IN-LINE NIR SPECTROSCOPY FOR THE UNDERSTANDING OF POLYMER-DRUG INTERACTION DURING PHARMACEUTICAL HOT-MELT EXTRUSION

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Abstract

The aim was to evaluate near-infrared spectroscopy for the in-line determination of the drug concentration, the polymer-drug solid-state behaviour and molecular interactions during hot-melt extrusion.

Kollidon®SR was extruded with varying metoprolol tartrate (MPT) concentrations (20, 30, and 40%) and monitored using NIR spectroscopy. A PLS model allowed drug concentration determination. The correlation between predicted and real MPT concentrations was good (R^2=0.97). The predictive performance of the model was evaluated by the root mean square error of prediction, which was 1.54%. Kollidon®SR with 40% MPT was extruded at 105°C and 135°C to evaluate NIR spectroscopy for in-line polymer-drug solid state characterization.

NIR spectra indicated the presence of amorphous MPT and hydrogen bonds between drug and polymer in the extrudates. More amorphous MPT and interactions could be found in the extrudates produced at 135°C than at 105°C. Raman spectroscopy, DSC and ATR FT-IR were used to confirm the NIR observations. Due to the instability of the formulation, only in-line Raman spectroscopy was an adequate confirmation tool. NIR spectroscopy is a potential PAT-tool for the in-line determination of API-concentration and for the polymer-drug solid state behaviour monitoring during pharmaceutical hot-melt extrusion.

KEY WORDS: NIR spectroscopy, Hot-Melt Extrusion (HME), Process Analytical Technology (PAT).

Introduction

Hot-melt extrusion (HME) is one of the most widely used processing technologies in the plastic, food and rubber industry[1]. Recently, it also found its application in pharmaceutical manufacturing operations, offering many advantages compared to traditional pharmaceutical processing techniques[1-5] for solids: the process is anhydrous; poorly compactable materials can be incorporated into tablets; the materials have a short residence time in the extruder during processing; HME enables superior mixing (both distributive and dispersive); it allows the production of formulations with modified release; it allows masking of the bitter taste of several active pharmaceutical ingredients (API's) and in addition it improves the dissolution rate and the bioavailability of poorly water soluble drugs by the formation of solid solutions or solid dispersions[6]. A solid dispersion consists of at least two different components, generally a hydrophilic matrix and a hydrophobic drug[7]. The polymer matrix can be either crystalline or amorphous, and the drug can be dispersed molecularly, in amorphous clusters or in crystalline particles. Each of these solid states has its own properties such as storage stability, dissolution rate, etc. The degree of crystallinity or amorphism in pharmaceutical materials is recognized as a critical factor that may affect drug stability and dosage form performance[8].

Nowadays, extruders already allow in-line monitoring and control of process parameters (e.g. barrel and die temperature, powder feed rate and screw speed, torque and melt pressure in the extruder and die). In-line monitoring and control of quality parameters corresponding to the extruded product itself, such as drug load and solid state, has been performed recently with Raman spectroscopy[9], but not yet with NIR spectroscopy. Besides real-time assessment of product characteristics, in-line spectroscopic monitoring helps to increase the understanding of the product behaviour during extrusion.

Today, the intention within the pharmaceutical industry is to move from traditional batch processing towards continuous processing, hereby increasing process efficiency and production. Continuous processes are based on the one-in-one-out principle and offer many advantages: no scale-up issues resulting in a shorter development time, possible automation of the production line, reduction of production costs, faster product release, less product variability and improved product quality[10,11]. Hot-melt extrusion can be operated as a continuous process, capable of consistent product flow at relatively high throughput rates[1], making it suitable for large scale production.

The FDA has introduced the concept of Process Analytical Technology (PAT) in 2004[12]. Pharmaceutical products must meet very strict specifications. However, conventional pharmaceutical manufacturing is generally accomplished using batch processing followed by time-consuming, expensive and less efficient off-line laboratory testing on randomly collected samples to evaluate the intermediate or end product quality. The processes themselves are not fully understood and are often inefficient black-boxes. PAT-tools such as near-infrared (NIR) spectroscopy provide in-line and real-time process information concerning critical formulation parameters, which might contribute to steering processes towards their desired state through adaptations of process settings. It is evident that continuous manufacturing needs continuous process monitoring and control.

Near-infrared spectroscopy is a fast, non-destructive analytical technique, which requires (nearly) no sample pre-treatments[13]. In the near infrared area (800-2500 nm or 12500-4000 cm^{-1}), mainly vibrations of CH, OH, NH and SH bonds are observed as overtones or combinations of the fundamental IR bands, resulting in overlapping absorption bands in the spectra. Hence, NIR spectra are more complex and difficult to interpret compared to IR spectra. Therefore, chemometrics are often required to extract the useful information from the NIR spectra[14]. Because of its unique properties[14], like high analysis speed, no need for sample preparations, its non-destructive and non-invasive nature of analysis and the use of fibre optical probes, NIR spectroscopy is an ideal process analyzer for hot-melt extrusion. Furthermore, due to the fact that NIR spectra are sensitive to changes in hydrogen bonding and packing in the crystal lattice, NIR can be applied for solid state analysis and the understanding of molecular interactions[15].

NIR spectroscopy has been applied in-line and in the transmission mode during single screw hot-melt extrusion to monitor the HDPE/PP[16,17] and LDPE/PP[18] polymer melt composition in the extrusion die. Further, NIR spectroscopy has been used to monitor the ethylene vinylacetate copolymer composition in the extrusion die during single screw extrusion[19-21], and for the quantification of the copolymer composition in a polypropylene and ethylene vinyl acetate blend[22] during twin screw extrusion. NIR has also been applied to measure the polymer melt flow index[21] in single screw extrusion and to detect and quantify small amounts of Irganox in polypropylene[23] and $Mg(OH)_2$ in LDPE[20] and HDPE[24] during twin screw extrusion. Further, NIR spectroscopy was used to monitor the content of pulverised chalk in polypropylene[22], to quantify the melamin cyanurate concentration in polyamid 12[25] and to quantify the composition of a PE/PS blend[25] during twin screw extrusion.

The aim of this study was to evaluate the suitability of NIR spectroscopy in its reflectance mode for the in-line monitoring of pharmaceutical HME processes. Via fibre optic cables, an NIR probe was

implemented in the HME equipment, to monitor the API content and the polymer-drug behaviour (solid state and molecular interactions) during hot-melt extrusion. To our best knowledge, no literature describing the use of NIR spectroscopy as a PAT-tool for this type of formulation characterisation in a pharmaceutical hot-melt twin screw extrusion process is available.

Materials and Methods

1. Materials

Metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) (Fig. 1a) was chosen as a model drug. It has a melting temperature around 120°C. Kollidon® SR (Fig. 1b) was kindly donated by BASF (Ludwigshafen, Germany). This amorphous polymer consists of 8 parts polyvinyl acetate (w/w) and 2 parts polyvinyl pyrrolidone (w/w). The solubility parameters of both components were calculated by SPWin, version 2.11[26] to predict the solid state miscibility.

2. Hot-melt extrusion

Hot-melt extrusion was performed with a Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruder (Thermo Fisher Scientific, Germany). The temperature of each segment of the extruder and of the die can be controlled separately. The hot-melt extruder was equipped with a DD Flexwall® 18 feeder (Brabender Technologie, Germany), which was set in its gravimetric feeding mode.

For the development of a calibration model allowing in-line API quantification, 3 different polymer-drug mixtures, consisting of Kollidon® SR and 20%, 30% and 40% (w/w) MPT respectively, were extruded. Prior to hot-melt extrusion, the polymer and drug were blended in a mortar. Each mixture was hot-melt extruded with a feeder speed of 0.5 kg/h and a screw speed of 80 rpm. The barrel temperature profile was set at 90-135-135-135-135-135°C (from hopper to die) for all mixtures. The minimum batch size used was 700g of polymer-drug mixture.

In a second part of the study, two identical polymer drug-mixtures were prepared to evaluate the suitability of NIR spectroscopy for in-line polymer-drug solid state characterization. Both physical mixtures contained 40% MPT and 60% Kollidon® SR (w/w), and were extruded with a powder feed rate of 0.5 kg/h and a screw speed of 80 rpm. The first mixture was extruded using a barrel temperature profile of 90-135-135-135-135-135°C, which is above the melting temperature of pure

MPT. The other mixture was extruded using a barrel temperature profile of 90-105-105-105-105-105°C.

3. NIR spectroscopy

Diffuse reflectance NIR spectra were continuously collected in-line and noninvasively during hot-melt extrusion using a Fourier-Transform NIR spectrometer (Thermo Fisher Scientific, Zellik, Belgium, Nicolet Antaris II near-IR analyzer) equipped with an InGaAs detector, a quartz halogen lamp, and a fibre-optic probe which was mounted in the extrusion die (Fig. 2). Spectra were collected every 30 seconds in the 9000 – 4500 cm^{-1} region with a resolution of 16 cm^{-1} and averaged over 32 scans. For the monitoring of the stability of the extruded end products, spectra of the extrudates were continuously collected off-line for 20 minutes immediately after extrusion at room temperature. Here, spectra were collected every 13 seconds with a resolution of 16 cm^{-1} and averaged over 32 scans.

Data analysis was performed using the Result software (Version 3.0, Thermo Fisher Scientific, Zellik, Belgium) and SIMCA-P+ (version 12.0.1.0, Umetrics, Umeå, Sweden). Spectra collected in the diffuse reflectance mode mostly require spectral pre-treatment before analysis. The degree of scattering depends on the wavelength of the light and the refractive index of the sample, which causes a non-equal scatter over the whole spectrum. This can result in a baseline shift[22]. Therefore, multiplicative signal correction (MSC) was used before chemometric analysis of the spectra. Using MSC, undesired scatter is removed from the raw spectra to prevent it from dominating over the chemical information within the spectra. The result of MSC pre-processing is that each corrected spectrum has the same offset and amplitude, eliminating the difference in light scatter in the spectra from the different samples, before developing the calibration model[27]. Furthermore, second derivative pre-processing was done after MSC correction. Second derivatives of NIR spectra magnify differences in spectral features, provide baseline normalization and remove data offsets due to scattering effects and pathlength variation[28]. For principal component analysis (PCA) and for the development of the partial least squares (PLS) model, 20 spectra of each polymer-drug mixture (20%, 30% and 40% MPT) were used. Prior to PCA and PLS, spectra were mean centred. The PLS model was developed by regressing the MPT-concentrations (Y) versus the corresponding in-line collected NIR spectra (X). This model was validated using 5 new NIR spectra collected during new extrusion runs of each polymer-drug mixture. These validation spectra were used to evaluate the predictive performance of the PLS model.

4. Raman spectroscopy

To confirm the in-line NIR polymer-drug solid state observations, Raman spectra were collected using a Raman Rxn1 spectrometer (Kaiser Optical Systems, Ann Arbor, MI, USA), equipped with an air-cooled CCD detector. A fibre-optic Raman Dynisco probe was used to monitor the extrusion process in-line. The Raman Dynisco probe was implemented into the extrusion die[9], in an identical manner as the NIR probe (see Fig. 2). The laser wavelength was the 785 nm line from a 785 nm Invictus NIR diode laser. All spectra were recorded with a resolution of 4 cm^{-1} and an exposure time of 2 seconds, using a laser power of 400 mW. Spectra were collected every 15 seconds. Data collection and data transfer were automated using the HoloGRAMS™ data collection software, the HoloREACT™ reaction analysis and profiling software, the Matlab software (version 7.1, The MathWorks Inc., Natick, MA) and SIMCA-P+ (version 12.0.1.0, Umetrics, Umeå, Sweden) was used for data analysis . The analyzed spectral region was 0 – 1800 cm^{-1}, since this region contained all useful drug and polymer information. Savitzky-Golay and SNV pre-processing were applied on the in-line collected spectra to exclude inter-batch variation and variation caused by baseline-shifts, respectively.

5. DSC analysis

Differential scanning calorimetry was performed with a DSC Q 2000 (TA Instruments, Belgium). The thermograms were produced with the Thermal Advantage Release 5.1.2 software and analysed with TA Instruments Universal Analysis 2000 4.7A (TA Instruments, Belgium). Hermetically sealed aluminium pans (TA Instruments, Belgium) were used containing the samples of approximately 5 mg. Measurements were carried out in a nitrogen atmosphere. The flow rate of dry nitrogen gas was 50 mL/min. Temperature and enthalpic calibration was done using indium as standard. Samples were subjected to three cycles. First, the pans were heated with a heating rate of 10,0°C/min from -30°C up to 180°C in the first heating cycle. Then, a cooling cycle was started with a cooling rate of -10,0°C/min to -30°C, followed by a second and final heating cycle which was identical to the first.

6. ATR FT-IR spectroscopy

In addition to DSC analysis and Raman spectroscopy, attenuated total reflectance (ATR) Fourier transform (FT) infrared (IR) spectroscopy was also used to confirm the solid state observations in the NIR spectra. Spectra were collected from MPT and Kollidon® SR, from the physical mixture containing 40% MPT in Kollidon® SR and from the extrudates of this physical mixture extruded at 135°C and

105°C. The ATR FT-IR spectra were collected with a Bruker Vertex 70 FT-IR spectrometer, equipped with a DTGS detector and a PIKE accessory, equipped with a diamond ATR crystal.

Results and Discussion

1. In-line monitoring of API concentration

Mixtures of 20, 30 and 40% (w/w) MPT in Kollidon® SR were hot-melt extruded. Fig. 3 shows the differences in the pre-processed in-line collected NIR spectra (6150 - 4500 cm^{-1}). PCA was applied on 60 NIR spectra (20 spectra per extruded MPT concentration level) leading to a model with two principal components covering nearly all spectral variation. The first principal component (PC1) captures 99.0% of the variation; the second component (PC2) covers 0.4% of extra variation. The variation captured by the first component is caused by differences in API concentration, as confirmed by the PC1 versus PC2 scores plot (Fig. 4). The variation captured by the second principal component, contains only a minor part of the total spectral variation, which is not caused by differences in drug loading.

A PLS model, allowing prediction of the MPT concentration in unknown samples during hot-melt extrusion processes, was developed. The in-line collected NIR spectra (X) were regressed versus the known MPT concentrations (Y). A model with two PLS components was chosen, since the goodness of prediction of the model (Q^2) did not increase significantly after adding extra components[27]. The predictive performance of this PLS model was evaluated using five test spectra collected during new hot-melt extrusion runs of three mixtures, also containing 20%, 30% and 40% (w/w) MPT in Kollidon® SR. The PLS model was used to predict the corresponding MPT concentrations of these 15 NIR test spectra. When plotting the predicted versus the observed MPT concentration values an R^2 of 0.97 was obtained. The resulting root mean square error of prediction (RMSEP) was 1.54%. The spread in predicted concentration values was larger for mixtures containing a drug load of 20% compared to the 30% and 40% MPT mixtures. NIR absorption bands are typically broad, and due to overlapping of peaks, it is more difficult to accurately predict small drug concentrations, since the peaks of MPT are masked by larger peaks of Kollidon® SR.

2. In-line monitoring of solid state and polymer-drug interactions

2.1. Near-infrared spectroscopy

To obtain a good compatibility between polymer and drug, the difference between solubility parameters (δ) of polymer and drug should be less than 2.0 $MPa^{1/2}$ [29]. When this is achieved, miscibility is optimal and, therefore, a glass solution can be formed during melt extrusion. Components with a difference in solubility parameters higher than 10 $MPa^{1/2}$ are likely to be immiscible. The solubility parameter for MPT is 23.59 $MPa^{1/2}$ and 20.93 $MPa^{1/2}$ for Kollidon® SR, as calculated. As the difference between these solubility parameters is 2.66 $MPa^{1/2}$ a glass solution formation will probably not be obtained during hot-melt extrusion, though sufficient miscibility between Kollidon® SR and MPT may be expected.

Two mixtures containing both 40% MPT and 60% Kollidon® SR (w/w) were extruded at 105°C and 135°C, respectively. It was expected that the fraction of crystalline MPT would be larger when extrusion was performed at 105°C, since this temperature is below the melting temperature of MPT (± 120°C). At 135°C, more MPT was expected to transform to the amorphous state. It is evident that formulations containing a mixture of crystalline and amorphous API are not stable and therefore not desired in pharmaceutical dosage forms. However, the aim of this paper was not to develop a stable pharmaceutical formulation, but to demonstrate the potential of NIR spectroscopy to monitor different states of a drug within a formulation, to detect unwanted changes in the solid state of the drug during the hot-melt extrusion process.

Fig. 5 shows the NIR spectra of the physical mixture (Kollidon® SR with a drug load of 40% MPT (w/w)) and the in-line collected spectra during extrusion of this physical mixture at 105°C and 135°C. When comparing the spectra of the extrudates to those of the physical mixture, peak shifts throughout the entire spectrum are visible (Fig. 5a). These shifts indicate molecular interactions between polymer and drug. The shifts are smaller for the extrudate produced at 105°C compared to the extrudate processed at 135°C, suggesting more interaction between Kollidon® SR and MPT in the latter. Some of the MPT in the extrudates produced at 135°C (above Tm of MPT) is amorphous, which enhances interaction with the polymer. At 105°C (below Tm of MPT), a larger fraction of MPT remains crystalline, explaining the smaller peak shifts in the spectra of this extrudate. Polymers can improve the physical stability of drugs in solid dispersions, due to specific interactions such as ion-dipole interactions and intermolecular hydrogen bonding with functional groups of the drug [6,30]. These interactions are confirmed by the appearance of a peak at 6495 cm^{-1} (1540 nm) in the spectra of the

extrudates (Fig. 5b), which is absent in the spectrum of the physical mixture. This peak indicates the formation of hydrogen bonds in which the hydroxyl groups of MPT act as proton donors. In hydrogen bonded alcohols, a broad peak manifests in the 6850 – 6240 cm^{-1} region, which is attributed to the first overtone of the bonded hydroxyl[31]. At 135°C, more MPT is present in the amorphous state, which means that more MPT is free to interact with the polymer, leading to the formation of more hydrogen bonds. This explains why the peak at 6495 cm^{-1} is slightly more intense in the spectra of the extrudates produced at 135°C than at 105°C.

The NIR spectra of pure MPT contain well defined, rather narrow bands. Both extrudates still contain the MPT peaks (Fig. 5c), though they are broader, indicating that not all MPT remained in its crystalline form and that some MPT became amorphous. Broad bands indicate a lack of long-range three-dimensional order of the molecules[32]. The peaks in the extrudate at 135°C are slightly broader and less defined than at 105°C, indicating the presence of more amorphous MPT in the extrudate at 135°C. Since Kollidon® SR is an amorphous polymer, this broadening does not occur in polymer peaks. In the physical mixture, no interactions have occurred. Consequently, the peaks of MPT remain as sharp as the original MPT peaks.

2.2. Differential scanning calorimetry

DSC analysis, ATR FT-IR spectroscopy and Raman spectroscopy were used to confirm the interpretation of solid-state and drug-polymer interaction from the NIR spectra. Fig. 6a details the thermograms of the physical mixture and the extrudates of the physical mixture extruded at 105°C and 135°C. In the extrudates, the glass transition temperature (Tg) of Kollidon® SR decreased due to the extrusion process itself, which slightly lowers the Tg of a polymer[33], and due to the plasticizing effect of MPT on the polymer, shown in Fig. 6b. For confirmation of the NIR spectral information, data from the first heating cycle were used, whereas the data from the second heating cycle were used to confirm the plasticizing effect of MPT on Kollidon® SR. The higher the drug loading in a physical Kollidon® SR – MPT mixture, the lower the Tg in the second heating cycle of the DSC experiment. A lower Tg indicates a molecular dispersion and thus miscibility of the drug in the polymer, whereas an unchanged Tg implies separation of the polymer- and drug phase[34]. The thermogram of the physical mixture shows a Tg at 45.4°C for Kollidon® SR (Fig. 6a). The Tg of Kollidon® SR in the extrudates containing 40% MPT (w/w) at 105°C and 135°C is 40.2°C and 40.7°C, respectively. The chain mobility of the polymer has increased due to incorporation of MPT in the polymer matrix, which results into a decrease in glass transition temperature. However, the decrease in Tg is identical for both extrudates, suggesting that an equal level of interactions has occurred in

both extrudates, which is in contrast with the NIR measurements, where a stronger peak shift in the extrudate produced at 135°C was observed.

A similar shift in the endothermal melting peak of the crystalline MPT appears (Fig. 6.a.). The melting temperature of MPT in the physical mixture is measured at 120.7°C, with an onset temperature of the endothermal peak at 113.7°C. This melting peak is also present in both thermograms of the extrudates. However, the melting enthalpy for MPT in the extrudate at 135°C is much smaller than the one in the extrudate at 105°C, even though both extrudates contain 40% MPT (w/w). In the extrudate at 135°C, more MPT has transformed to the amorphous state, leaving a smaller fraction of crystalline MPT and thus a smaller area under the curve of the melting peak. The melt enthalpy for MPT in the physical mixture is 37.2 J/g. In the extrudate at 105°C, this enthalpy has reduced to 6.7 J/g, meaning that only 18.0% of the MPT is crystalline in this extrudate, assumed that MPT in the physical mixture is 100% crystalline. For the extrudate at 135°C, the amount of crystalline MPT is even lower, 9.1%, since the melt enthalpy is only 3.4 J/g. The melting points (Tm) for the extrudates produced at 105°C and 135°C can be found at 115.7°C and 117.1°C, with onset melting temperatures of the corresponding endotherms at 109.7°C and 110.0°C respectively. Compared to the physical mixture, this shift again implies interactions between the polymer and the drug, but no variations can be seen in interaction strength between both extrudates.

The extrudates show a second Tg, at a lower temperature than the Tg of Kollidon® SR. This is the glass transition temperature of amorphous MPT, at 16.9°C and 17.0°C in the extrudates processed at 105°C and 135°C, respectively. A fraction of the MPT in both mixtures has become amorphous during processing, but has not been dispersed at a molecular level in the polymer matrix as there are 2 Tg's visible in the thermograms. Hence, the extrudates exist of three phases: an amorphous polymer phase, an amorphous drug phase and a crystalline drug phase. These extrudates are in fact solid dispersions which are partially crystalline and partially amorphous. The free amorphous drug fraction has the tendency to recrystallize due to the poor physical stability of formulations in the amorphous state. These results do not completely confirm the observations drawn from the in-line NIR spectra. The NIR spectra suggest that more and stronger interactions occur in the extrudate at 135°C than at 105°C. However, in the DSC thermograms, no differences were obtained between both extrudates, with exception of the difference in amount of amorphous MPT.

2.3. ATR FT-IR spectroscopy

Figures 7a and 7b represent the FT-IR spectra of metoprolol tartrate and Kollidon® SR respectively. The FT-IR spectrum of the physical mixture of 40% metoprolol tartrate and 60% Kollidon® SR (w/w) (Fig. 7c) is a combination of the FT-IR spectra of the individual components (Figs. 7a and 7b). The MPT signals are sharp and the fingerprint area, 1500 cm^{-1} – 600 cm^{-1} shows an explicit pattern. The position of the bands in the IR spectra of the physical mixture remains unchanged compared to the corresponding bands in the spectra of the pure components. No new bands or band shifts can be seen.

The FT-IR spectra of the mixtures containing Kollidon® SR and MPT (60:40, w/w), which were extruded at a temperature of 105°C and 135°C (Fig. 7d), result in a significantly changed FT-IR pattern compared to the spectrum of the physical mixture. The FT-IR spectrum of the extrudate produced at 105°C shows that the IR absorption bands of the polymer are more explicitly present (Fig. 7). This indicates an association of the API with the polymer, forming coupled vibrations of MPT with the polymer. In the spectral region of 2800 cm^{-1} – 3800 cm^{-1}, the presence of OH stretch vibrations of alcohol groups indicates that some independent MPT molecules are still present and that not all drug molecules have interacted with the polymer. The infrared spectrum of the extrudate produced at 135°C is similar to the IR spectrum of the extrudate produced at 105°C (data not shown), showing no difference in interactions between the extrudates produced at different temperatures.

2.4. Raman spectroscopy

Both DSC analysis and the ATR FT-IR results confirm each other, but none of these off-line techniques confirm the differences in interaction level and amount between the extrudates as seen with NIR spectroscopy. Fig. 8 shows the in-line collected Raman spectra of the extrudates of the mixture at 105°C and 135°C, together with the spectrum of the physical mixture itself. The peaks of MPT broaden in the extrudates, indicating the transition from crystalline to amorphous MPT. This trend is more distinct in the spectra of the extrudates produced at 135°C, suggesting the presence of a larger fraction of amorphous MPT than in the extrudates produced at 105°C. Furthermore, peak shifts emerge in the spectra of the extrudates compared to the physical mixture. These shifts arise from changes in vibrational frequencies, caused by interactions between the polymer and the drug. Hydrogen bonding in Raman spectra can be mainly observed as a shift of the spectral bands to lower frequencies[35]. The shifts to lower Raman shifts are more explicit in the extrudates produced at

135°C, than in the extrudates created at 105°C. This confirms the NIR observations, implying that there is a difference in interaction strength between both extrudates.

It has been demonstrated that NIR spectroscopy is a more reliable technique to determine the hydrogen bond interaction level and amount for the studied formulation compared to DSC analysis and FT-IR. Furthermore, NIR spectroscopy can be used to monitor the stability over time of a certain formulation. When the extrudates produced at 105°C and 135°C were continuously monitored with NIR spectroscopy immediately after hot melt processing, it was evident that this is an unstable formulation. The extrudates were monitored for 20 minutes at room temperature (Fig.9). In these spectra, the peak at 6495 cm^{-1} (1540 nm), attributed to hydrogen bonded hydroxyl groups, reduces, indicating the loss of hydrogen bond interactions between drug and polymer, and thus the separation of polymer and drug phase. The peaks in the NIR spectra attributed to MPT become more distinct and sharp, since the amorphous MPT starts to recrystallize. As recrystallization occurred rapidly, DSC analysis and FT-IR spectra were unable to differentiate between both extrudates since the sample preparation time for these techniques is longer than the time needed for the destabilization process.

Conclusions

In this study, NIR spectroscopy was evaluated to monitor the API concentration and the polymer–drug melt behaviour during a pharmaceutical hot-melt extrusion process. With NIR spectroscopy, it was possible to detect variations in drug concentrations. A PLS model was developed and validated, allowing continuous drug concentration monitoring. It was possible to predict drug concentrations with an RMSEP of 1.54%.

With respect to the polymer-drug behaviour during extrusion, in-line NIR spectroscopy was able to detect changes in solid state of the extrudates, as well as in amount and strength of the intermolecular interactions during processing. Furthermore, the use of NIR spectroscopy allowed the determination of the type of interactions occurring during hot-melt extrusion. These interactions are manifested as hydrogen bonds between Kollidon® SR and MPT molecules.

In-line Raman spectroscopy confirmed these NIR observations. The collected spectra displayed similar peak shifts and peak broadening, demonstrating the equivalent changes in solid state and interactions during melt extrusion. Comparison of the in-line collected NIR spectra and the off-line

DSC analysis and off-line collected ATR FT-IR spectra showed that NIR is a more powerful process analyzer, able to differentiate between extrudates being processed under varying conditions, whereas DSC analysis and ATR FT-IR indicated no differences in occurring interactions between extrudates produced at different temperatures.

Acknowledgements

BASF is kindly acknowledged for the supply of the Kollidon® SR. Thermo Scientific and in particular G. Deprez is kindly acknowledged for providing the NIR probe and service during measurements.

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Figures

Fig. 1: Molecular structures of a) Metoprolol tartrate (Ph. Eur. 7.0) and b) Kollidon® SR.

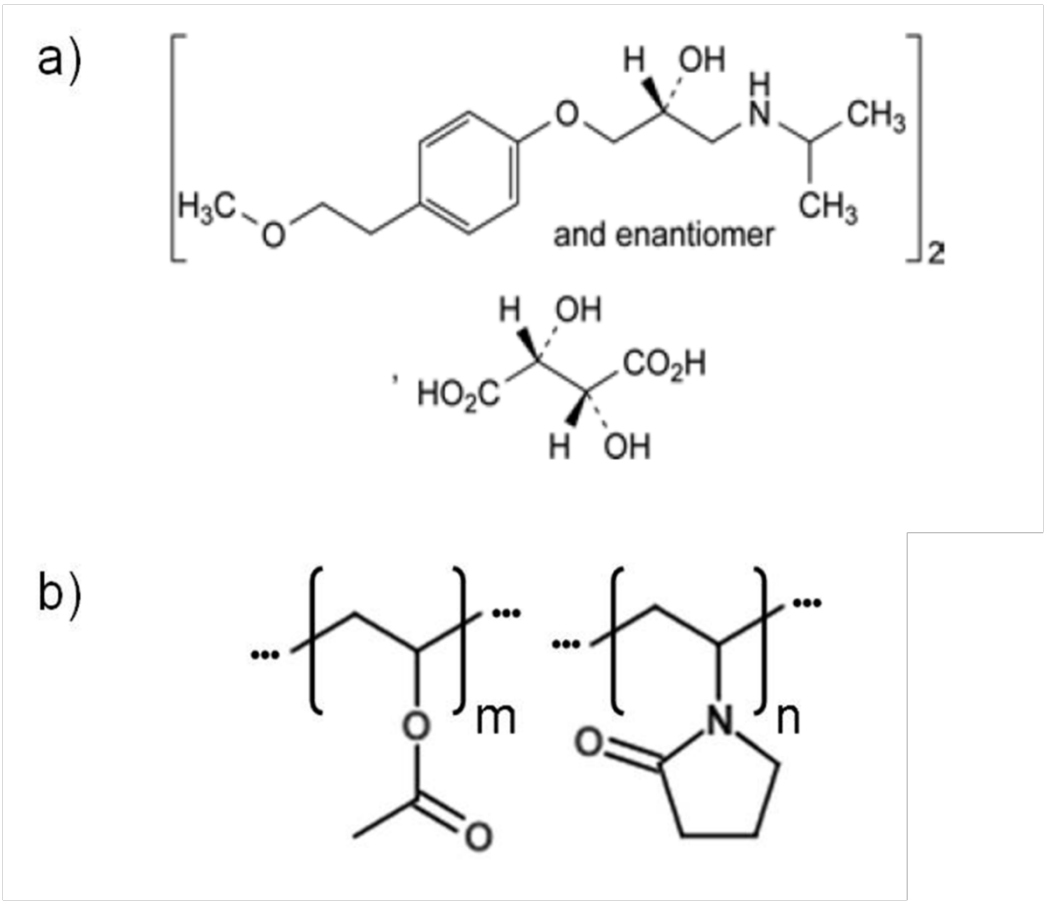


Fig. 2: In-line NIR spectroscopic monitoring setup.

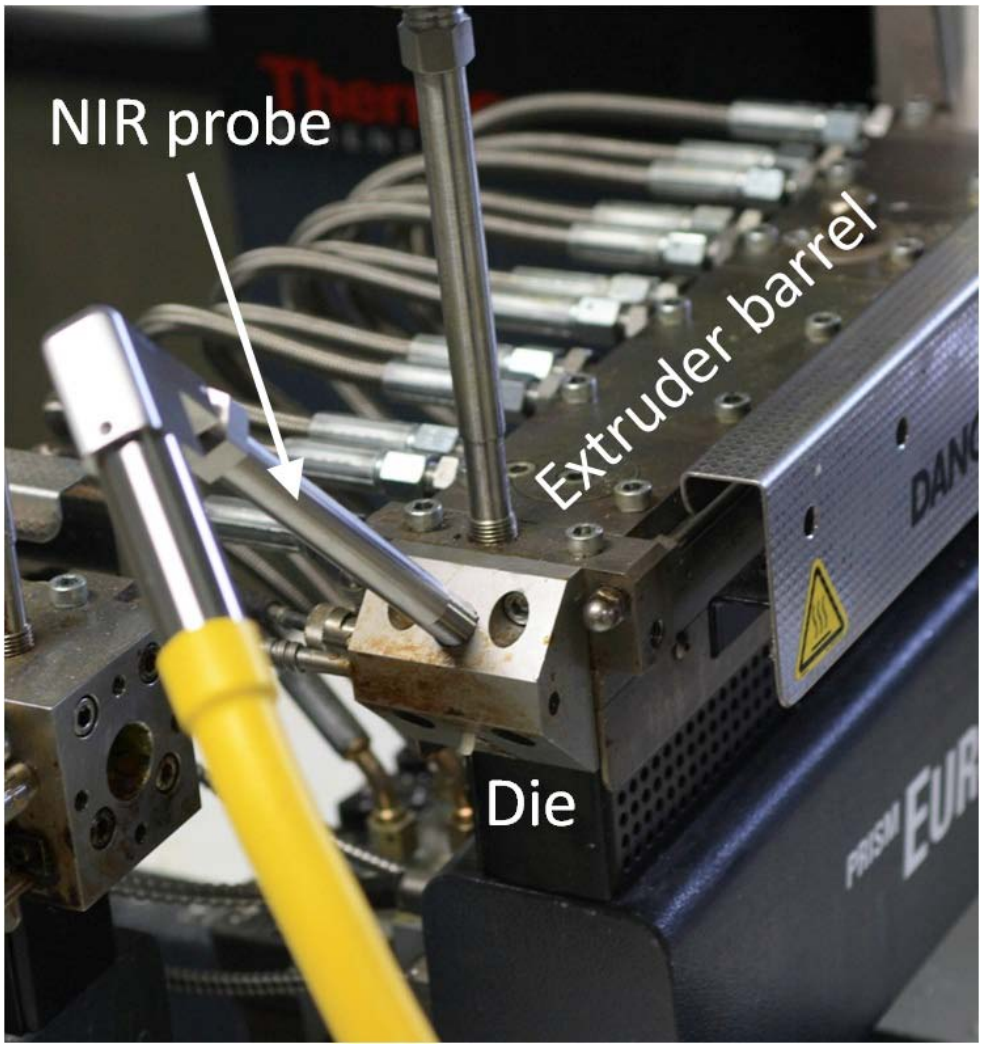


Fig. 3: Pre-processed in-line collected NIR spectra of different MPT – Kollidon® SR mixtures. Red = 20% MPT, green = 30% MPT, blue = 40% MPT (w/w).

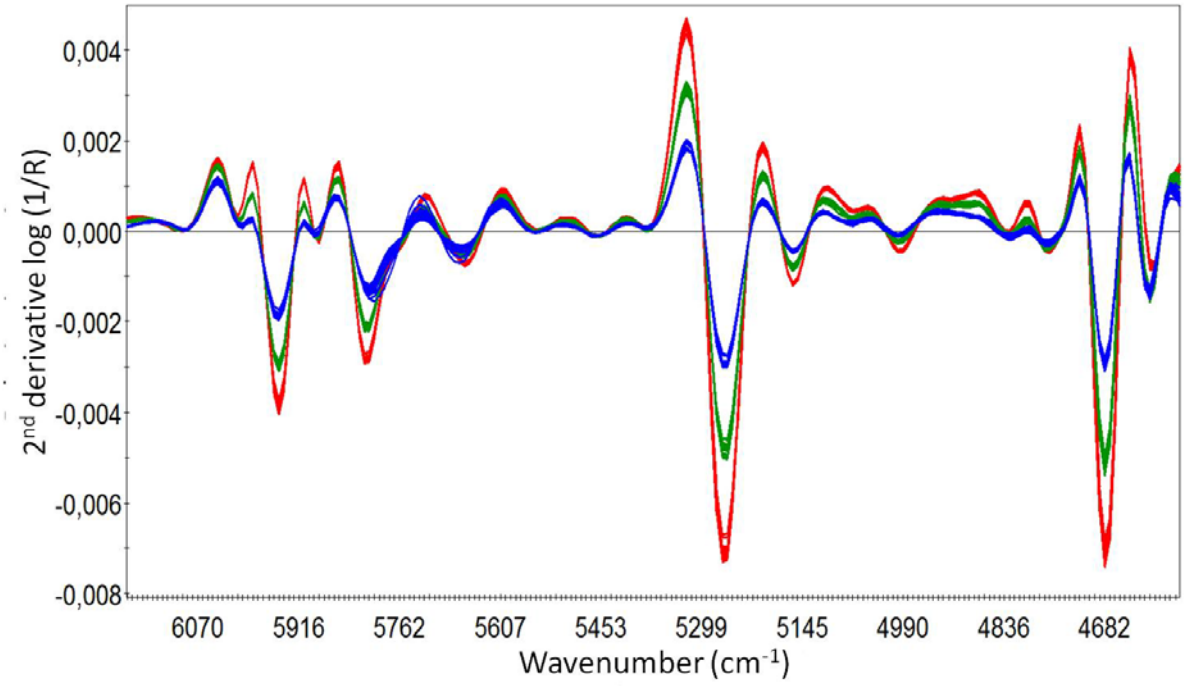


Fig. 4: PC 1 (99%) versus PC 2 (0.2%) scores plot obtained after PCA on the pre-processed in-line collected NIR spectra during extrusion of mixtures containing Kollidon® SR and 20% (red), 30% (green) and 40% (blue) MPT (w/w).

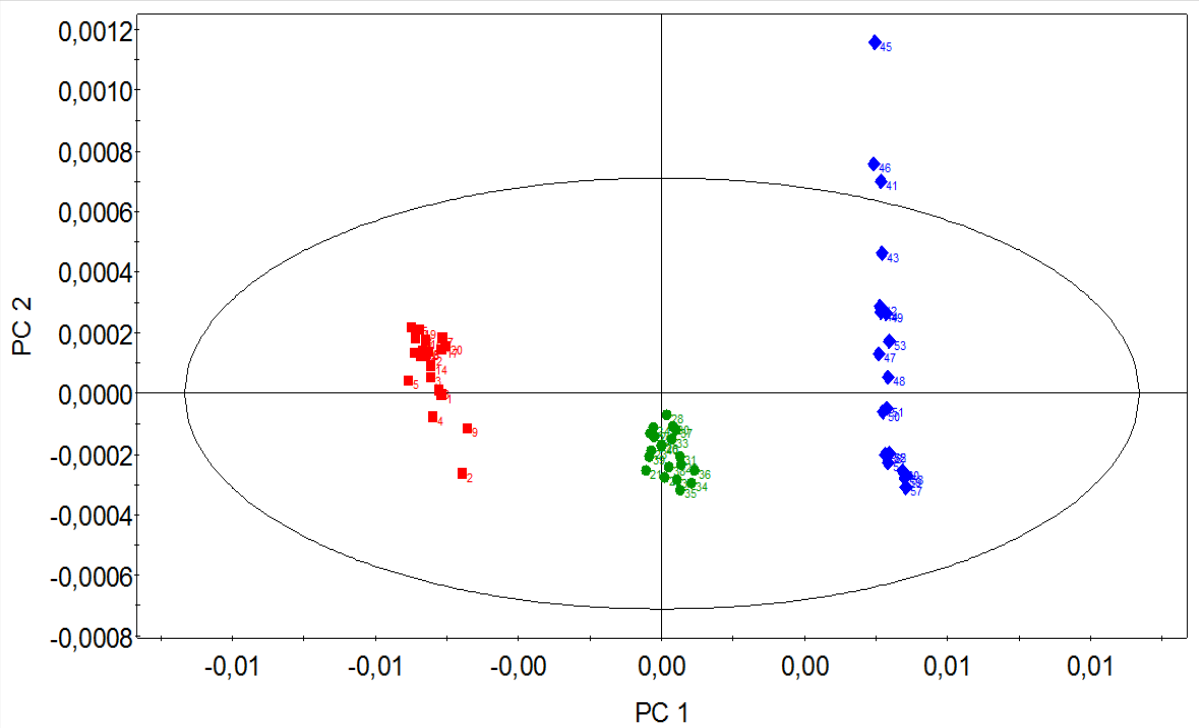


Figure 5: Pre-processed NIR spectra of the physical mixture containing 60% Kollidon® SR and 40% MPT (w/w) (blue) and of the in-line collected spectra during hot-melt extrusion at 105°C (green) and 135°C (red).

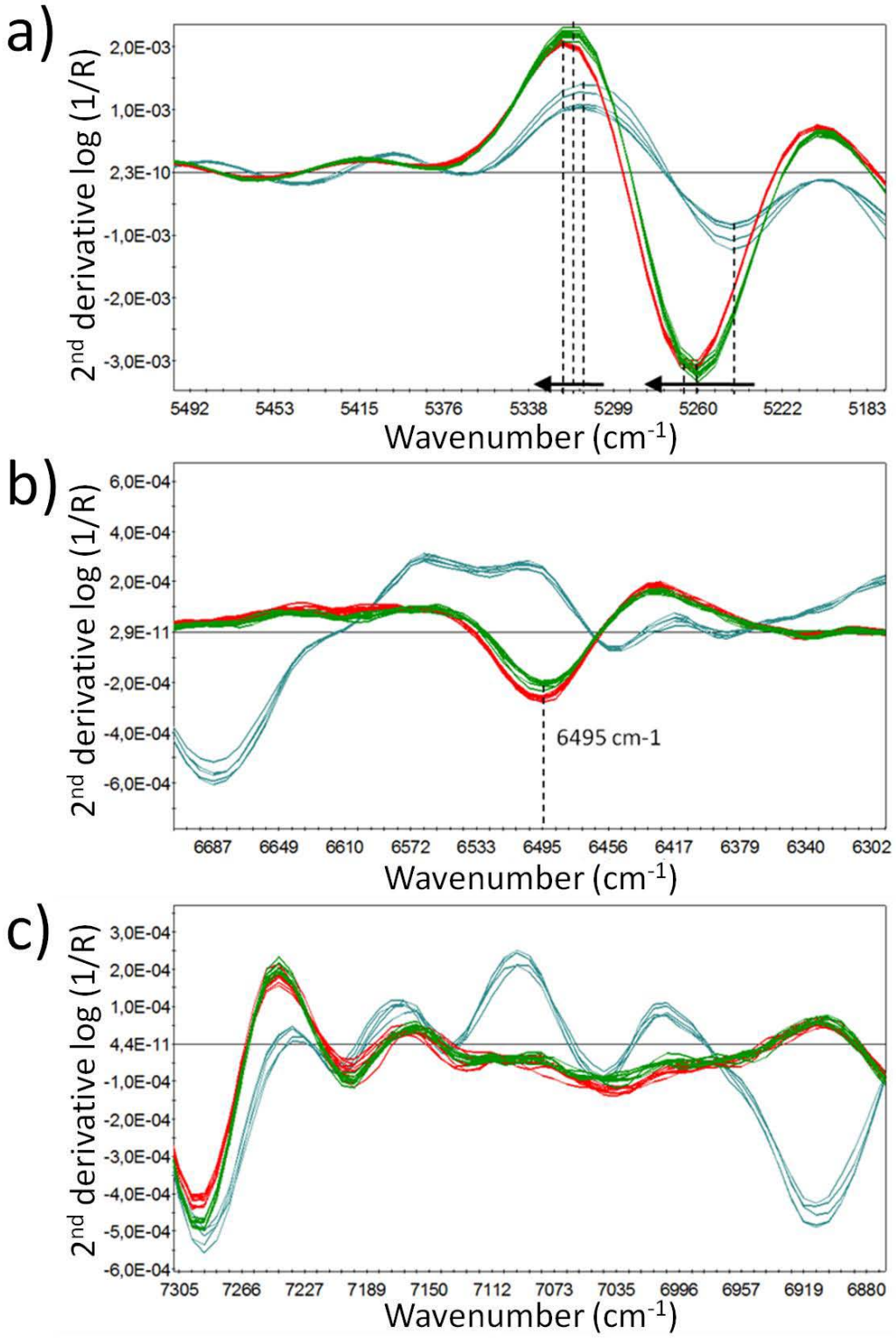


Fig. 6: a) Thermograms of the physical mixture containing 60% Kollidon® SR and 40% MPT (w/w) and the extrudates produced at 135°C and 105°C. b) Effects of MPT loading (% w/w) on glass transition temperature (Tg) of Kollidon® SR in physical mixtures.

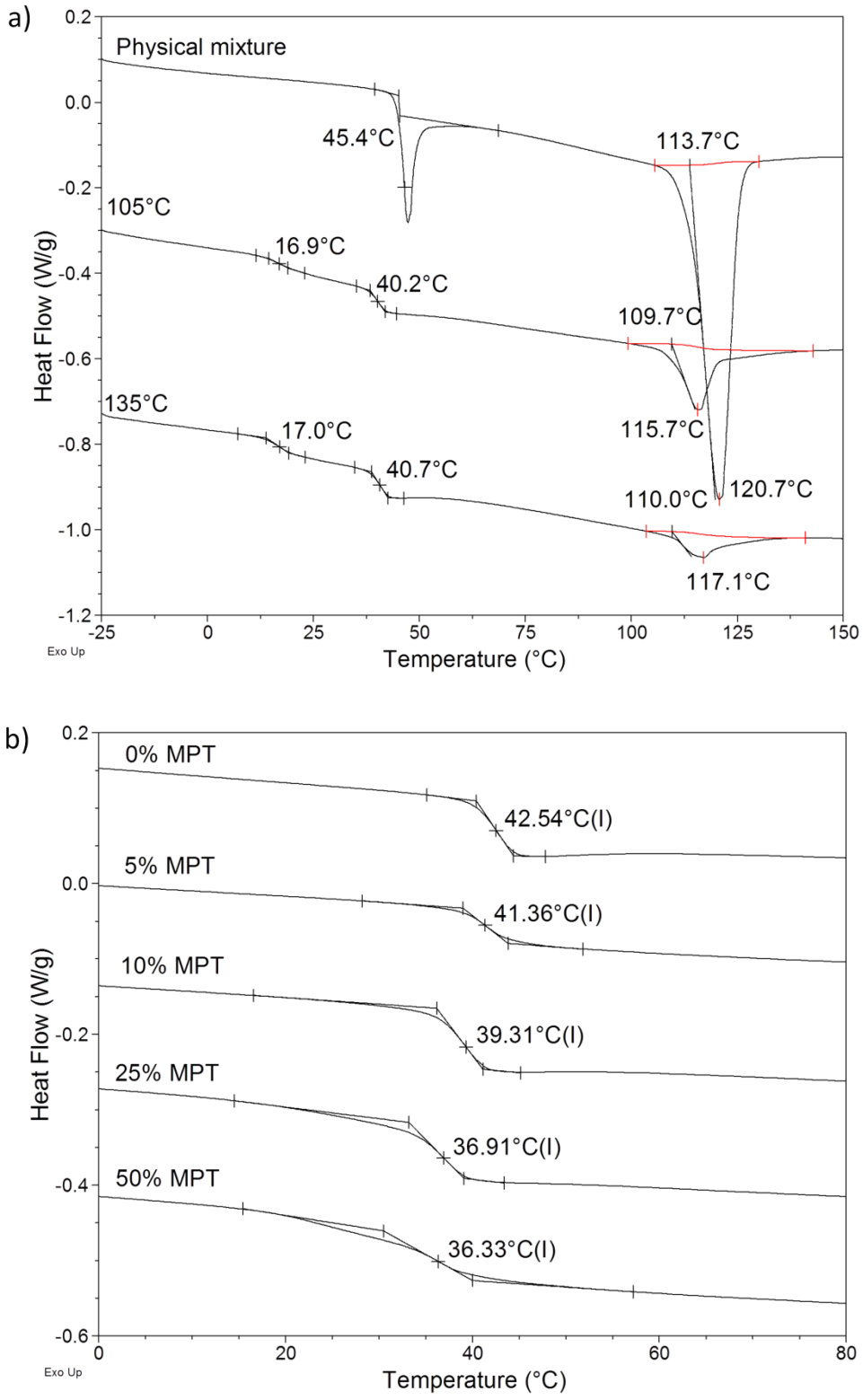
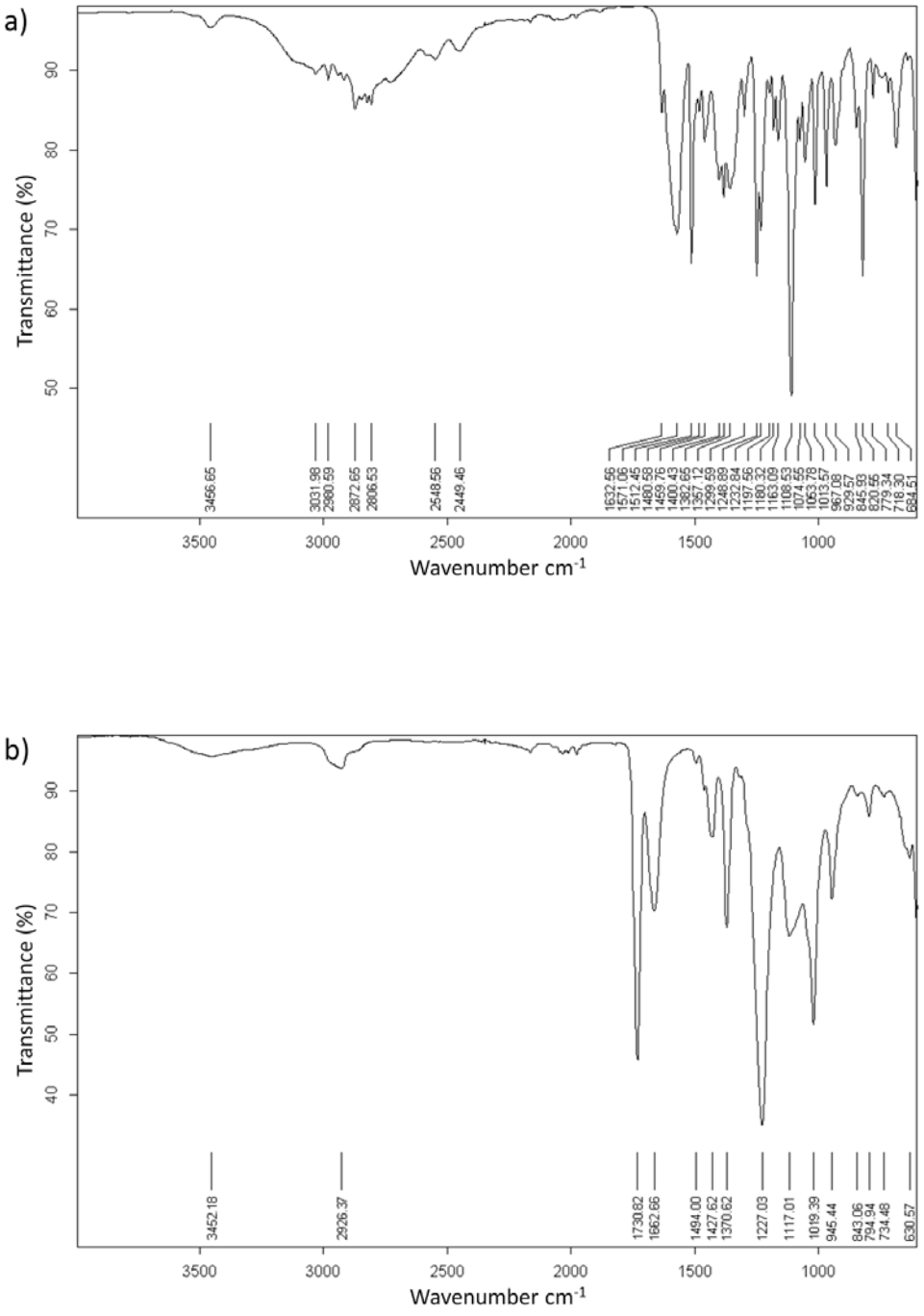
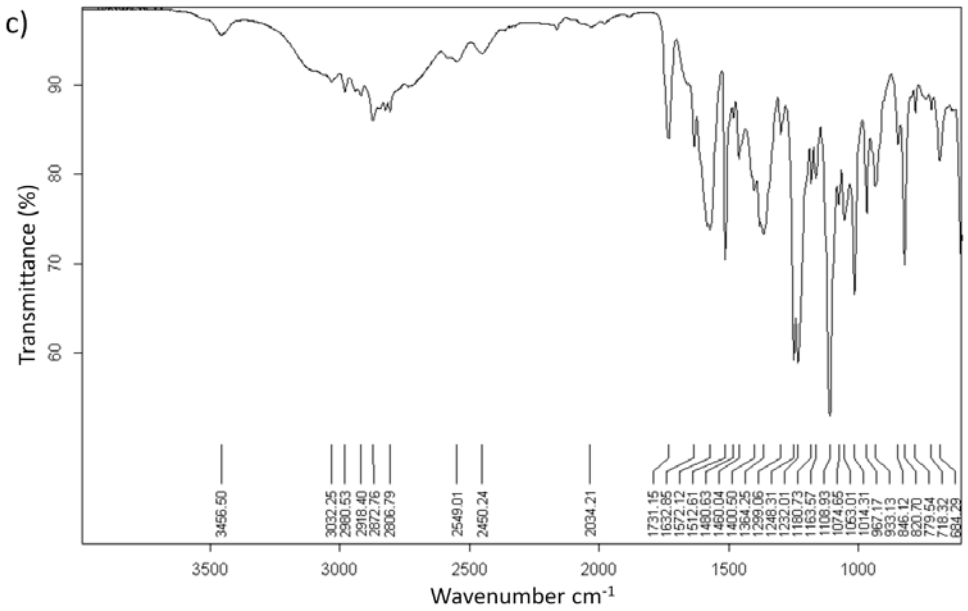


Fig. 7: ATR FT-IR spectra of a) MPT, b) Kollidon® SR, c) the physical mixture containing 40% MPT and 60% Kollidon® SR (w/w) and d) the extrudate of the physical mixture produced at 105°C.



c)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90
80
70
60
3456.50
3032.25
2960.53
2918.40
2872.76
2806.79
2549.01
2450.24
2034.21
1731.15
1632.85
1572.12
1512.61
1460.63
1440.50
1364.35
1296.06
1248.31
1232.01
1180.73
1163.57
1106.93
1074.65
1053.01
1014.31
967.17
933.13
846.12
820.70
779.54
718.32
684.29
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

d)

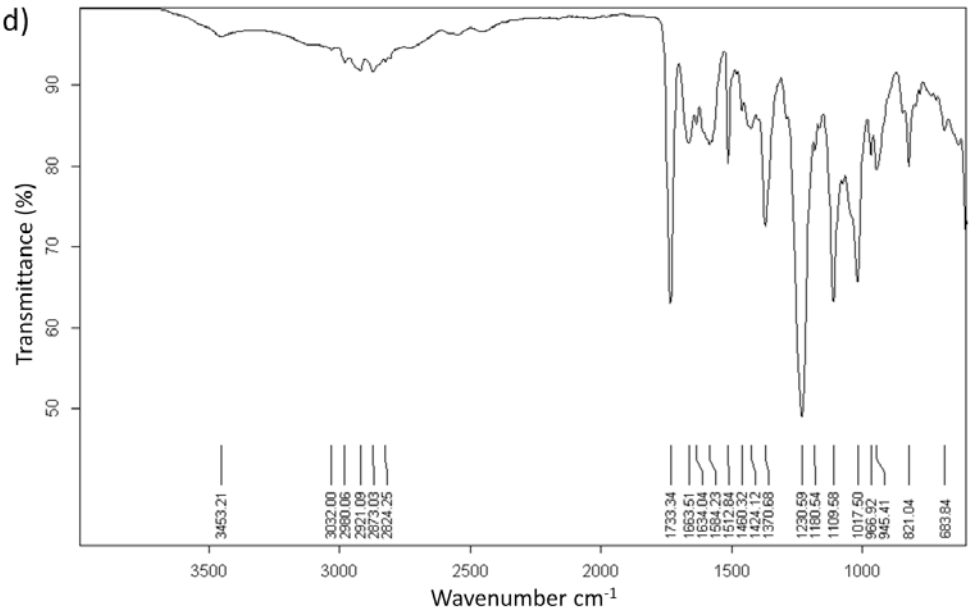
Transmittance (%)
90
80
70
60
50
3453.21
3032.00
2960.06
2921.09
2873.03
2824.25
1733.34
1663.51
1634.04
1584.23
1512.84
1460.32
1424.12
1370.68
1230.59
1180.54
1109.58
1017.50
966.92
945.41
821.04
683.84
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

Fig. 8: In-line collected Raman spectra. Blue = physical mixture (60% Kollidon® SR and 40% MPT, w/w), green = extrudate produced at 105°C, red = extrudate produced at 135°C.

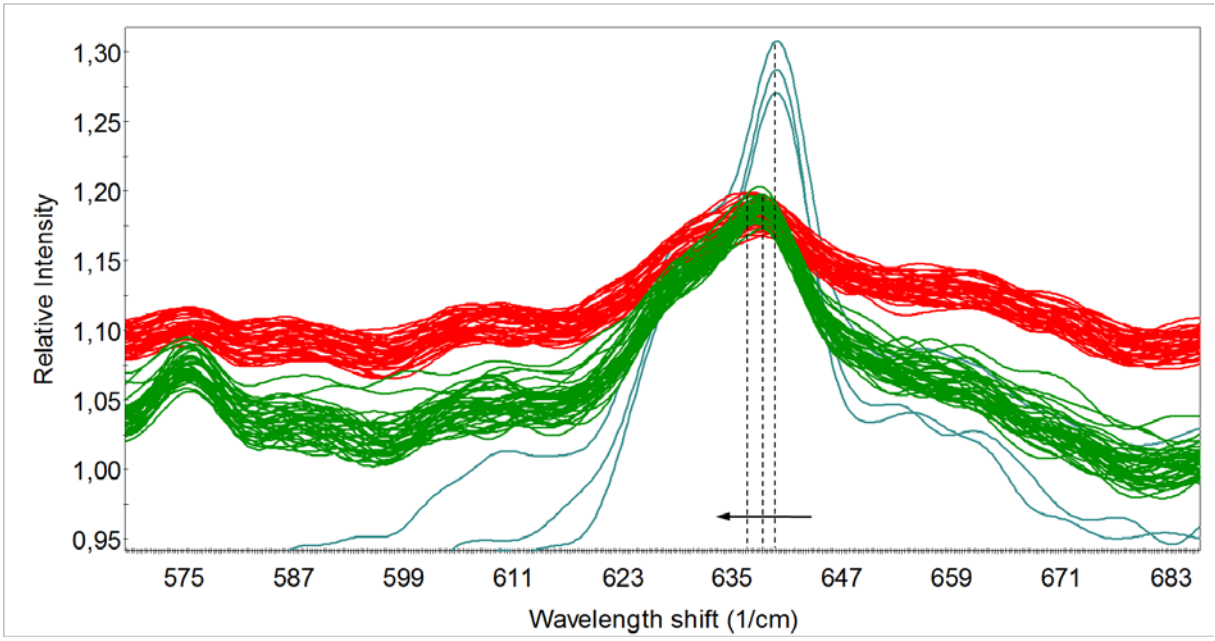

Fig. 9: Pre-processed off-line collected NIR spectra of the extrudate produced at 135°C at room temperature, immediately after processing, as a function of time.