degree upon exposure to microwave radiation (visually evaluated, Figure S5c-e). Hence, compacts containing 9 wt% PVP were excluded from any further studies.

3.3. Rate and degree of *in situ* amorphization of CCX in PEG-PVP compacts during exposure to microwave radiation:

Figure 2 shows a plot of the degree and rate of CCX amorphization obtained in the compacts exposed to microwave radiation for different amounts of time.

Figure 2a and b show the degree of amorphization for compacts prepared with a 30 wt% drug load and PEG 2000 or PEG 3000, respectively. Generally, the rate of amorphization decreased with decreasing content of PEG (i.e. increasing content of PVP). A slightly faster increase in forming amorphous CCX was found for PEG 2000 compacts compared to PEG 3000 compacts. Complete *in situ* amorphization was achieved for compacts containing 30 wt%, 40 wt% and 50 wt% PEG 2000 or PEG 3000 after 600 s of exposure to microwave radiation. The data obtained from the PLS quantification of the spectra from transmission Raman spectroscopy was supported by XRPD diffractograms (Figure S8).

Some of the compacts became amorphous even at exposure times lower than 600 s, e.g. 30 wt%, 40 wt% and 50 wt% PEG 2000 compacts were completely amorphous already after 420 s (Figure 2a). However, compacts containing 10 wt% or 20 wt% PEG 2000 or PEG 3000 did not become completely amorphous after 600 s of exposure to microwave radiation (Figure 2a/b).

Similarly, Figure 2c and d show plots of the rate and degree of CCX amorphization obtained with a 50 wt% drug load in PEG 2000 compacts or PEG 3000 compacts, respectively. Not surprisingly, the rates of amorphization were slower for the compacts with 50 wt% CCX as compared to compacts containing 30 wt% CCX (Figure 2 c/d vs Figure 2a/b). The formation of a completely amorphous ASD was possible for a drug load of 50 wt% using 30 wt% PEG 2000 or PEG 3000 and an exposure time of 600 s of microwave radiation (Figure 2c/d).

As can be seen in Figure 2, the initial degree of amorphization at t = 0 min varied from around -2% with PEG 3000 (Figure 2 b and d), to around 8% with PEG 2000 (Figure 2a and c). Furthermore, for compacts with high PEG content, a higher degree of amorphization of CCX was observed before exposure to microwave radiation compared to compacts with a lower PEG content. This can be explained by the low T_g of PEG and a possible short melting of PEG on the surface of the compact upon compression of the compacts. As the T_g of PEG is below room temperature partial dissolution of the drug into PEG was already possible during mixing and compaction.[22,54] This effect was more pronounced for compacts containing PEG 2000. This is not surprising given the lower viscosity of PEG 2000 due to the shorter chain length and lower overall crystallinity,[53] making it more mobile than PEG 3000 at room temperature.[50,55] Furthermore, when comparing Figures 2a/b and Figures 2c/d, the initial degree of amorphization was lower for systems containing 50 wt% CCX. The change in initial degree of amorphization for 30 wt% to 50 wt% CCX was due to a smaller ratio of CCX to PEG for compacts with 50 wt% CCX.

3.4. Analysis of the temperature of the compacts during *in situ* drug amorphization and the amorphization kinetics:

It has been suggested previously, that the amorphization process of a drug in a polymer, at temperatures above the T_g of the polymer, follows a dissolution process and is enhanced with increasing temperature above this temperature threshold.[22,56] Additionally,

it was suggested that the temperature of the compact increases faster above, than below the T_m of PEG due to the increased mobility of liquid PEG, as compared to solid PEG. In the present study, the temperature was measured on the surface of the compacts during exposure to microwave radiation in order to correlate it to the obtained rate and degree of amorphization. Figure 3 shows the compact surface temperature recorded during exposure to microwave radiation, as a function of time.

For all four groups of compacts, i.e. with both drug loadings in both PEG 2000 and PEG 3000, the PEG content did not affect the time to reach the T_m of the PEG ($p > 0.05$), i.e. approximately 200 s for PEG 2000 and 250 s for PEG 3000 (Figure 3a-d). Additionally, for all compacts, the maximum temperature reached after 600 s of exposure to microwave radiation increased with increasing PEG content (Figure 3a-d). As PEG melts, it absorbs the microwave radiation to a higher extent,[34,35] corresponding to the steeper temperature increase above its T_m as indicated by the dotted lines in Figure 3. The faster temperature increase is especially evident in compacts with high PEG content. This can be explained by the mobility increase of the dipoles in the liquid state compared to the solid state, and hence a change in the dielectric properties causing a better adaptability to the alternating electromagnetic field.[34,35] As there is not a strict correlation between the PEG content and the temperature increase, it is suggested that convective heating contributed to the heating to some extent.

When comparing Figures 2 and 3, it is apparent that the amorphization of CCX also occurred at temperatures below the T_m of the pure PEG, which can be assigned to a dissolution process of the drug into the amorphous fraction of the semicrystalline polymer PEG.

It has previously been shown that large amounts (20-30 wt%) of sorbed water can be used to achieve *in situ* amorphization upon exposure to microwave radiation.[16,19,22] It is therefore important to consider the effect of water on the temperature profile described in Figure 3. All compacts contained small amounts of water (< 5 wt%), mainly due to the bound water in the bulk PVP (Table S1 and S2). The water content before and after exposure to microwave radiation in the compacts was considered constant. Even though the water content was found constant, a dynamic process is suggested, where the compacts desorb and re-absorb water (from the steam) over the course of exposure to

microwave radiation. Small amounts of water (here the water of the bulk polymer PVP), in contrast to large amounts of sorbed water in PVP (e.g. 20-30 wt%), is less mobile and more bound to PVP (both water species are less mobile than free (bulk) water).[57] Therefore, the small amounts of water originating from bulk PVP are suggested to only contribute to a minor extent to the heating of the compacts during exposure to microwave radiation. Overall, the first part of the heating of the compact below the T_m of PEG is suggested to be generated by the amorphous fractions of solid PEG. Above the T_m of PEG, the molten PEG was responsible for the majority of the heating of the compacts.

Figure 1 revealed which temperatures are needed to achieve complete amorphization (temperature of black dots), which can be compared to the temperature plots shown in Figure 3. As PEG functioned as the dielectric heating source, lower temperatures were obtained for compacts with lower wt% PEG. For the 50 wt% CCX, 30 wt% PEG 2000 compacts, the temperature threshold was between 114 °C and 124 °C (Figure 1a). Figure 3a shows that this temperature was indeed obtained (119.8 °C ± 16.7 °C; Mean ± SD, n = 3) along with complete amorphization (Figure 2a). For the 30 wt% CCX, 20 wt% PEG 2000 compact, the temperature threshold was around 104 °C. However, this temperature was not reached during 600 s of exposure to microwave radiation (87.1 °C ± 9.2 °C (Mean ± SD, n = 3)) (Figure 3a) and hence, complete amorphization was not achieved (Figure 2a). It is suggested that the use of PEG and PVP as a binary polymer mixture is suitable for microwave-induced *in situ* amorphization also for other drugs apart from CCX, which are soluble in PEG. Furthermore, to the best of our knowledge, chemical instabilities of the drug CCX are not reported in the presence of PEG or PVP, which provides potentially another advantage over the use of sorbed water.

4. Conclusions

The influence of a mixture of PEG and PVP on the microwaved-induced *in situ* amorphization was studied using PEG 2000 and PEG 3000, and drug loadings of 30 wt% and 50 wt%. A polymeric blend of PEG and PVP in the compact was found favorable for the formation of a completely amorphous ASD to *(i)* allow sufficient dielectric heating by the polymer PEG and *(ii)* maintain the physical shape of the compact by PVP and *(iii)* hinder recrystallization of the obtained ASD upon cooling by PVP. Using compacts containing mixtures of PVP and PEG, completely amorphous solid dispersions were

obtained after 600 s of exposure to microwave radiation. Compacts containing PEG 2000 showed a slightly faster rate of amorphization than compacts with PEG 3000. Overall, the use of a mixture of PEG and PVP was found superior over the use of the individual polymers and suitable for *in situ* amorphization with a drug load of up to 50 wt%, which is the highest, so far reported.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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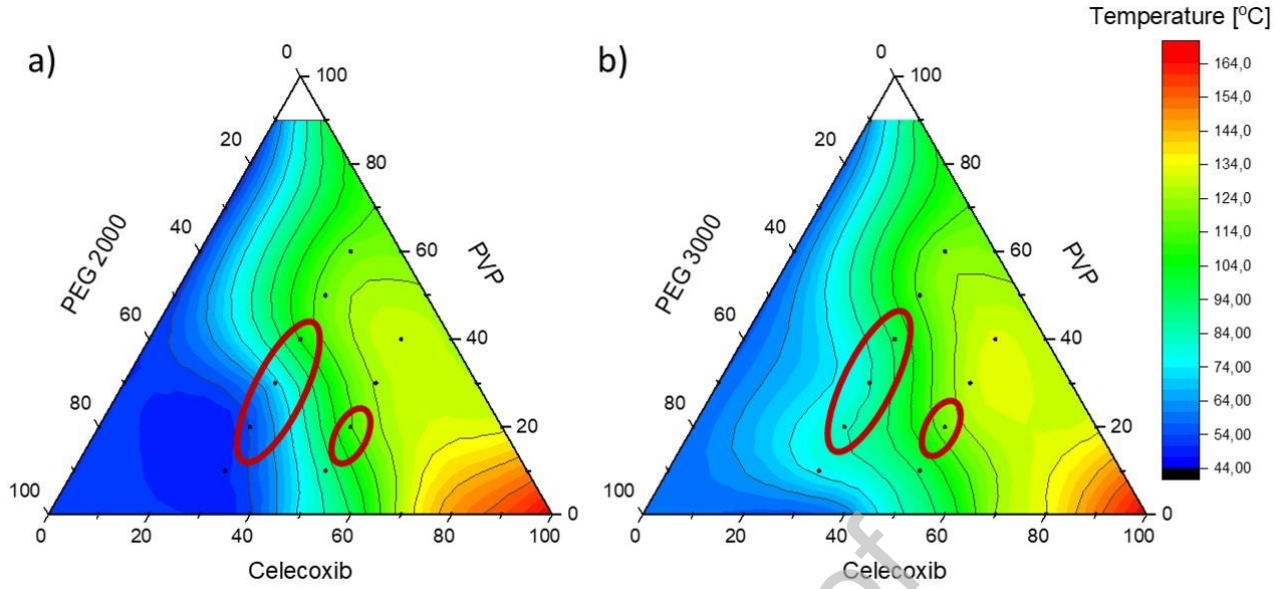


Figure 1: Contour plots obtained by thermal analysis (DSC) reporting the temperature threshold in each binary (CCX:PEG, PVP:PEG, CCX:PVP) and in the ternary systems of CCX, PEG and PVP for a) PEG 2000 and b) PEG 3000. The content of each component is given in wt%. The temperature scale is shown to the right hand side. The black dots indicate the compact compositions used for microwave-induced *in situ* amorphization (Table 1). The red circles indicate the compact formulations, which became completely amorphous after 600 s of exposure to microwave radiation. The thermal events were obtained in the total heat flow.

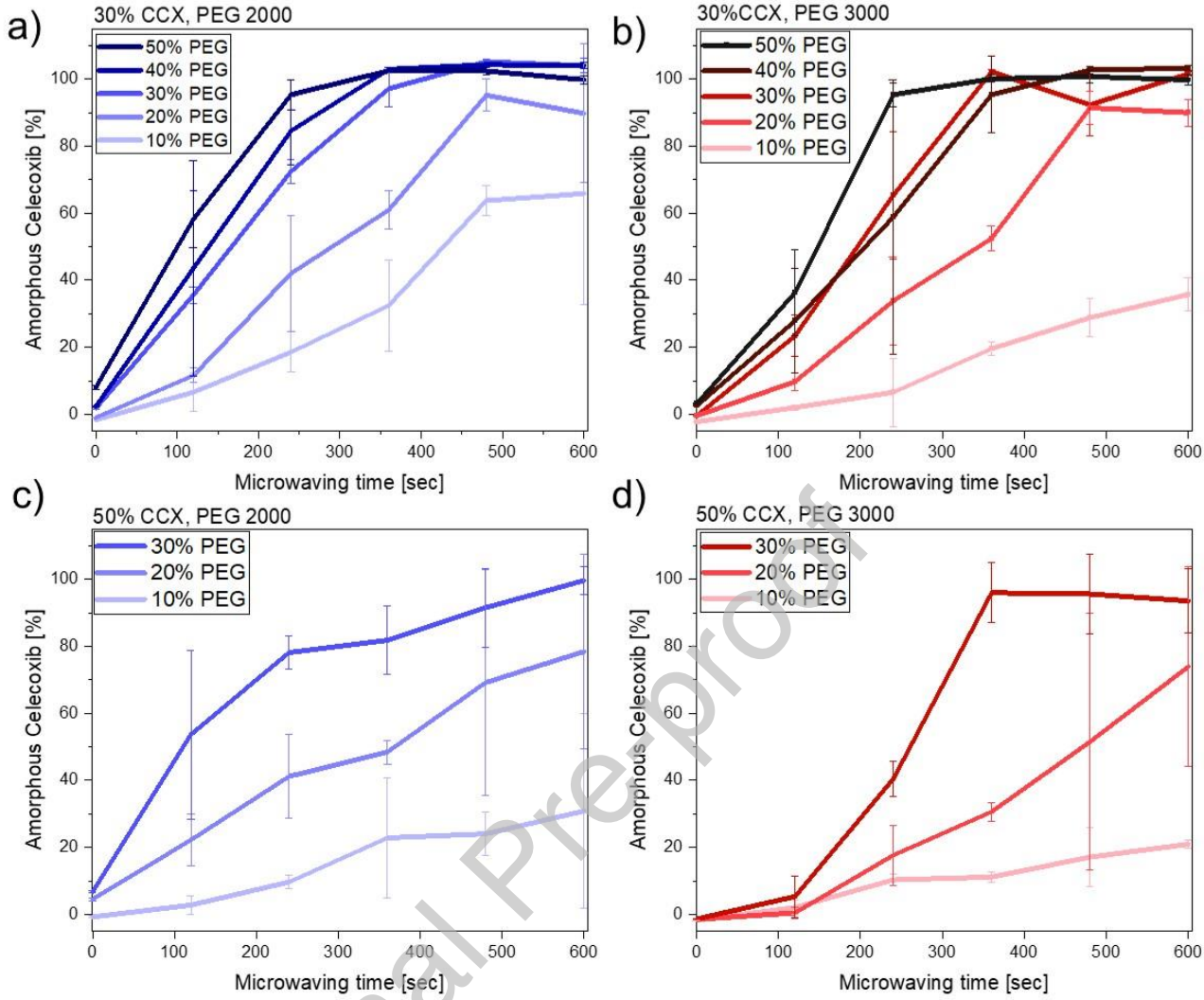


Figure 2: Degree of CCX amorphization quantified by transmission Raman spectroscopy for compacts prepared with: a) 30 wt% CCX, PEG 2000 and PVP, b) 30 wt% CCX, PEG 3000 and PVP, c) 50 wt% CCX, PEG 2000 and PVP, and d) 50 wt% CCX, PEG 3000 and PVP, after 120 s, 240 s, 360 s, 480 s and 600 s of exposure to microwave radiation (Mean ± SD, *n* = 3). Straight lines connecting each data point were drawn to guide the eye. PEG 2000 graphs are colored blue and PEG 3000 graphs are colored red.

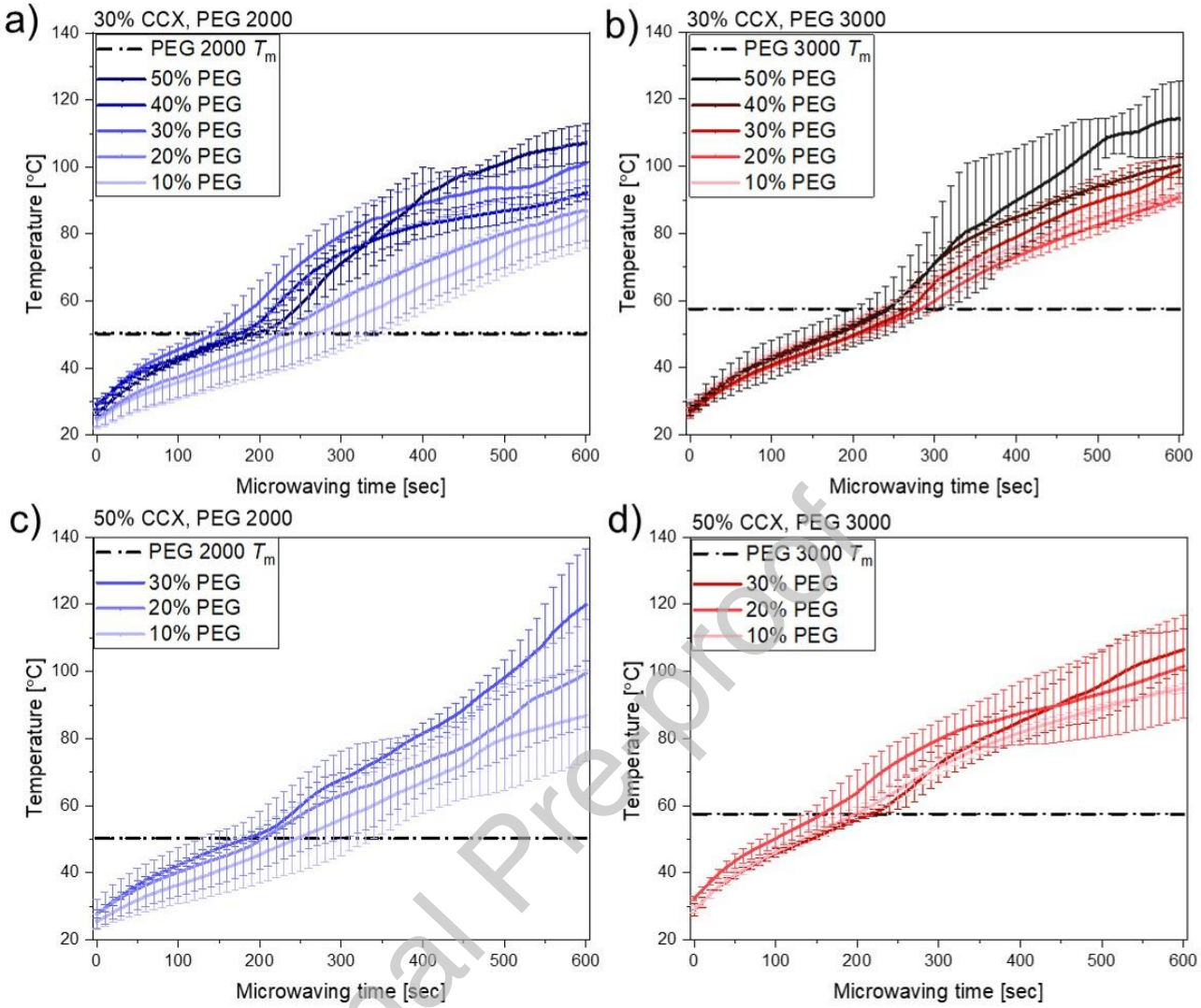
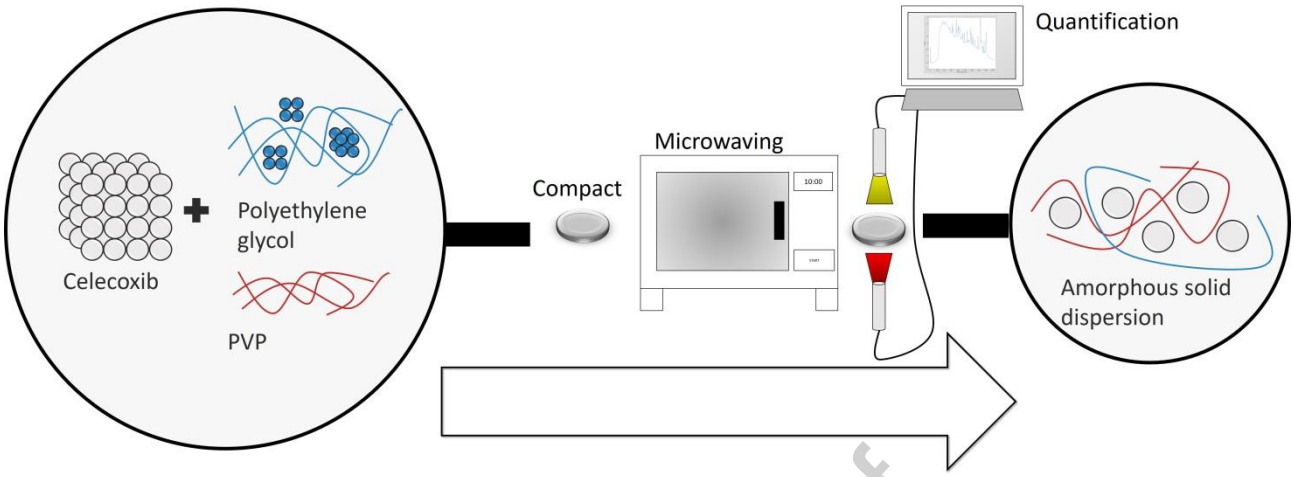


Figure 3: (Surface) temperature recorded during exposure to microwave radiation for 600 s as a function of time for compacts prepared with: a) 30 wt% CCX, PEG 2000 and PVP, b) 30 wt% CCX, PEG 3000 and PVP, c) 50 wt% CCX, PEG 2000 and PVP and d) 50 wt% CCX, PEG 3000 and PVP using a fiber optic temperature probe (Mean ± SD, n = 3). The dotted lines indicate the T_m of the respective PEG. Straight lines connecting each data point were drawn to guide the eye. PEG 2000 graphs are colored blue and PEG 3000 graphs are colored red.

Table 1: Composition of physical mixtures/compacts containing CCX, PEG 2000 or PEG 3000 and PVP. All compacts were prepared with 1 wt% MgSt as a lubricant. Compacts indicated with asterix liquefied upon exposure to microwave radiation and only their physical mixtures are used for the thermal analysis discussion. Compacts indicated with two asterix became completely amorphous within 600 s of exposure to microwave radiation.

Compact name	**CCX [wt%]**	**PEG 2000 or PEG 3000 [wt%]**	**PVP [wt%]**
30 wt% CCX, 10 wt% PEG	30	10	59
30 wt% CCX, 20 wt% PEG	30	20	49
30 wt% CCX, 30 wt% PEG**	30	30	39
30 wt% CCX, 40 wt% PEG**	30	40	29
30 wt% CCX, 50 wt% PEG**	30	50	19
30 wt% CCX, 60 wt% PEG*	30	60	9
30 wt% CCX, 69 wt% PEG*	30	69	0
50 wt% CCX, 10 wt% PEG	50	10	39
50 wt% CCX, 20 wt% PEG	50	20	29
50 wt% CCX, 30 wt% PEG**	50	30	19
50 wt% CCX, 40 wt% PEG*	50	40	9
50 wt% CCX, 49 wt% PEG*	50	49	0

Graphical abstract



Microwave-induced *in situ* amorphization was achieved using compact containing a physical mixture of the model drug celecoxib and the polymers, polyethylene glycol and polyvinylpyrrolidone.