Title: Analyzing the Impact of Different Excipients on Drug Release Behavior in Hot-Melt Extrusion Formulations Using FTIR Spectroscopic Imaging

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Running head: Impact of Excipients on Drug Release

Keywords: Hot-melt extrusion; FTIR imaging; Drug release; Drug-polymer interactions; Soluplus®; Copovidone

Abstract

The drug release performance of hot-melt extrudate formulations is mainly affected by its composition and interactions between excipients, drug and the dissolution media. For targeted formulation development, it is crucial to understand the role of these interactions on the drug release performance of extrudate formulations. Attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopic imaging was used with an in-situ flow-cell device to analyse the impact of different excipients on drug release from extrudates. The compositions differed in the type of polymer (copovidone and Soluplus®), the salt or acid form of ibuprofen and the addition of sodium carbonate. For comparison, conventional USP (United States Pharmacopeia)Apparatus 2 dissolution studies were performed. FTIR imaging revealed that differences in the drug release rate were mainly due to drug-polymer interactions. Ibuprofen acid showed interactions with the matrix polymer and exhibited a slower drug release compared to non-interacting ibuprofen salt. Addition of sodium carbonate to the ibuprofen acid containing formulations enhanced the drug release rate of these systems by interfering with the drug-polymer interactions. In addition, drug release rates also depended on the polymer type, showing faster drug release rates for extrudate formulations containing copovidone compared to Soluplus®. FTIR imaging revealed that the stronger the drug-polymer interaction in the formulations, the slower the drug release. The addition of sodium carbonate improved release as it reduces drug-polymer interactions and allows for the formation of the more water-soluble ibuprofen salt.

1. Introduction

In recent years, more than 50% of new drug candidates are speculated to be highly lipophilic and thus, poorly bioavailable (Alam et al., 2012). One very successful approach to increase bioavailability of such poorly water-soluble drugs is the formation of amorphous solid dispersions (ASD). In order to improve solubility, dissolution behavior and bioavailability of these drugs, different technologies such as melt quenching(Marsac et al., 2006; Paudel et al., 2010), hot melt extrusion (HME) (Breitenbach, 2002; Jijun et al., 2011; Zheng et al., 2007; Tho et al., 2010), spray drying, ball milling, and freeze-drying (Caron et al., 2011; Chiang et al., 2013; Caron et al., 2013) have been successfully employed for manufacturing ASD formulations. In typical ASD formulations, the amorphous form of the drug is dispersed and stabilized in a hydrophilic matrix which is usually a polymer.

The enhanced in-vivo performance of the ASD after dispersion in aqueous or physiological medium is attributed to the improved solubility of the amorphous form of the drug compared to the crystalline form and the maintenance of supersaturation through formation of nano/micro amorphous aggregates and micelles (Nagy et al., 2012; Frank et al., 2012a, 2014) In addition, the nature of the drug (e.g. dissociation state) (Geppi et al., 2005), the polymeric carrier (Kanaze et al., 2006; Kogermann et al., 2013; Najib et al., 1986; Miller-Chou et al., 2003), and the drug-polymer interaction are important factors that affect the dispersibility and in-vitro dissolution rate of the ASD (Alam et al., 2012). Among these factors, drug-polymer interactions is probably the most difficult and complex factor to directly monitor during dissolution. Nevertheless, it can impact strongly on the dissolution performance of an ASD.

For instance, it was observed that increasing the molecular weight and weight fraction of the matrix polymer significantly affects the dissolution rate of ibuprofen from ibuprofen/polyvinylpyrrolidone ASD formulations (Najib et al., 1986). This behavior was attributed to the different extents of drug-polymer interactions in the ASD. Kanaze et al. reported that specific interaction such as hydrogen bonding between phenolic hydroxyl groups of flavonoids and polyvinylpyrrolidone prevented recrystallization of the amorphous drug, but hindered drug release at low pH (Kanaze et al., 2006). The authors reasoned that when the pH of the dissolution medium was lower than the pKa of the drug, the phenolic hydroxyl groups were non-ionized and majority of the hydrogen bond between drug and polymer was maintained, leading to a slower dissolution rate. Subsequently increasing the pH of the medium above the pKa led to ionization of the phenolic hydroxyl groups and breaking of the hydrogen bonds which resulted in higher dissolution rate. Likewise, Geppi et al. demonstrated by solid-state nuclear magnetic resonance that strong complexation interaction between ibuprofen and Eudragit RL100 prevented release of the drug from the ASD during dissolution studies (Geppi et al., 2005).

Because interaction of water with the ASD matrix can be influenced by the nature of the intermolecular interactions between the matrix components (Rumondor et al., 2010), drug-polymer interactions can, therefore, play a crucial role in dissolution performance. Moreover, it has also been demonstrated that modification of the micro-environmental pH within the ASD influences the drug release rate (Tatavarti et al., 2006; Wray et al., 2011). Micro-environmental pH modification affects drug-polymer interactions in the ASD and can be considered as a strategy for tuning drug-polymer interactions to obtain desired drug release rate.

One important indicator to assess the influence of these factors on the performance of the ASD is the in-vitro drug release behavior (Azarmi et al., 2007). Typical

analytical methods such as different USP tests are often used for this purpose (Witzleb et al., 2012). These techniques analyze the overall drug released over time; however, no detailed information about the drug release mechanism and the physical processes at the interface between the formulation and the dissolution medium is obtained (Craig, 2002). Especially for ASD formulations of poorly water-soluble drugs, this knowledge is indispensable for the systematic development of optimal formulations.

A number of different techniques have been developed for the analysis of dissolution processes that provide more information than the common USP dissolution tests. In particular, various imaging techniques such as UV imaging (Boetker et al., 2013; Hulse et al., 2012), magnetic resonance imaging (Nott, 2010), and near infrared (NIR) imaging (Zidan et al., 2008) have been used. Furthermore, non-imaging studies have also been performed using Raman spectroscopy (Savolainen et al., 2009), photon correlation spectroscopy, asymmetrical field-flow fractionation (Kanzer et al., 2010, Tho et al., 2010) and inverse equilibrium dialysis (Frank et al., 2012b)

In this study, Fourier-transform infrared (FTIR) spectroscopic imaging was used to investigate the dissolution processes of different ASD formulations in order to understand the impact of the polymer and the form of ibuprofen on the drug release behavior. FTIR imaging was chosen because with this technique images can be generated in situ that reflect the spatial distribution of each formulation component during drug release based on the IR spectra of the components (Coutts et al., 2003; Kazarian et al., 2006; Rafferty et al., 2002; Kazarian and Chan, 2003; Kazarian and Ewing, 2013; van der Weerd et al., 2004). This information allows for the analysis of the release mechanisms of the individual component over time. It is also possible to spatially resolve drug-polymer interactions (Fan et al., 2009).

In order to compare the effect of different polymers on the drug release behavior, the random copolymer copovidone [60% vinylpyrrolidone (VP)/ 40% vinyl acetate (VA)] and the graft copolymer Soluplus® [13% polyethylene glycol (PEG)/ 57% vinylcaprolactam (VCL)/ 30% vinyl acetate (VA)] were used in this study. These two hydrophilic polymers are described to be suitable for hot melt extrusion processes (Caron et al., 2013). ASD formulations based on copovidone and Soluplus® were manufactured by hit melt extrusion and contained either the salt or acid form of ibuprofen. In addition, extrudate formulations containing a pH modifying substance (sodium carbonate) were also manufactured in order to analyze the impact of pH modifying substances on drug release behavior.

2. Materials and Methods

2.1. Materials

Soluplus® and copovidone were purchased from BASF SE (Ludwigshafen, Germany), ibuprofen from Sigma-Aldrich (Steinheim, Germany) and sodium carbonate from Riedel-de-Haen AG (Seelze, Germany). All organic solvents were of analytical grade and were purchased from Merck KGaA (Darmstadt, Germany).

2.2. Hot melt extrusion

Hot melt extrusion was performed on a bench-top extruder (Haake MiniLab, Thermo Scientific, Germany). The screw speed was set to 30 rpm, and the extrusion temperature varied from 90 °C to 150 °C depending on the composition of the drug/excipient mixture as listed in Table 1. After extrusion, the extrudates were examined with polarized light microscopy and were found to be free of crystalline drug, indicating the amorphous form of the drug is dispersed in the polymer matrix.

The extrudates were then cryo-milled for 2 minutes at 10 Hz (6870 Freezer/Mill, Spex Sample Prep., USA) and sieved to exclude particles bigger than 250 µm.

2.3. FTIR imaging and in-situ dissolution testing

FTIR imaging was conducted on a continuous scan spectrometer coupled with a macro sample chamber (Bruker Optics, Germany) and a Focal Plane Array (FPA) detector (Santa Barbara Focalplane, USA). The macro chamber was equipped with a Golden Gate^{TM} diamond attenuated total reflection (ATR) crystal accessory (Specac Ltd., UK). Images were acquired with a spectral resolution of 8 cm^{-1} and 16 co-added scans. The size of the images is (0.58 x 0.64) mm^2 with a spatial resolution of approximately 10-15 µm with an image acquisition time of approximately 2 minutes. Milled extrudate samples were compressed directly using an in-situ compaction cell, which was designed by van der Weerd et al. (van der Weerd et al., 2004). The resulting pellets had a diameter of 3 mm and weighed approximately 15 mg each. For the dissolution experiment, a pellet was positioned onto the ATR diamond to cover approximately half of its surface. This set-up allowed studying of the tablet–water interface. A Perspex flow cell was used, which had an inlet and outlet in order to realize a continuous flow of the dissolution medium (de-ionised water). The sample was sandwiched between the diamond and the dissolution cell, which was pressed onto an O-ring as described before (Wray et al., 2011; Kazarian et al., 2008; Velasco et al., 2011) and shown in Fig. 1**Error! Reference source not found.**. The dissolution medium was circulated in a closed-loop system with a flow rate of 0.5 ml/min and kept at a temperature of 37 °C within the dissolution cell. In addition to the collection of FTIR spectra, the total amount of drug released from copovidone-based extrudates was determined by using an inline UV/ Vis spectrometer. The

detection of the drug release from the Soluplus®-based extrudates was not possible because the UV absorption bands of Soluplus® overlapped with those of ibuprofen. The experimental set-up is shown in Fig. 2.

2.4. Spectra processing and image analysis

In each FTIR spectrum the relative concentration of each formulation component was determined by integrating characteristic spectral bands unique to each component. The integrated absorbance values of each component, for all 4096 spectra, were plotted spatially with a color scale, producing images showing the spatial distribution of individual components at a particular time. In these images, red color indicates domains of high concentration whereas blue color represents domains of low concentration. Thus the distributions of components such as drug, polymer and water can be visualized in a chemically specific manner. The characteristic bands that were used to generate the images are listed in Table 2.

2.5. Conventional USP dissolution tests

Conventional dissolution studies were performed using a USP apparatus 2 (Vision Elite 8, Hanson, USA). Milled extrudates (666 mg) were compacted directly into tablets using a 13 mm die on a conventional tablet press (Korsch EK0, Korsch AG – Berlin, Germany). The tablets were transferred into a Japan sinker to prevent the samples from floating. Dissolution testing was conducted in 900 ml deionized water at 37°C and at a stirring speed of 50 rpm. Samples were taken after 10, 20, 30, 45 and 60 minutes and analyzed by reversed-phase HPLC with UV detector.

3. Results

In order to study the impact of different excipients on the drug release rate of extrudate formulations two different matrix polymers and two different forms of the drug active were analyzed by both FTIR imaging and USP apparatus 2 dissolution tests. In addition, the effect of adding sodium carbonate as a pH modifying substance was investigated.

3.1. Dissolution of copovidone-based extrudates

The drug release profiles of all copovidone-based extrudates were analyzed by performing USP apparatus 2 drug release tests (see Fig. 3). The extrudates loaded with ibuprofen salt showed a complete drug release after 60 minutes. A significantly lower drug release rate was found for extrudates containing ibuprofen acid, as only 47% of drug was released after 60 minutes. The addition of sodium carbonate resulted in a significant increase of the drug release rate, as 96% of drug was released after 60 minutes.

To understand the differences observed between the drug release profiles of the ibuprofen salt and acid formulations, both formulations were studied by in-situ ATR-FTIR imaging. This technique allows for analyzing the dissolution of both drug and polymer over time. The dissolution behavior of the copovidone-based extrudate formulation containing ibuprofen salt was analyzed by plotting spatially the integrated absorbance values of ibuprofen salt and copovidone (see Fig. 4). The images in the top row of Fig. 4 reveal that ibuprofen salt was continuously released from the tablet. After 30 minutes no more drug was detected on the imaging area indicating complete drug release. A similar trend was obtained for the dissolution of copovidone from the tablet as shown in the bottom row of Fig. 4. Careful examination of the images of ibuprofen salt after 1.5 minutes shows the formation of a broad “yellow layer” at the

edge of the tablet (highlighted by a bar within Fig. 4). This layer contains wet ibuprofen salt that was not yet dissolved. In contrast, the images obtained for copovidone showed a more homogenous distribution.

In the case of the ibuprofen acid formulation, which showed a significant slower drug release in the USP 2 test compared to the salt formulation, a different drug release behavior was also observed from FTIR imaging data (Fig. 5). The images revealed that the drug and the polymer were detectable over the entire course of the dissolution test. After 10 minutes the imaging area was completely covered by the sample and subsequently the signal for both components decreased only slightly over time. Within the image that reflects the ibuprofen acid distribution after 5 minutes, high drug concentration regions (red domains) appear near the tablet surface which are perhaps due to re-crystallization or precipitation of ibuprofen acid onto the diamond; the same phenomenon was also observed by Chan and Kazarian in a similar setup (Kazarian and Chan, 2003). Due to overlap with the polymer bands, it was not possible from the spectral information to identify if the ibuprofen in this area is of crystalline or amorphous nature. Furthermore, complete penetration of water into the tablet was observed after 20 minutes.

The comparison between extrudate formulations that are either loaded with the salt or the acid form of ibuprofen shows that the salt loaded extrudate dissolved significantly faster than extrudate loaded with the acid form. In order to understand the differences between the dissolution behaviors of these formulations, the individual spectra of the dry formulations were studied in addition to the pure components (Fig. 6). The focus of this comparison was to study the band changes or differences especially with respect to the polymer, which should provide evidence of drug-polymer interactions. Spectral comparison revealed that the carbonyl band of the VP part of copovidone (1700-1600 cm^{-1}) shows a shoulder at lower wavenumbers

for the ibuprofen acid formulation (dotted line) compared to the pure polymer (continuous line). Furthermore, the development of the shoulder band resulted in reduced signal intensity of the VP band relative to its VA band (1750-1700 cm^{-1}). In contrast, the ibuprofen salt formulation spectrum did not show any such shoulder band; however, a slight shift of the carbonyl band to lower wavenumbers was detected when compared to the spectrum of the pure polymer. This slight shift is due to the effect of absorbed water as this formulation is quite hygroscopic due to the highly hygroscopic nature of the contained dehydrated ibuprofen salt (Zhang and Grant, 2005). The band at 1585-1520 cm^{-1} that is solely visible in the spectrum from the ibuprofen salt formulation is due to the ibuprofen salt.

The influence of a pH modifying excipient on the drug release behavior of the ibuprofen acid formulation was studied through the addition of sodium carbonate to the formulation. It was expected that this pH-modifying substance would increase the local pH within the extrudate matrix, resulting in a faster drug release of ibuprofen as ibuprofen is a weak acid (Wray et al., 2011). FT-IR imaging results of pH modification (i.e. copovidone-based extrudate loaded with ibuprofen acid and sodium carbonate) are shown in Fig. 7, where the spatial distributions of both acid and salt forms of ibuprofen, as well as the water ingress into the sample during drug release are shown. The images indicate that, in the dry sample, a small amount of ibuprofen acid was already converted into the salt form. During drug release additional ibuprofen acid is converted into the salt form (indicated by * in Fig. 7) and together with unconverted ibuprofen acid are released from the tablet at the same rate as water ingresses into the tablet. Comparative image analysis indicates that the overall release rate is relatively faster than in the formulation without sodium carbonate (refer to Fig 5). After 10 minutes the water penetrated the entire sample and almost all the drug in the imaging area dissolved.

Overall, drug release rate is increased by the addition of sodium carbonate compared to the extrudate that was solely loaded with ibuprofen acid as also shown in the UV/ Vis spectroscopic data (Fig. 8). However, the drug release was not as fast as for the extrudate loaded with pure ibuprofen salt. The differences in shape and release time between curves from USP (Fig. 3) and FTIR imaging (Fig. 8) experiments are due to different flow conditions around the tablet and the geometry of the FTIR imaging flow cell (dissolution allowed in the radial direction only). Nevertheless, the results obtained during USP 2 dissolution tests correspond well to the FTIR imaging and UV/Vis spectroscopy data and with more laminar flow conditions in the FTIR imaging experiments, mechanical erosion of the tablet will be much less of a contributing factor to release profile differences, allowing other factors affecting release to become more apparent.

3.2. Dissolution of Soluplus®-based extrudates

In order to study the influence of the type of polymer on the dissolution behavior, Soluplus®-based extrudates were also analyzed. Drug release behavior of extrudate formulations loaded with the two forms of ibuprofen (i.e., the acid and the salt form) were investigated with the same apparatus and condition used for the copovidone-based formulations. In addition, the impact of addition of sodium carbonate to the formulations on drug release behavior was investigated. The results obtained from USP apparatus 2 dissolution test reflect that the amount of drug released after 60 minutes is only 0.2% for the acid loaded extrudate and 7% for the extrudate containing additionally sodium carbonate (Fig. 9). Overall, the fastest drug release rate was obtained for the Soluplus®-based extrudate loaded with ibuprofen salt, with complete drug release after 60 minutes. However, the release rate appears slower compared to the same formulation containing copovidone (see Fig. 3)

Similar to the copovidone-based extrudates, these samples were analyzed using FTIR imaging. As shown in Fig. 10, extrudate formulation loaded with ibuprofen salt dissolved rapidly. The FTIR images showed that both ibuprofen salt and Soluplus® dissolved completely after 30 minutes at a similar rate, but the same formulation with copovidone dissolved out of the imaging area in just 10 minutes.

In contrast, the drug release behavior of Soluplus®-based extrudates containing ibuprofen acid revealed that no dissolution took place over the entire course of the measurement. Both signals for the drug active and the polymer remained unchanged (Fig. 11). Furthermore, the analysis of the distribution of water over time revealed that there was no water ingress into the tablet over the entire course of the test. To understand the differences observed between the Soluplus®-based extrudates containing either the salt or the acid form of ibuprofen, the individual FTIR spectra were analyzed. Besides the spectral difference that is present due to the signal from the ibuprofen salt form (1585-1520 cm^{-1}), these spectra differ in the signal from the carbonyl band of the VCL part of Soluplus® (1680-1580 cm^{-1}) (Djuris et al., 2013; Liu et al., 2012) as shown in Fig. 12. In this spectral region, the signal from the salt loaded extrudate (dashed line) shows a slightly lower signal intensity and a slight shift to higher wavenumbers compared to the signal from the pure polymer (continuous line). However, the spectrum of the acid loaded extrudate (dotted line) exhibits a double band (maxima at 1627 cm^{-1} and 1596 cm^{-1}) as well as a distinct decrease of the signal intensity relative to its VA band (1750-1700 cm^{-1}) when compared to the spectrum of the pure polymer. The position of the signal from the carbonyl group of the VA part of Soluplus® (1750-1700 cm^{-1}) is similar for all three samples. Addition of sodium carbonate to the Soluplus®-based ibuprofen acid formulation resulted in an increase of the drug release rate (Fig. 13) but the rate increase was much less compared to the copovidone-based formulation.

As in the case of the copovidone-based formulation, both forms of ibuprofen (acid and salt) are detectable within the dry sample. However, no further salt formation was detectable over the course of the dissolution experiment as shown for the copovidone-based formulation. During dissolution, the signal intensity of ibuprofen acid slightly decreased over time. The ibuprofen salt on the other hand dissolved much faster, after 10 minutes only a small amount of salt was detectable. The imaging results also showed that the water could ingress or penetrate the tablet after addition of sodium carbonate, though more slowly compared to the copovidone-based extrudates.

4. Discussion

In this section, two attributes of the polymers that influence the dissolution and drug release performance of the extrudates are analyzed: the interactions between the drug and the polymer and the hydrophilic properties of the polymer. These factors play a crucial role in drug release (Kanaze et al., 2006; Najib et al., 1986; Rawlinson et al., 2007). Drug release performance, bioavailability and stability of a solid dispersions is not only influenced by the nature of the polymer but also depends on the dissociation state of the drug (Geppi et al., 2005). In general, salt forms exhibit higher aqueous solubility in contrast to their corresponding unionized form (acid/base). The FTIR images that were obtained during in-situ dissolution tests for the different samples illustrated that both the type of polymer and the form of the drug have a major impact on the drug release performance of the extrudates.

4.1. Copovidone-based extrudates

The results from USP dissolution and FTIR imaging showed significantly faster drug release rates for the copovidone-based extrudate loaded with ibuprofen salt

compared to the acid loaded samples. In order to identify the reasons for these differences, one focus was to study the interactions between the drug and the polymer. Interactions such as hydrogen bonding between the drug and the polymer can be detected by shifts or changes in the carbonyl band of the polymer. The ibuprofen salt molecule does not possess any H-bond donor and is incapable of forming H-bonds with the polymer. Therefore, the carbonyl band of the extrudate loaded with ibuprofen salt does not distinctively differ from the band of the pure copovidone (Fig. 6).

In contrast, in the ibuprofen acid loaded extrudate, the VP carbonyl band of the polymer was broader and showed decreased band intensity compared with the pure polymer. In addition, the presence of a shoulder was also observed (Fig 6). Typically, the carbonyl band of VP is shifted to lower wavenumbers when hydrogen bonded (Taylor et al., 1997; Kazarian et al., 2002; Kyerematenga et al., 2007). Therefore, the reduction in the VP carbonyl band intensity and appearance of an adjacent shoulder band is due to H-bonding between the hydroxyl group of ibuprofen acid and some VP carbonyl group of the polymer (El-Hinnawi and Najib, 1987; Kazarian and Martirosyan, 2002). As indicated earlier, VP constitutes 60% of the total molecular weight of copovidone and is the hydrophilic component of the polymer. In aqueous environment, VP mainly interacts with water molecules through H-bonding with its carbonyl group (Maeda et al., 2002). As well noted for polymers, such H-bonding interactions reduce the number of freely available water binding sites on the polymer, leading to the polymer chains becoming less hydrophilic (Chang et al., 1997; Rumondor et al., 2010; Kyerematenga et al., 2011) and thus unable to dissolve quickly when in contact with water as evidenced by the relatively slow water ingression seen in the FT-IR images (Fig. 5). Similar findings were reported for the analysis of water vapor sorption of the ASD of the acidic drug indomethacin and PVP, which showed

that the drug-polymer interactions changed significantly the water-polymer interactions leading to low water sorption of the ASD (Rumondor et al., 2010). We therefore attribute the reduced drug release rate of the extrudate loaded with ibuprofen acid to H-bonding that occurs between the hydroxyl group of the drug and the water binding sites (carbonyl groups) of the VP component of the polymer (Fig. 14). Thus, the dissolution of polymer and drug in the ibuprofen acid loaded extrudate is slower compared to the ibuprofen salt loaded extrudate as the latter is incapable of forming hydrogen bonds with the polymer. Consequently, for the ibuprofen salt extrudate the water binding sites on the polymer are not occupied and are therefore available for interactions with water as illustrated in Fig. 14. Hence, the polymer dissolves as soon as the ASD comes into contact with water leading to fast drug release as seen in the FTIR images in Fig 4. Similar differences in drug release behavior have also been reported for Eudragit® ASD containing either ibuprofen acid or ibuprofen salt and has been attributed to drug-polymer interactions (Geppi et al., 2005).

To confirm that the slow drug release in the ibuprofen acid extruadate is a result of drug-polymer interactions, 2% of a basic pH modifier, sodium carbonate was added to the formulation. In theory, this addition should modify the microenvironmental pH of the formulation when in contact with water and hence, increase dissociation of the hydroxyl group of the drug which should result in reduced or weakened H-bonding between the drug and polymer. Reduction or weakening in H-bonding should increase hydrophilicity of the polymer and formulation as a whole. In addition, the pH modifier is also capable of converting some of the ibuprofen acid molecules to the more water soluble sodium salt form (Kararli et al.,1989). The expected partial conversion of acid into salt was observed in the FTIR images in Fig. 7. The addition of the pH modifier also resulted in increased hydrophilicity of the formulation as

confirmed by the relatively fast ingress of water (FTIR images in Fig. 7) compared to the formulation without pH modifier (FTIR images in Fig. 5). Therefore, overall drug release from the formulation with the pH modifier increased significantly as seen the drug release profiles in Fig. 3 and 8.

4.2. Soluplus®-based extrudates

Similar to the copovidone based extrudates, the ibuprofen salt load Soluplus®extrudate showed a faster drug release than ibuprofen acid loaded Soluplus® extrudate as seen in drug releases profiles shown in Fig. 9. However, unlike the ibuprofen acid loaded copovidone extrudate, the ibuprofen acid loaded Soluplus® extrudate surprisingly released virtually no drug in the entire duration of the measurement. Spectral analysis shows that similar to copovidone, ibuprofen acid forms H-bonding with the major hydrophilic component of Soluplus®, VCL, as evidenced by reduction and shifting of the VCL carbonyl band from 1627 cm^{-1} to 1596 cm^{-1} in the spectrum of the extrudate (Fig. 12). Therefore, as previously pointed out, less water binding sites on the polymer chain will be available for interaction with water molecules in the ibuprofen acid containing extrudate, thus making this formulation less hydrophilic compared to the ibuprofen salt containing extrudate. FTIR imaging revealed for the ibuprofen acid Soluplus® extrudate, water could not penetrate the formulation. This is most likely due to the reduced hydrophilicity of the formulation resulting from the H-bonding formed by the drug and the major hydrophilic component of Soluplus®. This explains the inability of this formulation to release drug compared to ibuprofen salt containing formulation under the tested conditions. Similar to the copovidone extrudate, ibuprofen acid loaded Soluplus® containing 2% pH modifier (sodium carbonate) was investigated. As explained earlier, the pH modified is expected to reduce and weaken the drug polymer interactions thereby increasing the hydrophilicity of the formulation. FTIR imaging

results in Fig 13 show that the formulation became hydrophilic, and water was able to penetrate the formulation leading to slightly greater overall drug release which is also confirmed by the drug release profile shown in Fig. 9. However, the total drug release is lower compared to the same formulation with copovidone.

4.3. Comparison of the impact of copovidone and Soluplus® on the drug release behavior of extrudates

In general it was found that the drug release behavior of the extudates is dependent on both drug-polymer interactions and the nature of the matrix polymer. Overall, drug release for the copovidone-based extrudates was faster than for the Soluplus®-based extrudates. To find out the rationale behind the marked dissolution performance differences between the polymers the chemical structural units of the two polymers need to be considered. Both polymer are amphiphilic and have in common VA as their hydrophobic component. Copovidone has VP as its hydrophilic component and Soluplus® has VCL and ethylene glycol as its major and minor hydrophilic components, respectively. Studies have shown that the aqueous solution of VCL homopolymer exhibits phase separation above ~31 °C whereas VP homopolymer does not exhibit such temperature dependent behavior (Maeda et al., 2002; Laukkanen et al., 2004; Meeussen et al., 2000). This suggests that H-bonding of water molecules with the carbonyl group of VCL are relatively weak compared to VP. Consequently, hydrophilicity of copovidone is expected to be higher than Soluplus® which also suggests that in water copovidone will dissolve faster than Soluplus® as clearly demonstrated by the FTIR imaging for the two polymers in Fig. 15.

Therefore, the negative impact of H-bonding between the drug and the hydrophilic component of polymer on drug release will be more pronounced for Soluplus®-based formulations than for copovidone-based formulations. Also, based on the shift of the VCL carbonyl band in the dry state and the aqueous state (where greater shift indicates stronger interaction), the strength of the H-bond between the carbonyl group and the water molecules in terms of wavenumbers is estimated to be approximately 17cm^{-1} (Maeda et al., 2002) compared to 39 cm^{-1} estimated for the H-bond between ibuprofen acid and VCL in this work. As a result, the H-bond formed between the ibuprofen acid and Soluplus® is stronger than that of water and the polymer, thus making it extremely difficult for water molecules to displace drug molecules H-bonded to the polymer. It is worth mentioning that although physical stability of the extrudates was not the scope of this work, H-bonding on the other side improves solubility of the drug in the polymer matrix and positively affects physical stability of the amorphous drug in the ASD (Kyerematen et al., 2014).

5. Conclusions

In this study we successfully applied FTIR imaging to study hot-melt extrudates containing the model drug ibuprofen and commercially available polymer excipients copovidone and Soluplus ®. FTIR imaging results were also confirmed using industry-standard USP 2 dissolution tests, demonstrating the applicability of FTIR imaging in assessing the performance of extrudates and highlighting the additional information revealed using spectroscopic imaging over USP apparatus 2. It was shown through spectral analysis that, both the nature of the polymer and the form of the drug have significant impact on the drug release behavior of extrudates. It was found that the salt form of ibuprofen did not interact with either copovidone or Soluplus®. In contrast, the acid form of ibuprofen interacted through H-bonds with

both polymers. These interactions led to a significantly reduced drug release as the water binding sites on the hydrophilic part of the polymer were occupied through interactions with the drug and therefore no longer available to interact with water. However, the copovidone-based sample showed substantially faster drug release because of its higher hydrophilicity compared to Soluplus®. Incorporation of small amounts of sodium carbonate into the extrudates resulted in an improved drug release rate for both the copovidone- and Soluplus®-based extrudates which is explained by increase in water binding sites of the polymer due to dissociation of the hydroxyl group of the drug resulting in reduced or weakened drug-polymer interactions and also formation of the more water-soluble sodium salt form of the drug. As for the ibuprofen acid loaded samples, the copovidone-based extrudates showed a faster drug release, which was attributed to the higher hydrophilic properties of copovidone in contrast to Soluplus®. Further investigations with complex dissolution media such as buffered solutions and simulated intestinal media will be conducted in the future to gain more insights on the interplay between drug-polymer interactions, in vitro drug release rate, and colloidal structures formed during in vitro drug release in ASDs.

Acknowledgements & Disclosures

This study was financially supported by AbbVie. Sergei G. Kazarian and James A. Kimber are employees, and Leonardo A.M. Williams is a student, at the Department of Chemical Engineering, Imperial College London and have no conflicts of interest to report. Sergei G. Kazarian acknowledges research funding from the European Research Council under the European Community's Seventh Framework Programme (FP7/2007–2013)/ERC advanced grant agreement no. [227950] that supported his research in spectroscopic imaging that led to this collaboration. Marieke Pudlas is a

former employee of AbbVie and has no conflicts of interest to report. Samuel O. Kyerematen, Holger van Lishaut, and Gerd Woehrle are AbbVie employees and may own AbbVie stock/options. AbbVie participated in the interpretation of data, review and approval of manuscript.

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Figure(s)

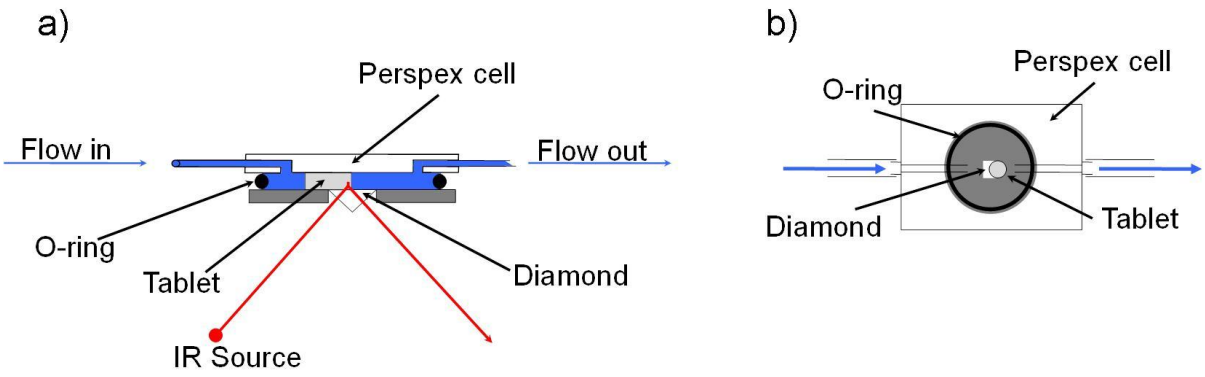

Fig. 1 : Schematic of in-situ dissolution cell. a) Side view; b) top view

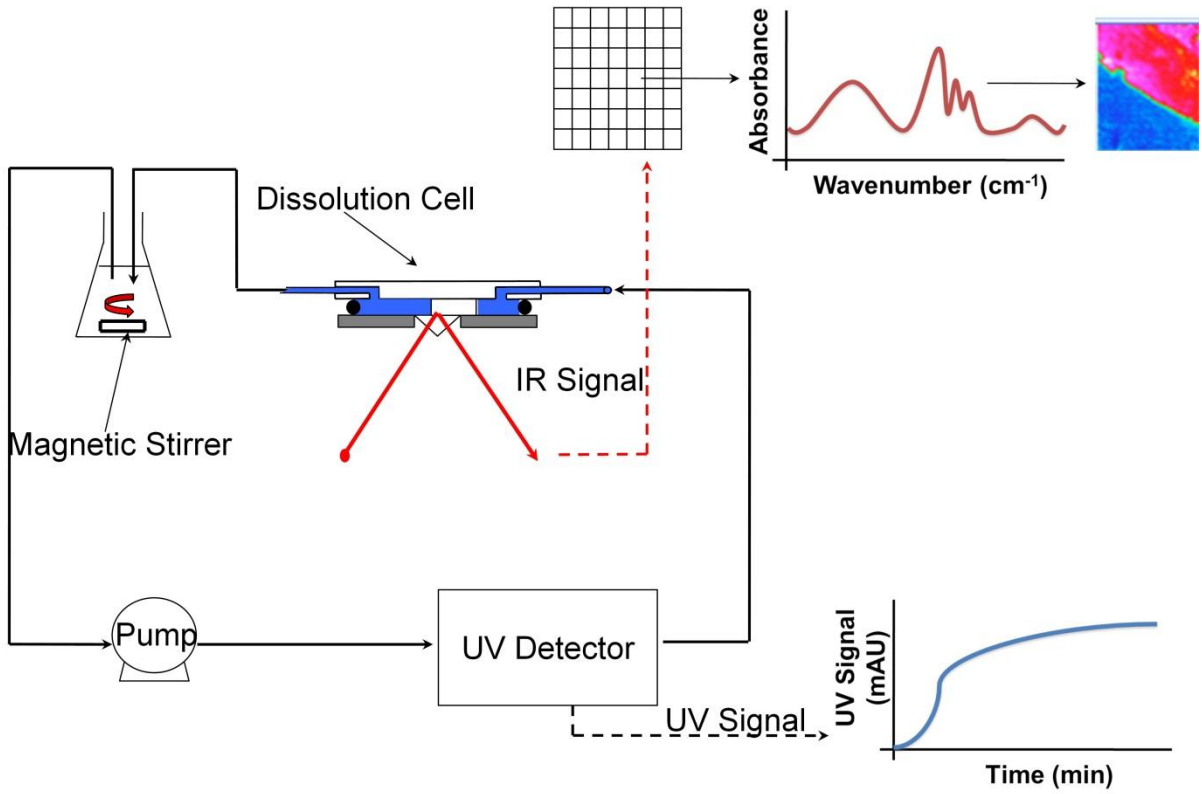

Fig. 2: Diagram of combined in-situ ATR-FTIR imaging and UV/Vis dissolution apparatus.

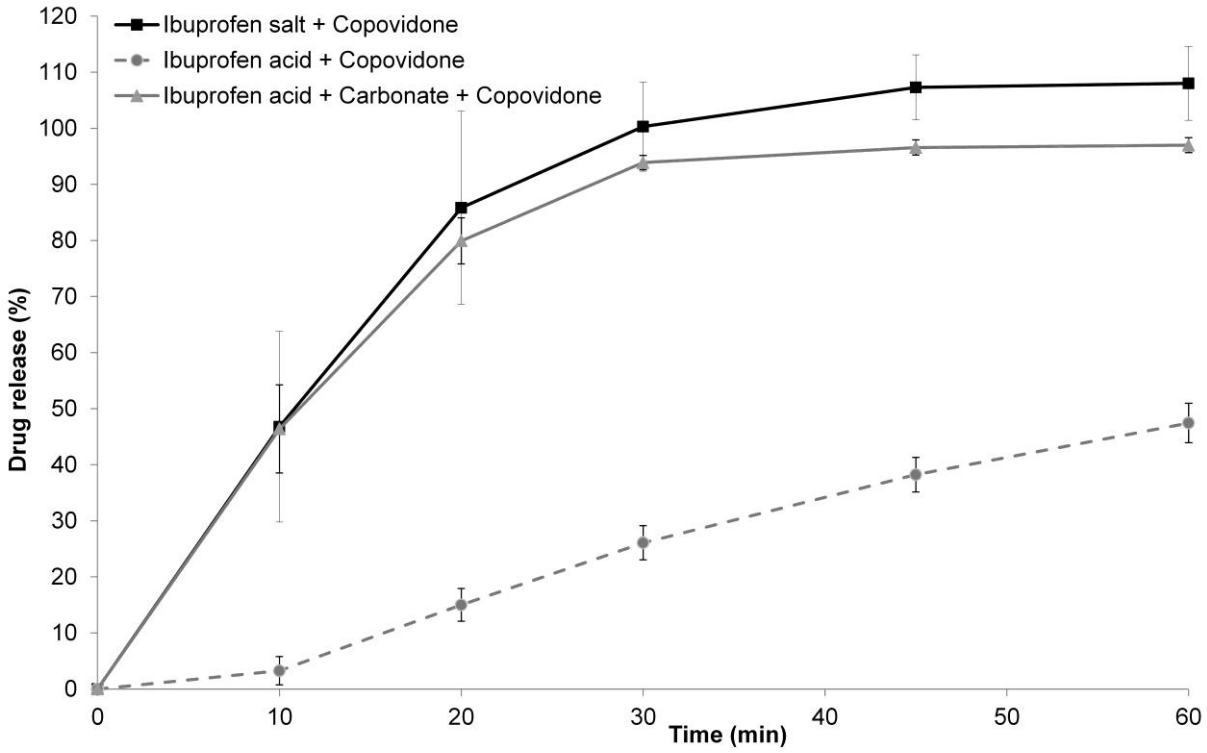

Fig. 3: In vitro drug release of copovidone-based extrudate formulations in deionized water at 37 °C using USP apparatus 2. Rapid drug release rates were detected for formulations containing ibuprofen salt, in contrast to ibuprofen acid extrudate formulations. The addition of sodium carbonate resulted in a significant increase of the drug release rate.

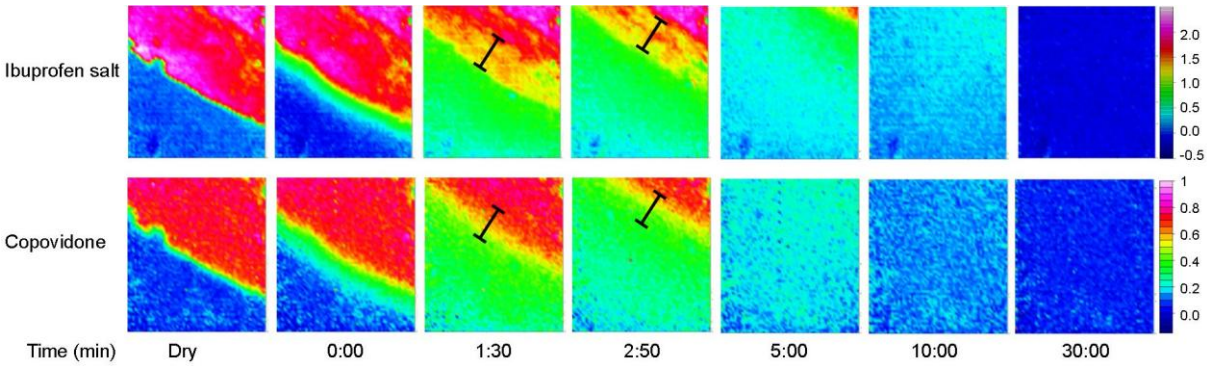

Fig. 4: FTIR images showing the dissolution performance for extrudates containing 30% ibuprofen salt and 70% copovidone. The top row reflects the distribution of the drug and the bottom row the distribution of the polymer over time. The ibuprofen images were generated based on the band from 1573 to 1530 cm^{-1} and the copovidone images from 1044 to 1013 cm^{-1}. Blue indicates domains with a low concentration and pink indicates a high concentration. Image size is (0.58 x 0.64) mm^2.

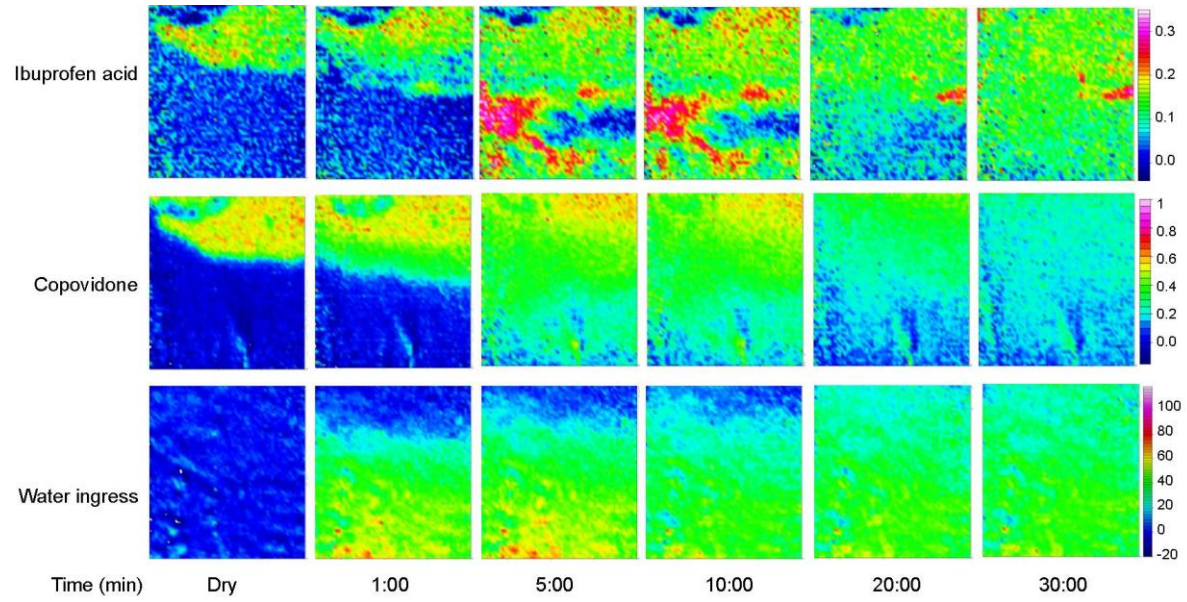

Fig. 5: Dissolution of copovidone-based extrudates loaded with ibuprofen acid. In the top row the distribution of ibuprofen acid is displayed. The middle row shows the distribution of copovidone and the bottom row the water ingress over time. The images were generated for ibuprofen acid based on the band from 1523-1501 cm^{-1}, for copovidone from 1044-1013 cm^{-1} and for water from 3600-3100 cm^{-1}.

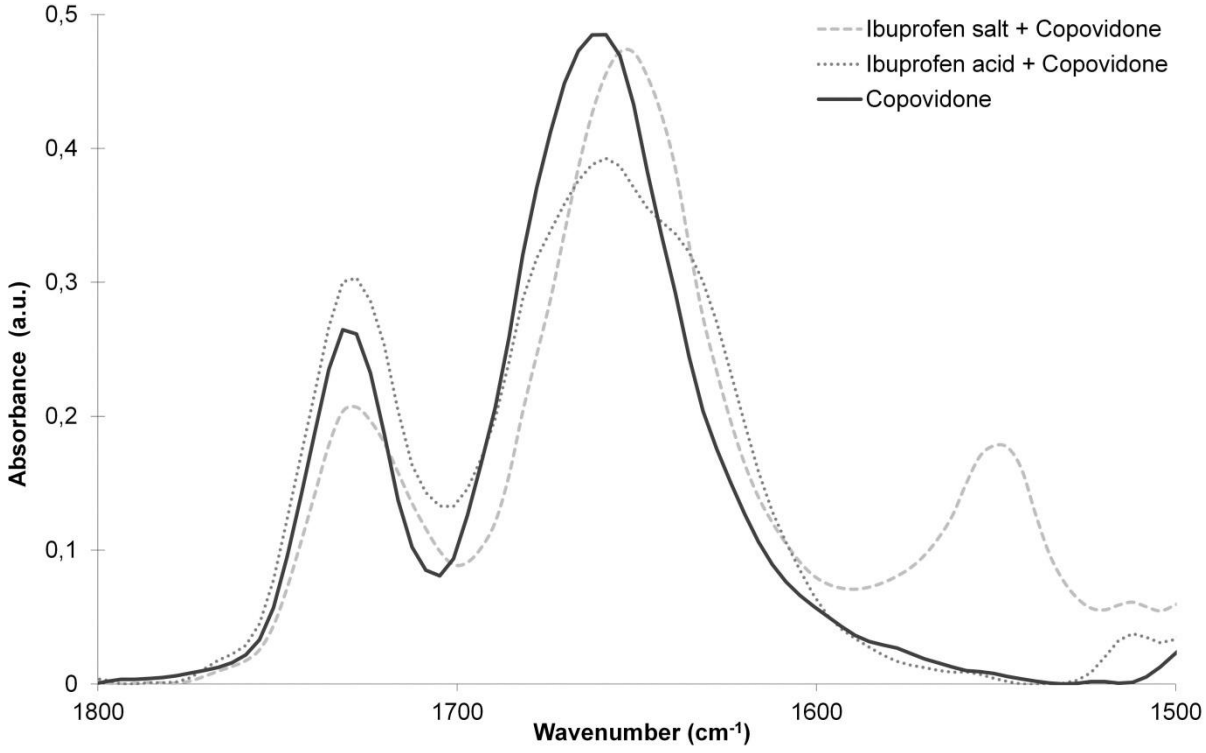

Fig. 6: Comparison of FTIR spectra of extrudate formulations containing ibuprofen salt or acid and pure copovidone in the range from 1800 to 1500 cm^{-1}.

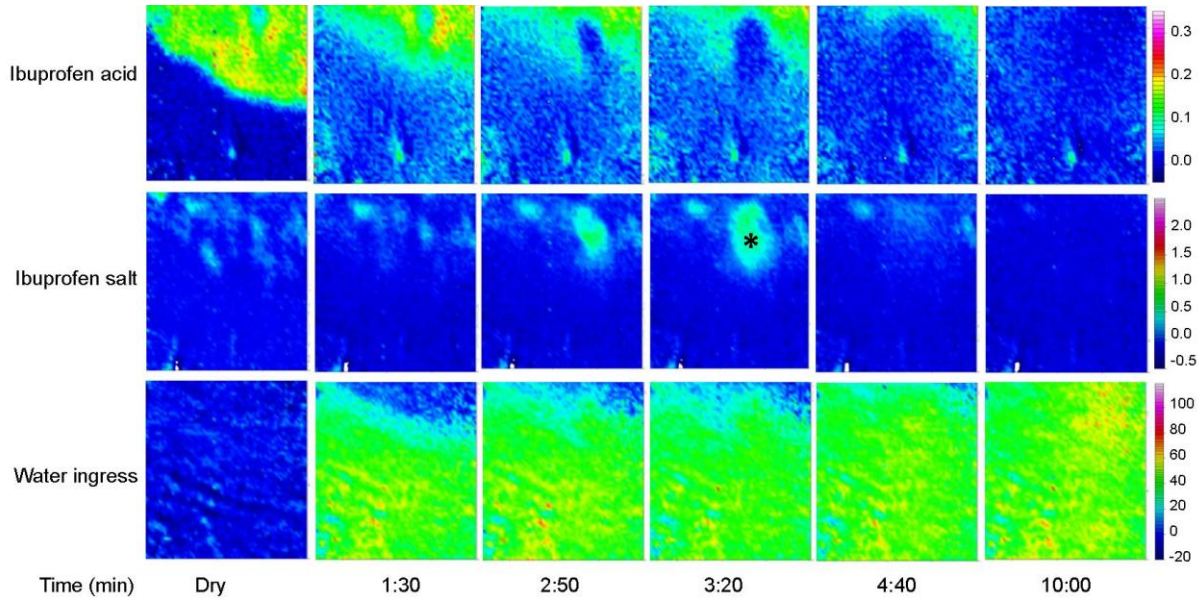

Fig. 7: Dissolution behavior of extrudate formulation containing copovidone, ibuprofen acid and sodium carbonate is shown in these FTIR images. Top row demonstrates the distribution of ibuprofen acid (1523-1501 cm^{-1}), middle row the distribution of ibuprofen salt (1573-1530 cm^{-1}) and the bottom row the water ingress (3600-3100 cm^{-1}). * indicates domain of high salt concentration.

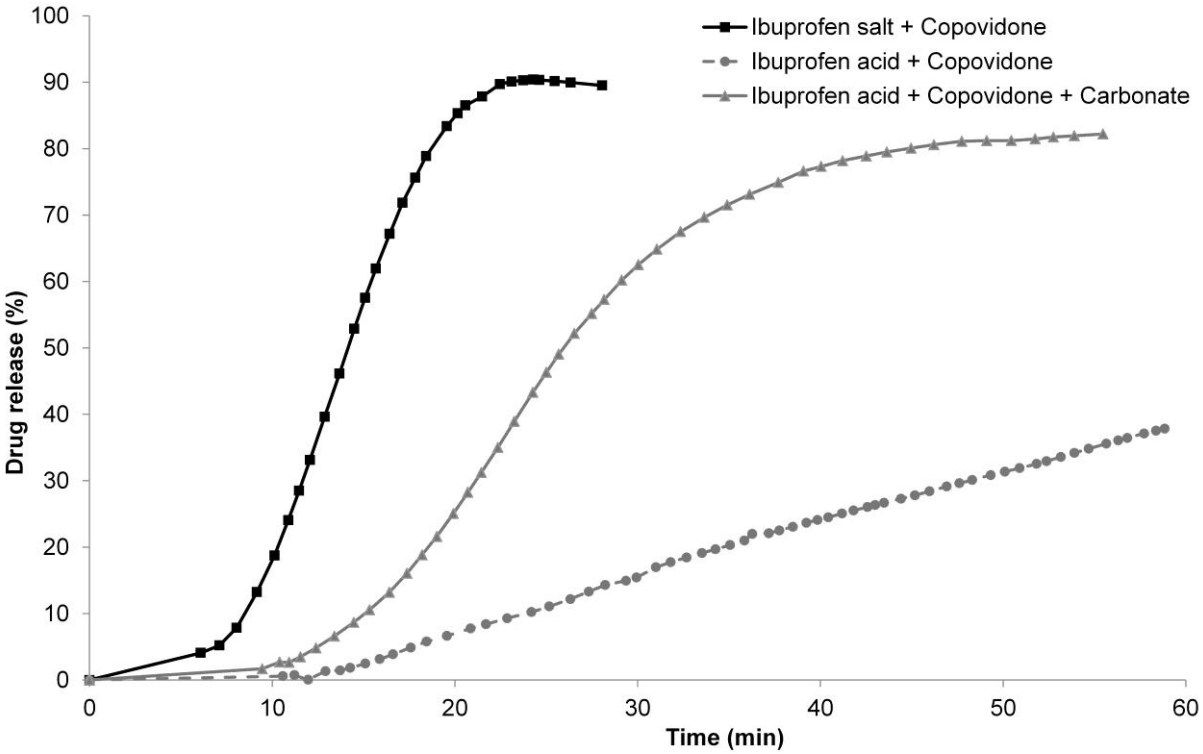

Fig. 8: Drug release rates obtained during FTIR dissolution tests of copovidone-based extrudates by UV/ Vis spectroscopy. The fastest release was detected for the extrudate sample loaded with ibuprofen salt, followed by the extrudate containing additional sodium carbonate and ibuprofen acid loaded extrudates showed the slowest release rate over the course of 60 minutes.

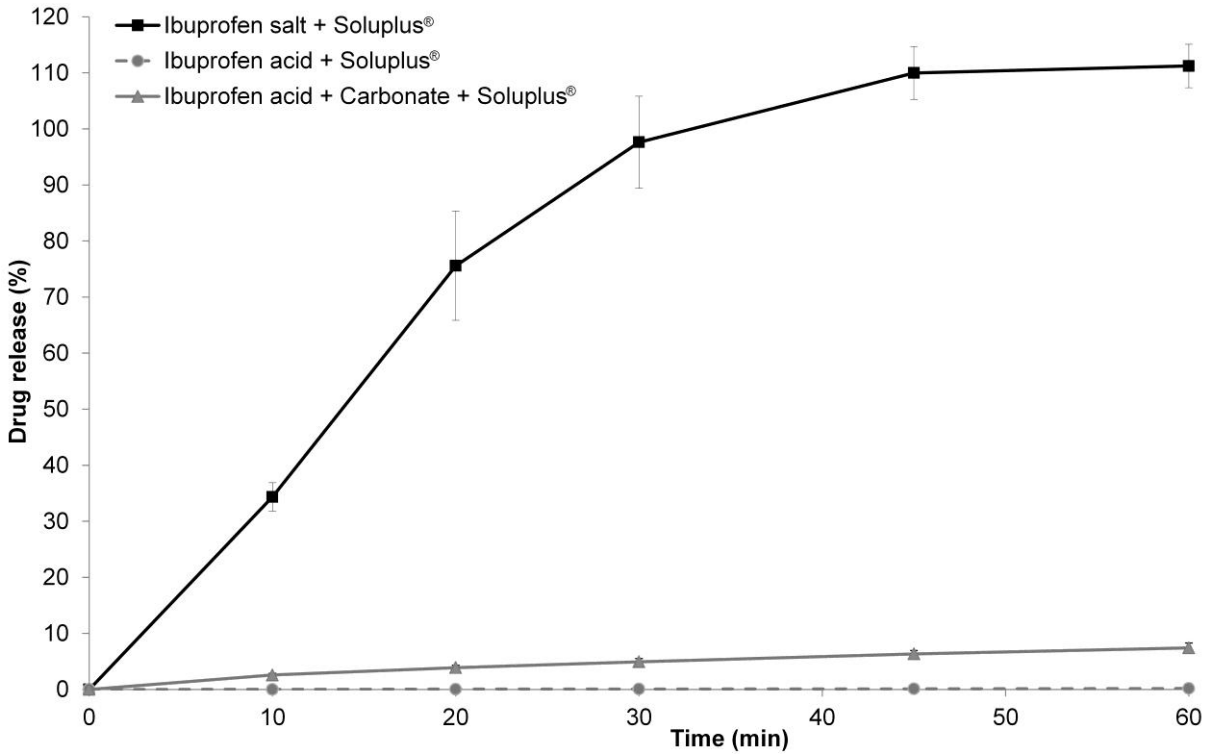

Fig. 9: In vitro drug release of Soluplus®-based extrudate formulations in deionized water at 37 °C using USP apparatus 2. Rapid drug release rates were detected for formulations containing ibuprofen salt, in contrast to ibuprofen acid extrudate formulations. The addition of sodium carbonate resulted in a slight increase of the drug release rate.

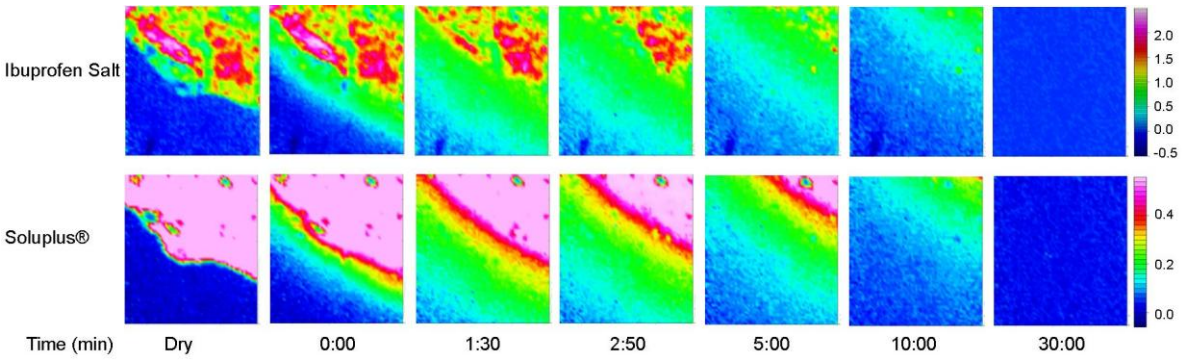

Fig. 10: Dissolution of Soluplus®-based extrudates loaded with ibuprofen salt. In the top row the distribution of the ibuprofen salt is shown over time. These images were generated based on the band from 1573-1530 cm^{-1}. In the bottom row, the distribution of Soluplus® is demonstrated. The images were generated based on the band from 1208-1187 cm^{-1}.

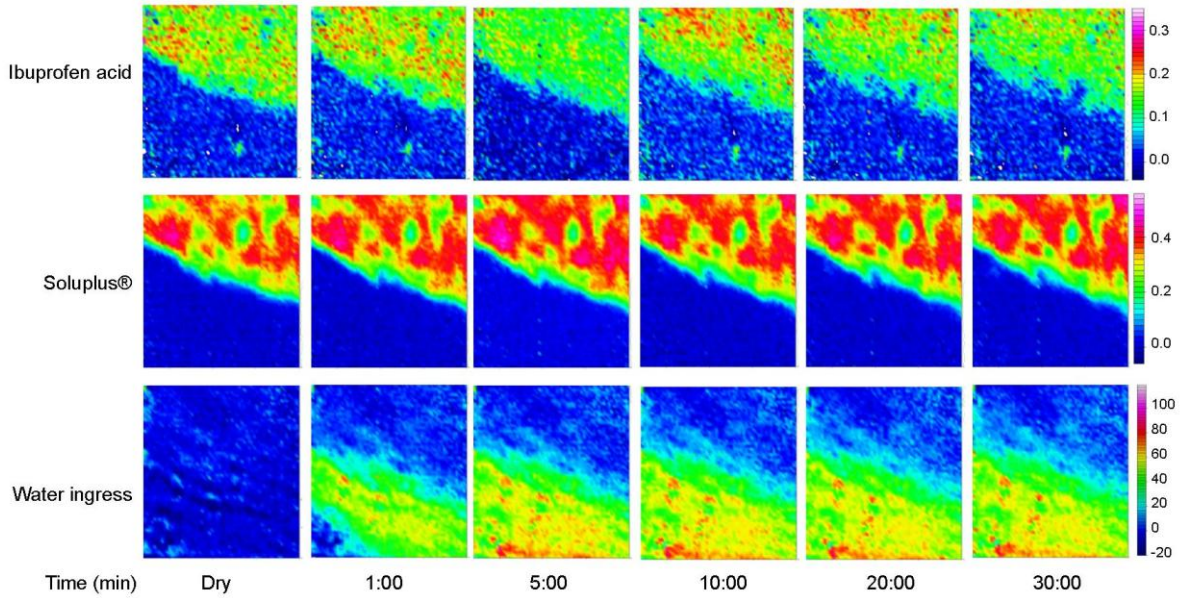

Fig. 11: FTIR images of ibuprofen acid, Soluplus® and water ingress during dissolution testing of a Soluplus®-based extrudate loaded with ibuprofen acid as a function of time. The images in the top row show the distribution of the ibuprofen acid, generated using the band between 1523 to 1501 cm^{-1}. The middle row reflects the distribution of Soluplus®. These images were generated using the band between 1208 to 1187 cm^{-1}. The bottom row demonstrates the water ingress over time.

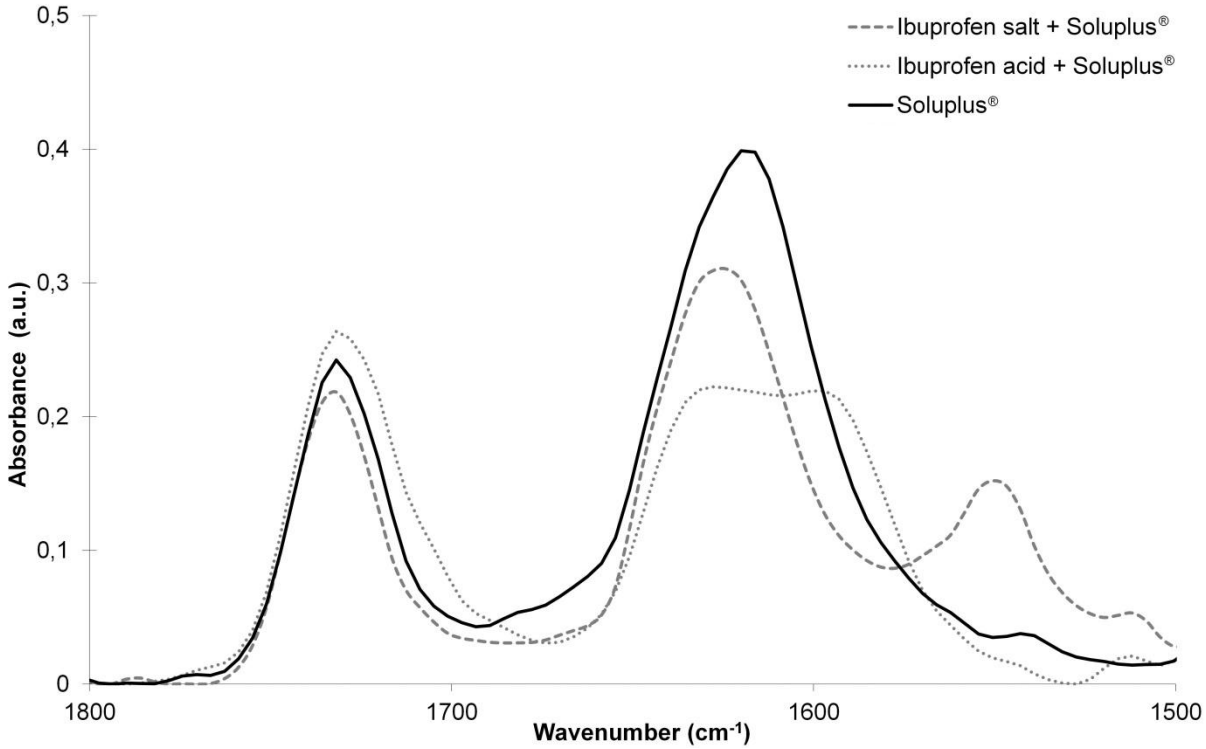

Fig. 12: Comparison of FTIR spectra of extrudate formulations containing ibuprofen salt or acid and pure Soluplus® in the range from 1800 to 1500 cm^{-1}.

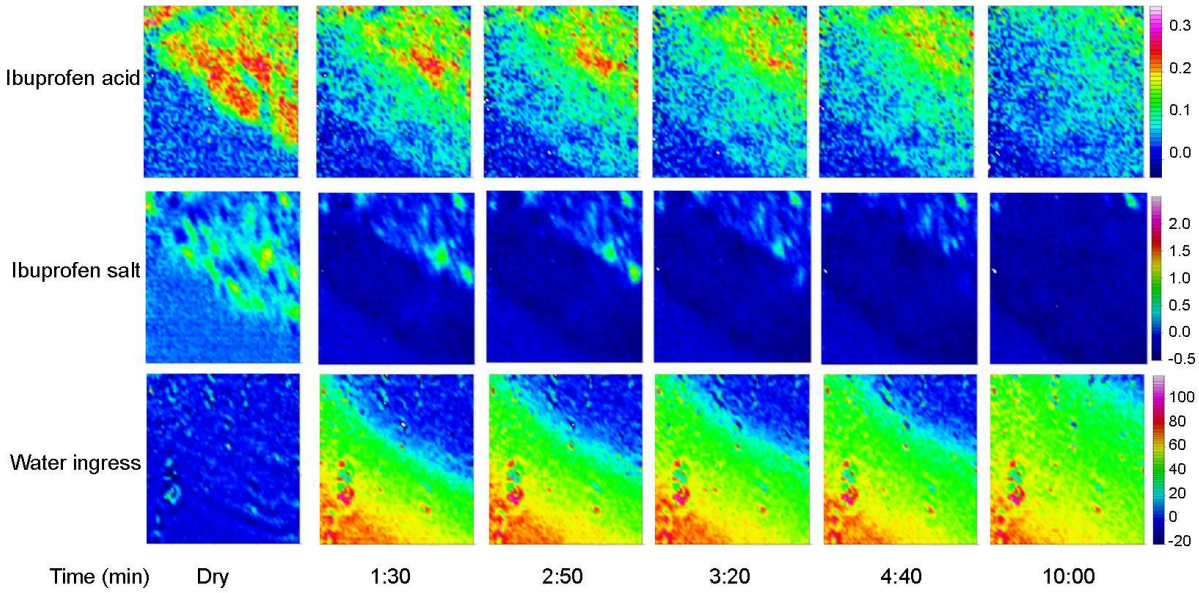

Fig. 13: Dissolution behavior of extrudate formulation containing Soluplus®, ibuprofen acid and sodium carbonate is shown in these FTIR images. Top row demonstrates the distribution of ibuprofen acid (1523-1501 cm^{-1}), middle row the distribution of ibuprofen salt (1573-1530 cm^{-1}) and the bottom row the water ingress (3600-3100 cm^{-1}).

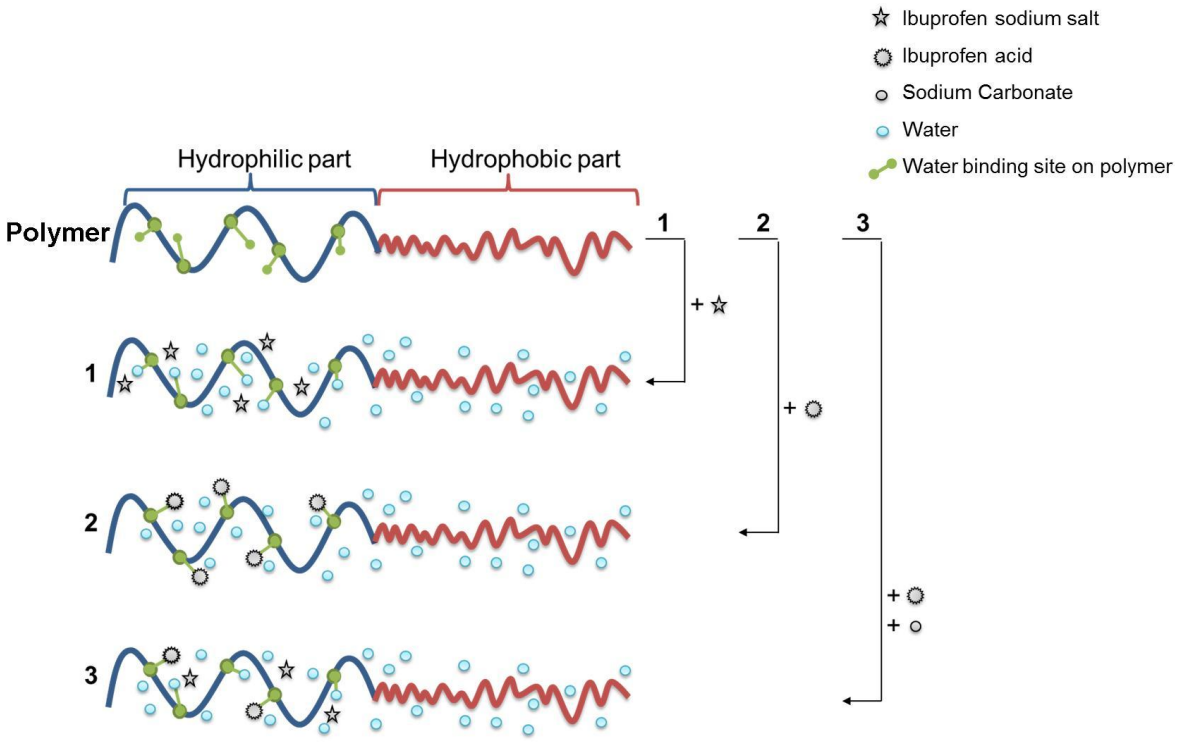

Fig. 14: Schematic illustrating the interaction between the three different formulations containing either ibuprofen salt, ibuprofen acid or both. 1) Ibuprofen salt does not interact with the polymer, which results in a good polymer dissolution in water as the water bindings sites on the polymer are available to interact with water molecules. 2) Shows interaction between the hydrophilic part of the polymer and ibuprofen acid molecules resulting in, less water binding sites available on the polymer for interaction with water molecules. 3) Shows that the water binding sites on the polymer are partially occupied by molecules of ibuprofen acid resulting in more water binding sites available for interaction with water molecules.

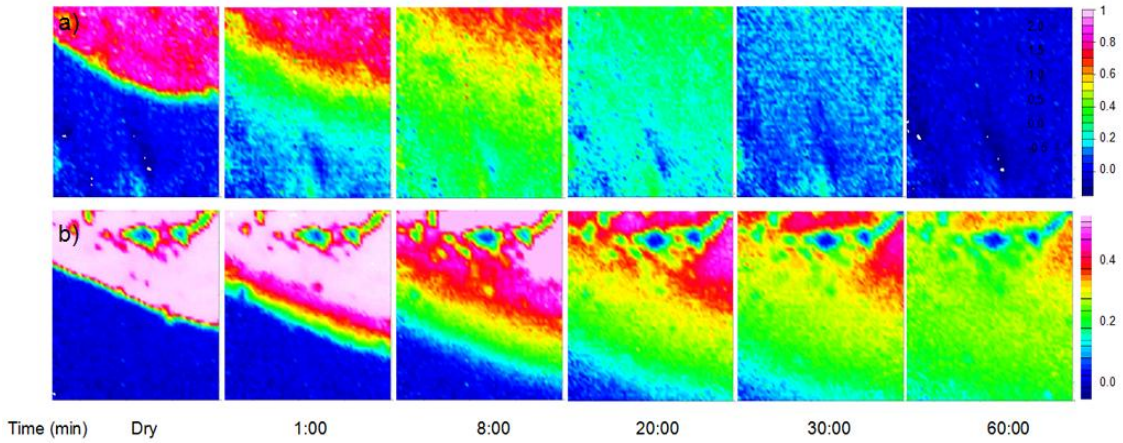

Fig. 15: FTIR images showing dissolution behavior of pure polymer. a) Dissolution of copovidone based on the band from 1044-1013 cm^{-1}. b) Dissolution of Soluplus based on the band from 1208 to 1187 cm^{-1}.

Table 1: Extrudate composition and extrusion temperature

Formulation	Components (w/w%)				Extrusion temperature (°C)
	Copovidone	Soluplus®	Ibuprofen salt	Ibuprofen acid	
1	70	-	30	-	150
2	70	-	-	30	120
3*	68	-	-	30	100
4	-	70	30	-	150
5	-	70	-	30	100
6*	-	68	-	30	90

*Contains 2 w/w% Na_2CO_3

Table 2: Integration ranges used to generate FT-IR spectroscopic images

Substance	Integration range (cm^{-1})	Assignment	Reference
Ibuprofen salt	1573-1530	*v*(COO^-)	(Wray et al., 2011)
Ibuprofen acid	1523-1501	*v*(C-C)	(Brás et al., 2011)
Copovidone	1044-1013	*v*(C-O)	(Nishikida et al., 2003)
Soluplus®	1208-1187	*v*(C-O-C)	(Thakral et al., 2012)
Water	3600-3100	*v*(OH)	(Wray et al., 2011)