The Electronic Conference on Pharmaceutical Sciences
ECPS2011

sciforum
e-conferences
www.sciforum.net

Communication

Raman spectroscopy for the in-line polymer-drug quantification and solid state characterization during a pharmaceutical hot-melt extrusion process

Lien Saerens[1,*], Peter Adriaensens[2], Robert Carleer[2] ,Chris Vervaet[3], Jean Paul Remon[3], Thomas De Beer[1]

[1]Laboratory of Pharmaceutical Process Analytical Technology, Ghent University
[2]Division Chemistry, Institute for Material Research (IMO), Hasselt University, Belgium
[3]Laboratory of Pharmaceutical Technology, Ghent University

E-Mail: Lien.Saerens@UGent.be

* Author to whom correspondence should be addressed; Tel.: +32-9-264-8355; Fax: +32-9-264-8196

Abstract:

The aim of this study was to evaluate the suitability of Raman spectroscopy as a Process Analytical Technology (PAT) tool for the in-line determination of the active pharmaceutical ingredient (API) concentration and the polymer-drug solid state during a pharmaceutical hot-melt extrusion process.
For in-line API quantification, different metoprolol tartrate (MPT) - Eudragit® RL PO mixtures, containing 10, 20, 30, and 40% MPT respectively, were extruded and monitored in-line in the die using Raman spectroscopy. A PLS model, regressing the MPT concentrations versus the in-line collected Raman spectra, was developed and validated, allowing real-time API concentration determination. The correlation between the predicted and the real MPT concentrations of the validation samples was acceptable (R^2=0.997) The predictive performance of the calibration model was rated by the root mean square error of prediction (RMSEP), which was 0.59%.
Two different polymer-drug mixtures were prepared to evaluate the suitability of Raman spectroscopy for in-line polymer-drug solid state characterization. Mixture 1 contained 90% Eudragit® RS PO and 10% MPT, and was extruded at 140°C, hence producing a solid solution. Mixture 2 contained 60% Eudragit® RS PO and 40% MPT, and was extruded at 105°C, producing a solid dispersion. The Raman spectra collected during these extrusion processes provided two main observations. First, the MPT Raman peaks in the solid solution broadened compared to the corresponding solid dispersion peaks, indicating the presence of amorphous MPT. Secondly, peak shifts appeared in the spectra of the solid dispersion and solid solution compared to the physical mixtures, suggesting interactions between Eudragit® RS PO and MPT, most likely hydrogen bonds. These shifts were larger in the spectra of the solid solution. DSC analysis and ATR FT-IR confirmed these Raman solid state observations and the

interactions seen in the spectra. Raman spectroscopy is a potential PAT-tool for in-line determination of the API-concentration and the polymer-drug solid state during pharmaceutical hot-melt extrusion.

Keywords: Raman spectroscopy, Hot-Melt Extrusion (HME), Process Analytical Technology (PAT), In-line measurements, solid dispersions, solid solutions

---

1. 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]. Nowadays, extruders allow in-line monitoring and control of the process parameters feed rate, screw speed and barrel and die temperature, and in-line monitoring of the motor load and the melt pressure in the extruder and die. The in-line monitoring and control of quality parameters corresponding to the extruded product itself, such as drug load and solid state, will provide real-time product quality evaluation and an increased understanding of the product behaviour during extrusion.

There exists now the tendency within the pharmaceutical industry to move from traditional batch processes towards continuous processing, hereby increasing process efficiency and production. Continuous processes 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 and improved product quality[6]. 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 PAT in 2004[7]. Pharmaceutical products must meet very strict specifications. 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. The general principle of PAT is to build quality into products rather than testing it into products. PAT-tools such as Raman spectroscopy provide in-line and real-time process information concerning critical formulation parameters, which allows the steering of processes towards their desired state through adaptations of process settings. Consequently, the final product quality can be ensured, the end product characteristics can be predicted and real-time release becomes possible, hence avoiding batch losses.

Raman spectroscopy enables rapid, non-destructive and in-line measurements, and has previously been used during hot-melt extrusion (single screw extrusion) to monitor EVA copolymer melt composition[8,9], to analyze film formulations[10], and to monitor the composition of a series of high-

density polyethylene (HDPE)/polypropylene (PP) blends[11,12]. It has also been implemented in a twin screw extrusion process to determine the concentration of Irganox additive in polypropylene[13]. Raman spectroscopy has also been applied for off-line confirmation of drug dispersions within PEO and interaction with PEO in extrudates[14], for characterization of the hydrogen bonding nature in α and amorphous indomethacin[15], and for comparison of the solid state properties of solid dispersions prepared by HME and solvent co-precipitation processes[16].

2. Materials and Methods

2.1. Materials and Hot-Melt Extrusion

Hot-melt extrusion was performed using a Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruder (ThermoFisher Scientific, Germany). The hot-melt extruder was equipped with a DD Flexwall® 18 gravimetric feeder (Brabender Technologie, Germany), which was set in its gravimetric feeding mode.

For the development of a calibration model allowing in-line API quantification, 4 different polymer-drug mixtures, containing 10, 20, 30 and 40% (w/w) API respectively, were extruded. Eudragit® RL PO (Evonik Röhm, Germany) was used as polymer and metoprolol tartrate (MPT) was used (Esteve Quimica, Spain) as API. The Hansen solubility parameters of all polymers and MPT were calculated using SPWin version 2.1 (J. Breitkreutz, 1998)[17]. Before extrusion, the polymer and drug were pre-mixed in a mortar. Each premix was fed into the extruder with a feeder speed of 0.3 kg/h and extruded then with a screw speed of 50 rpm. The barrel temperature profile was set at 90-140-140-140-140-140°C (from hopper to die, each segment of the extruder can be heated separately). The torque dropped from 70% motor capacity for the 10% MPT mixture, over 35% for the 20% MPT mixture and 20% for the 30% MPT mixture to 15% for the mixture containing 40% MPT. The die pressure, measured with a pressure probe, decreased with increasing MPT content, from 2 bar in the 10% MPT mixture to 0 bar in the 40% mixture.

Two different polymer-drug mixtures were prepared to evaluate the suitability of Raman spectroscopy for in-line polymer-drug solid-state characterization. Mixture A contained 10% MPT and 90% Eudragit® RS PO (Evonik Röhm, Germany), which has an identical molecular structure as the RL PO form, but contains fewer ammonium groups. This mixture was extruded with a barrel temperature profile of 90-140-140-140-140-140°C, which is above the melting temperature of pure MPT, 120°C, to produce a solid solution. This resulted in a torque of 50% of the motor capacity and a die pressure of 1 bar. Mixture B consisted of 60% Eudragit® RS PO and 40% MPT, and was extruded with a barrel temperature profile of 90-105-105-105-105-105°C, resulting in a solid dispersion. The torque was 65% and the die pressure 0 bar. For both mixtures, the feeder speed rate was set at 0.4 kg/h and the screw speed at 80 rpm.

2.2. Raman spectroscopy

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 built into the extrusion die, to monitor the process stream before the melt is forced through the die. 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 1 second, using a laser power of 400 mW. Spectra were collected every 5 seconds. Data collection and data transfer were automated using the HoloGRAMS^{TM} data collection software, the HoloREACT^{TM} reaction analysis and profiling software and the Matlab software (version 7.1, The MathWorks Inc., Natick, MA). The analyzed spectral region was 50 – 1800 cm^{-1}, since this region contained all useful drug and polymer information.

Data analysis was performed using SIMCA P+ (Version 12.0.1.0, Umetrics, Umeå, Sweden). Mean centering, Savitzky-Golay and SNV pre-processing were applied on the in-line collected spectra before principal components analysis (PCA) and partial least squares analysis (PLS), to exclude inter-batch variation and variation caused by baseline-shifts, respectively. For PCA and PLS, 20 spectra of each polymer-drug mixture were used to develop the models. A PLS model was developed, regressing the MPT-concentrations (Y) versus the corresponding in-line collected Raman spectra (X). This model was validated with 20 other spectra from each polymer-drug mixture, which were not used to develop the PLS model.

2.3. DSC analysis

Differential scanning calorimetry with a DSC Q 2000 (TA Instruments, Belgium) was used to confirm the Raman solid state observations. 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). Aluminium hermetic pans (TA Instruments, Belgium) were used to contain the samples. Measurements were carried out in a nitrogen atmosphere, with a heating/cooling rate of 10°C/min.

2.4. ATR FT-IR

Attenuated total reflectance (ATR) Fourier transform (FT) infrared (IR) spectroscopy was also used to confirm the solid state observations in the Raman spectra. Spectra were collected from the pure samples, MPT and Eudragit® RS PO, from the physical mixtures A and B and from the extrudates of physical mixture A at 140°C and B at 105°C. The ATR FT-IR spectra were collected with a Bruker Vertex 70 FT-IR spectrometer, equipped with a DTCS detector and a PIKE accessory, equipped with a diamond ATR crystal.

3. Results and Discussion

3.1. In-line API concentration monitoring

10, 20, 30 and 40% MPT (API) - Eudragit® RL PO (polymer) mixtures were extruded. The concentration variations are visible in the collected Raman spectra (Fig. 1). PCA on all in-line collected spectra showed that two principle components covered nearly all spectral variation (98%). The PC1 versus PC2 scores plot (Fig. 2) shows a clear distinction between the spectra of the different mixtures and confirms that the first principal component mainly captures the variation caused by differences in API-polymer concentration.

Figure 1. In-line collected Raman spectra of different MPT – Eudragit® RL PO mixtures. Red = 10% MPT, green = 20% MPT, blue = 30% MPT, yellow = 40% MPT.

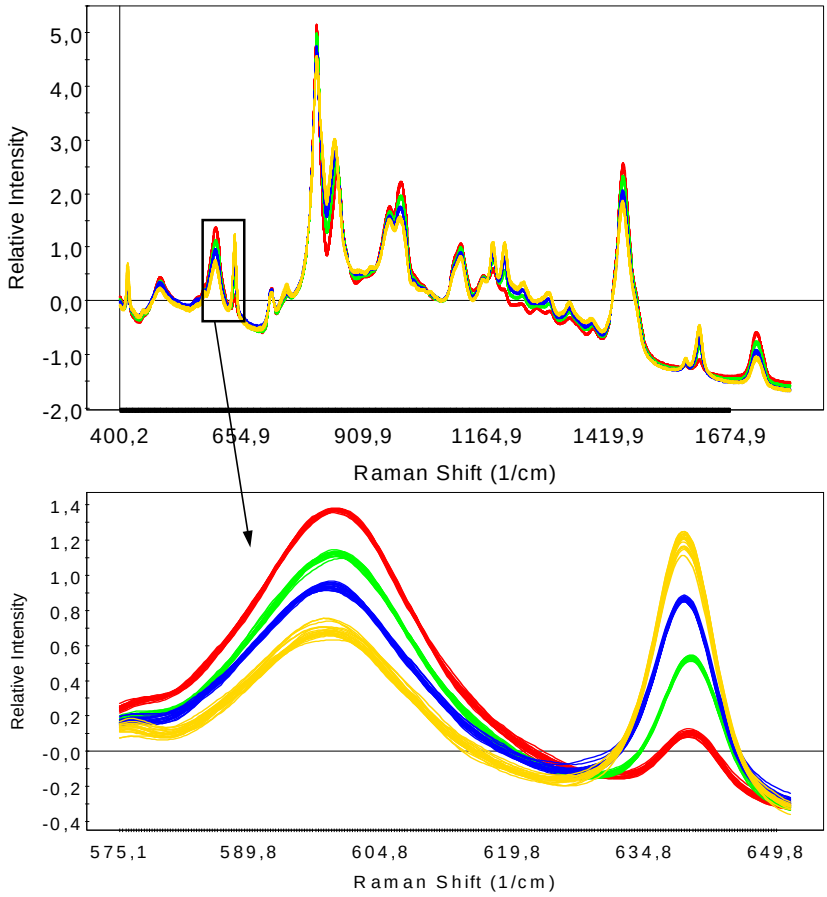
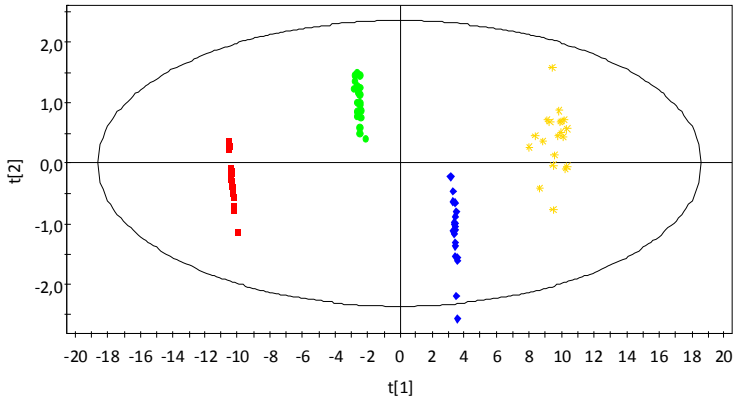
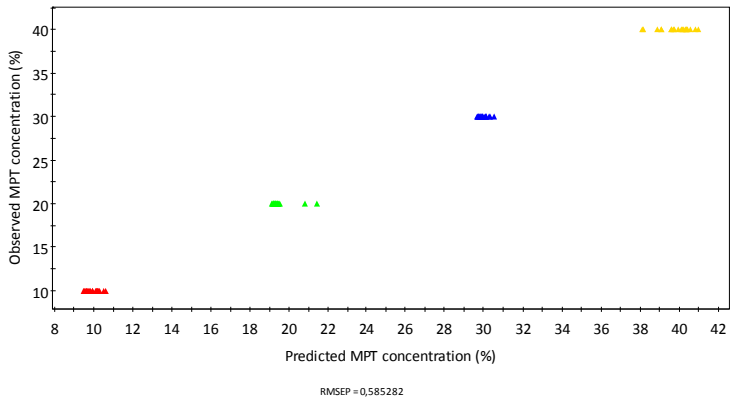


Figure 2. PC1 vs. PC2 scores plot of the in-line collected Raman spectra. Red = 10% MPT, green = 20% MPT, blue = 30% MPT, yellow = 40% MPT.



For the development of the PLS model, allowing prediction of the MPT concentration in unknown samples during hot-melt extrusion processes, the in-line Raman collected spectra (X) were regressed versus the known MPT concentrations (Y). Two PLS components were chosen, since the goodness of prediction of the model (Q^2 =0.997) did not increase significantly after adding extra components[18]. To evaluate the predictive performance of this model, 20 test spectra of each mixture were used (i.e., other spectra than used for composing the PLS model) and projected onto the model to predict the corresponding MPT concentrations. Fig. 3 shows the predicted versus the observed MPT concentration values for these validation spectra (R^2 = 0.997). The resulting root mean square error of prediction (RMSEP) is 0.59%.

Figure 3. Predicted vs. observed MPT concentrations for the validation spectra. Red = 10% MPT, green = 20% MPT, blue = 30% MPT, yellow = 40% MPT.



3.2. In-line solid state monitoring

To obtain a good compatibility between polymer and drug, the difference between solubility parameters (δ) of polymer and drug should not be much more than 2.0 $(MPa)^{1/2}$ [19]. When this is achieved, miscibility is significant and, therefore, glass solution formation during melt extrusion can be obtained. The Hansen solubility parameter for MPT is 23.59 $(MPa)^{1/2}$, 19.64 $(MPa)^{1/2}$ for Eudragit® RS PO and 19.58 $(MPa)^{1/2}$ for Eudragit® RL PO. The smaller the difference in solubility parameters, the greater the miscibility between two compounds. Hence, a good miscibility and possible formation of a solid solution between Eudragit® RS PO and MPT is expected.

Two mixtures (A and B, see materials and methods) were extruded at two different extrusion temperatures (140°C and 105°C respectively). Mixture A was expected to result in a solid solution where the MPT has transferred from the crystalline to the amorphous state. This would result from a high processing temperature (above the melting temperature of pure MPT) and a good miscibility between both components. Mixture B was expected to result in a solid dispersion, since the extrusion temperature is below the melting temperature of MPT, which will prevent the transfer of all MPT in the melt into the amorphous state. Hence, a fraction of the MPT will remain crystalline and the extrudate of mixture B will exist of at least 2 phases.

Fig. 4a shows a detail of the in-line collected Raman spectra for the extruded mixtures A and B and the Raman spectra of the physical mixtures before extrusion. Comparison of these spectra resulted into two major observations. First, throughout the entire Raman spectrum, the extrudates show peak shifts compared to the spectra of the pure components and the spectra of the physical mixtures. These peak shifts in the spectra of the extrudates indicate interactions between MPT and Eudragit® RS PO. These interactions are stronger for extruded mixture A, as the shifts are larger. All MPT in extruded mixture A is amorphous, which enhances interaction with the polymer. In extruded mixture B, some MPT is amorphous, but the largest fraction remains crystalline, explaining the smaller peak shifts for this mixture. The occurring interactions are most likely hydrogen bonds between MPT and Eudragit® RS PO, which can take place between the hydroxyl functions or amino functions from MPT and the carbonyl groups from the polymer (Fig. 5). Shifts of the corresponding Raman peaks from these groups are indeed visible (Fig. 4b). Hydrogen bonding in Raman and IR spectra can be mainly observed as a broadening of the spectral bands and a shift of these bands to lower frequencies[19]. The peak of ν(C=O) stretch vibration[20] of Eudragit® RS PO has shifted from 1729.5 cm^{-1} in pure Eudragit to 1729.2 cm^{-1} in extruded mixture B and 1729.2 cm^{-1} in extruded mixture A. The shift of the vibration of this bond is much smaller than that of the O-H or N-H stretch[19]. The peak of ν(C-N) in pure MPT can be found at 1181 cm^{-1}[21], and shifts over 1179.6 cm^{-1} in extruded mixture B to 1178.7 cm^{-1} in extruded mixture A. The ν(C-O) peak of pure MPT[21] is located at 1109.7 cm^{-1}, but shifts cannot be seen in the in-line collected spectra, since Eudragit® RS PO also has a ν(C-O) peak, appearing at 1116.3 cm^{-1}. These peaks overlap in the spectra of the extruded mixtures, causing difficulties to see the peak shifts. The decrease in vibration frequency of ν(C-N) adjacent to the hydrogen bond is due to weakening of these bonds, caused by the hydrogen bond formation.

Figure 4. (a) Raman spectra of the physical mixtures of 10% MPT in Eudragit® RS PO (PM A,orange) and 40% MPT in Eudragit® RS PO (PM B, blue) and the in-line collected Raman spectra of extruded mixture A (red) and extruded mixture B (green). **(b)** Raman spectra of pure MPT (yellow) and pure Eudragit® RS PO (purple) and the in-line collected Raman spectra of extruded mixture A (red) and extruded mixture B (green).

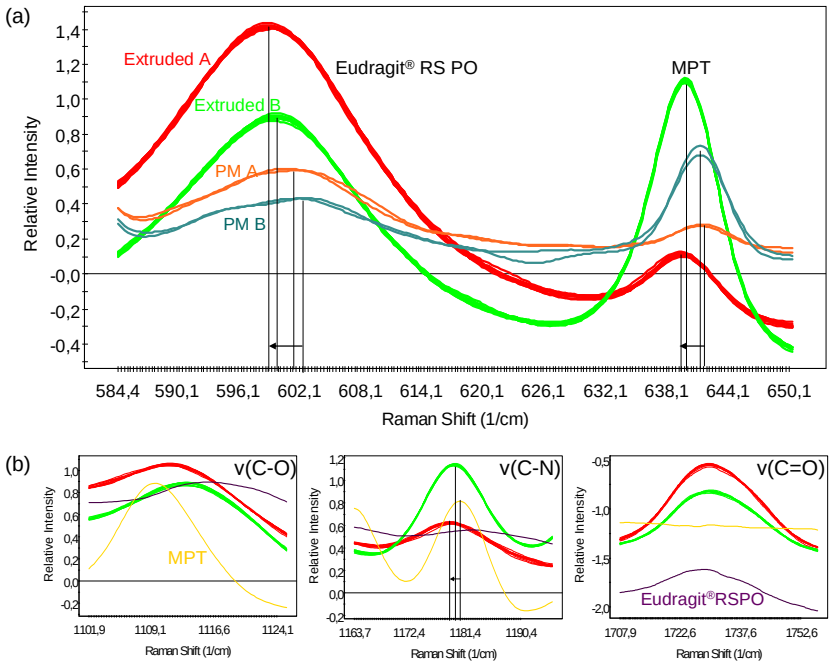
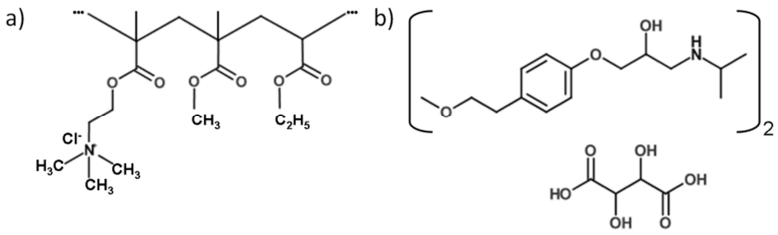


Figure 5. Molecular structures of a) Eudragit® RL/RS PO and b) Metoprolol tartrate.

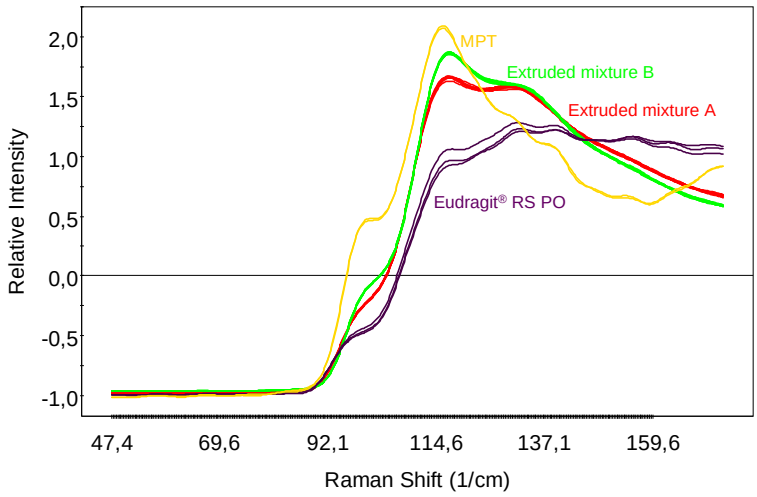


A second observation of interest lies in the peaks of MPT. Since pure MPT is crystalline, its Raman spectrum contains narrow, well defined peaks. Extruded mixture B still contains a fraction of MPT in the crystalline state. The peaks of MPT have slightly broadened, but are still well defined. In extruded mixture A, the MPT peaks have broadened or even disappeared, indicating amorphous MPT. In the physical mixtures, the peaks of MPT remain as sharp as the original peaks. Interactions or transitions have not taken place in these physical mixtures.

The spectra in the 150 – 50 cm^{-1} region of the Raman spectrum contain information about lattice vibrations corresponding to vibrations and translations of the entire molecule in the lattice[15]. These vibrations are characteristic for the crystal structure and sensitive to local order or disorder. For the spectrum of pure MPT, this region has sharp, well defined peaks, which are still present in the spectra

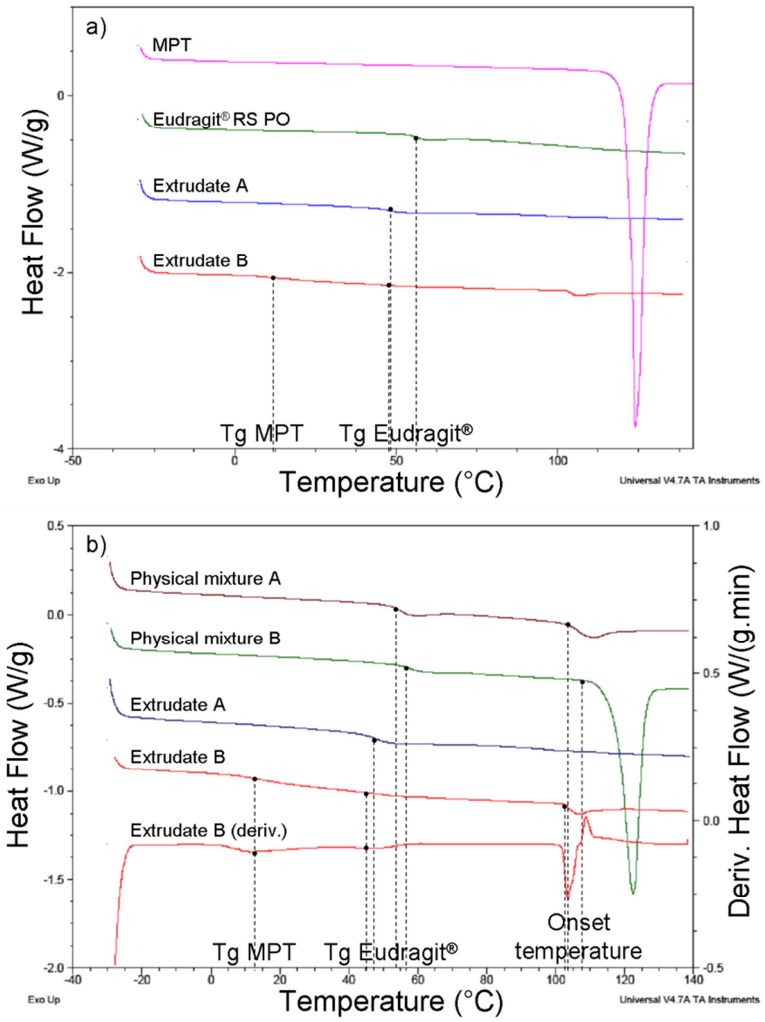
of extruded mixture B, but which are nearly disappeared in the spectra of extruded mixture A. In extruded mixture A, broad bands are visible, indicating a more disordered structure (Fig. 6) .

Figure 6. Detail of the Raman spectra for the 50 cm^{-1} to 150 cm^{-1} spectral region. Yellow = pure MPT; Purple = pure Eudragit® RS PO; red = extruded mixture A; green = extruded mixture B.



DSC analysis (Fig. 7) was performed to confirm these interpretations drawn from the Raman spectra. For the samples containing Eudragit® RS PO, the maximum heating temperature was restricted to 140°C, to avoid degradation of the polymer, which can occur above 150°C. The glass transition temperature (Tg) of Eudragit® RS PO reaches a lower temperature in the extrudates, due to the plasticizing effect of MPT on the polymer, and due to the extrusion process, which slightly lowers the Tg of a polymer[22]. A lower Tg indicates a molecular dispersion of the drug in the polymer, whereas an unchanged Tg implies separation of the polymer- and drug phase[23]. The Tg of Eudragit® RS PO in the extrudates of 10% and 40% MPT is 46.6°C and 46.5°C respectively, whereas the Tg of Eudragit® RS PO of the physical mixtures A and B used to prepare these extrudates is 55.1°C and 58.1°C respectively, which is higher than the Tg after extrusion. This decrease in Tg after extrusion is caused by the interaction between Eudragit® RS PO and MPT during hot-melt extrusion. The chain-mobility of the polymer increases due to incorporation of MPT in the polymer matrices, which translates into a decrease in Tg.

Figure 7. (a) Thermograms of pure MPT and Eudragit® RS PO and of mixture A and B after hot-melt extrusion. **(b)** Thermograms of physical mixtures A and B before hot-melt extrusion and of mixture A and B after hot-melt extrusion.



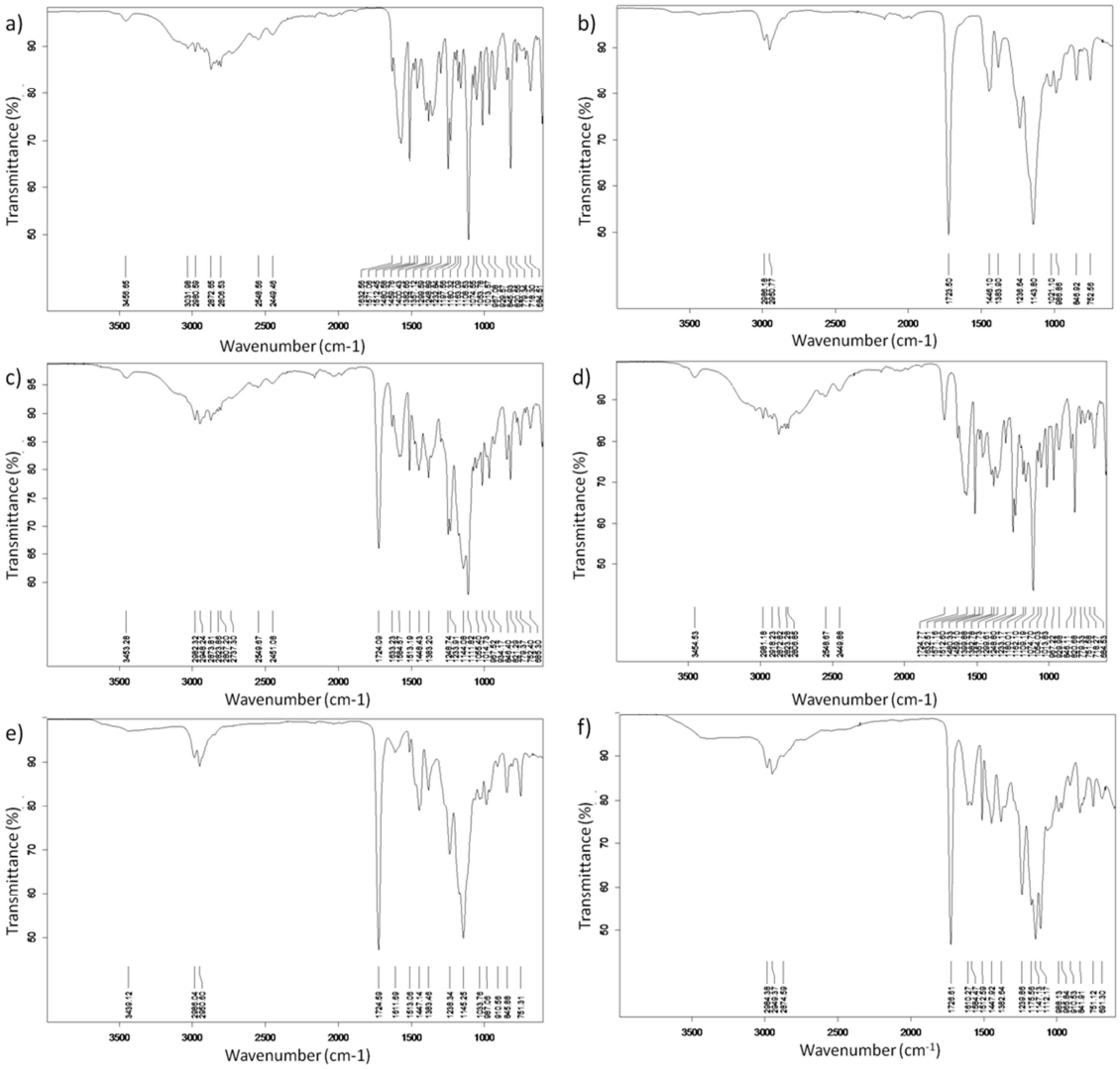
A similar shift in the endothermous melting peak of the crystalline MPT appears. The melting temperature of pure MPT is measured at 124°C, and its onset temperature at 122.3°C. In the physical mixtures A and B, this melting temperature has shifted to 110°C and 122.3°C respectively, and the onset temperature to 103.3°C and 117.3°C respectively. An even larger shift occurs in the thermogram of extrudate B, where the Tm of MPT is 105.6°C and its onset temperature 102.5°C. This shift again implies interactions between the polymer and the drug. These interactions are more explicit in extrudate B, but also appear in the physical mixtures. This endothermic peak has disappeared in the thermogram of extrudate A, indicating that all of the MPT has become amorphous during processing. Since there is only one Tg present, MPT and Eudragit® RS PO have interacted to form one single phase. Hence, the extrudate of mixture A is a solid solution.

The first derivative of the thermogram of extrudate B shows 2 Tg's, one for Eudragit® RS PO (46.5°C) and one for MPT (12°C, Tg of pure MPT = 14.2°C). A fraction of the MPT in this mixture

has become amorphous during processing, but has not interacted with the polymer phase. Hence, this extrudate exists of three phases: an amorphous polymer phase, an amorphous drug phase and a crystalline drug phase. This extrudate is in fact a solid dispersion which is partially crystalline and partially amorphous. Therefore, the DSC thermograms confirm the observations from the in-line Raman spectra.

Figures 8a and 8b represent the ATR FT-IR spectra of metoprolol tartrate and Eudragit® RS PO respectively. The IR spectra of the physical mixtures of metoprolol tartrate and Eudragit® RS PO (Fig. 8c and 8d) can be seen as the combinations of the IR spectra of the independent products in their respective ratios. 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 mixtures remains unchanged compared to the corresponding bands in the spectra of the pure components. No new bands or band shifts occur.

Figure 8. ATR FT-IR spectra of **(a)** MPT **(b)** Eudragit® RS PO **(c)** physical mixture A **(d)** physical mixture B **(e)** extrudate of mixture A at 140°C **(f)** extrudate of mixture B at 105°C.



The IR spectrum of mixture B, which was extruded at a temperature of 105°C, results in a significantly changed IR pattern (Fig. 8f). In the spectral area of 3800 cm^{-1} – 2800 cm^{-1}, the C-H stretch vibrations of the acrylate polymer are dominantly present. The pattern of the different OH and NH vibrations of the API has disappeared. They are replaced by a broad band between 3700 cm^{-1} and 2300 cm^{-1}, which can be assigned to associated hydroxyl groups due to hydrogen bonding with the carbonyl functions of the polymer. The bond representing the ester group of the acrylate polymer is dominantly present compared to the corresponding physical mixture (Fig. 8f vs. 8d). The bands in the 1610 cm^{-1} – 1585 cm^{-1} area, belonging to the metoprolol carboxylate groups, have shifted. In the fingerprint area (1500 cm^{-1} – 600 cm^{-1}), the pattern has disappeared and the bonds arising from the polymer are explicitly present compared to the physical mixture. This indicates a strong association of the API with the polymer, forming coupled vibrations of MPT with the polymer.

In the IR spectrum of mixture A, which was extruded at a temperature of 140°C, this effect is even more distinct (Fig. 8e), showing only the vibrational state (and thus spectrum) of the polymer. Due to the formation of strong hydrogen bonds between the hydroxyl groups of MPT and the ester carbonyl groups of the polymer, a macromolecular structure with its own vibrations is generated, where the MPT is no longer present as an independent molecule. With exception of very weak IR absorption bands at 1612 cm^{-1} and 1513 cm^{-1}, no typical absorption bands of MPT can be detected in the IR spectrum. The spectral area of 3500 cm^{-1} – 2800 cm^{-1} also shows only 1 weak and broadened band of the associated hydroxyl groups of the drug.

4. Conclusions

In this study, Raman spectroscopy was evaluated as a PAT tool to monitor the API concentration and polymer-drug melt solid state during pharmaceutical hot-melt extrusion processes. Comparison between the in-line collected Raman spectra and the off-line obtained DSC thermograms and ATR FT-IR spectra demonstrated that information about the solid state of a polymer-drug melt can be obtained from the Raman spectra, allowing monitoring and prediction of the polymer-drug solid state throughout the extrusion process. Using Raman spectroscopy, it was possible to detect differences between amorphous and crystalline polymer drug melts. The in-line collected Raman spectra also gave an indication of the occurring interactions during the hot-melt extrusion process, which leads to a better understanding of the process.

A PLS model was developed and validated, allowing drug concentration monitoring during hot-melt extrusion.

Acknowledgements

Kaiser Optical Systems Inc. is kindly acknowledged for providing the Raman Dynisco probe. Evonik Röhm is kindly acknowledged for the supply of the polymers.

References and Notes

1. R. Chokshi and H. Zia, Hot-melt extrusion technique: A review, Iranian J. Pharm. Res. **2004**, 3, 3-16.
2. J. Breitenbach, Melt extrusion: From process to drug delivery technology, Eur. J. Pharm. Biopharm. 2002, 54, 107-117.
3. M.M. Crowley, F. Zhang, M.A. Repka, S. Thumma, S.B. Upadhye, S. Battu, J.W. McGinity and C. Martin, Review article: Pharmaceutical Applications of Hot-Melt Extrusion: Part I, Drug Dev. Ind. Pharm. **2007**, 33, 909-926.
4. M.A. Repka, S. Battu, S.B.Upadhye, S. Thumma, M.M. Crowley, F. Zhang, C. Martin and J.W. McGinity, Review article: Pharmaceutical Applications of Hot-Melt Extrusion: Part II, Drug Dev. Ind. Pharm **2007**, 33, 1043-1057.
5. M.A. Repka, S. Majumdar, S. Battu, R. Srirangam and S.B. Upadhye, Applications of hot-melt extrusion for drug delivery, Expert. Opin. Drug Deliv. **2008**, 5, 1357-1376.
6. E.I. Keleb, A. Vermeire, C. Vervaet and J.P. Remon. Twin screw granulation as a simple and efficient tool for continuous wet granulation. Int. J. Pharm. **2004**, 273, 183–194.
7. Food and Drug Administration, Process Analytical Technology Initiative, Guidance for Industry PAT - A Framework for Innovative Pharmaceutical development, Manufacturing and Quality Assurance **2004**.
8. S.E. Barnes, M.G. Sibley, H.G.M. Edwards and P.D. Coates, Process monitoring of polymer melts using in-line spectroscopy, Trans. Inst. Meas. Control **2007**, 29, 453-465.
9. S.E. Barnes, E.C. Brown, M.G. Sibley, H.G.M. Edwards and P.D. Coates, Vibrational spectroscopic and ultrasound analysis for the in-process monitoring of poly(ethylene vinyl acetate) copolymer composition during melt extrusion, Analyst **2005**, 130, 286-292.
10. V.S. Tumuluri, M.S. Kemper, I.R. Lewis, S. Prodduturi, S. Majumdar, B.A. Avery and M.A. Repka, Off-line and on-line measurements of drug loaded hot-melt extruded films using Raman spectroscopy, Int. J. Pharm. **2008**, 357, 77-84.
11. S.E. Barnes, E.C. Brown, M.G. Sibley, H.G.M. Edwards, I.J. Scowen and P.D. Coates, Vibrational spectroscopic and ultrasound measurements for in-process characterisation of high density polyethylene/polypropylene mechanical blends during melt extrusion, Appl. Spectrosc. **2005**, 59, 611-619.
12. P.D. Coates, S.E. Barnes, M.G. Sibley, E.C. Brown, H.G.M. Edwards and I.J. Scowen, In-process vibrational spectroscopy and ultrasound measurements in polymer melt extrusion, Polymer **2003**,44, 5937-5949.
13. I. Alig, D. Fischer, D. Lellinger and B. Steinhoff, Combination of NIR, Raman, Ultrasonic and Dielectric Spectroscopy for In-line Monitoring of the Extrusion Process, Macromol. Symp. **2005**, 230, 51-58.
14. L. Li, O. AbuBaker and Z.J. Shao, Characterization of Poly(Ethylene Oxide) as a drug Carrier in Hot-Melt Extrusion, Drug Dev. Ind. Pharm. **2006**, 32, 991-1002.
15. L.S. Taylor and G. Zografi, Spectroscopic Characterization of Interactions Between PVP and Indomethacin in Amorphous Molecular Dispersions, Pharm. Res. **1997**, 14, 1691-1698.
16. Z. Dong, A. Chatterji, H. Sandhu, D.S. Choi, H. Chokshi and N. Shah, Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation, Int. J. Pharm. **2007**, 355, 141-149.
17. J. Breitkreutz, Prediction of Intestinal Drug Absorption Properties by Three-Dimensional Solubility Parameters, Pharm. Res. **1998**, 15, 1370-1375.
18. L. Eriksson, E. Johansson, N. Kettaneh-Wold, J. Trygg, C. Wikström and S. Wold, Multi- and Megavariate Data Analysis Part I: Basic Principles and Applications, Umetrics Academy, Sweden **2006**, 63-101.
19. Y. He, B. Zhu and Y. Inoue, Hydrogen bonds in polymer blends, Prog. Polym. Sci. **2004**, 29, 1021-1051.

20. M. De Veij, P. Vandenabeele, T. De Beer, J.-P. Remon and L. Moens, Reference Database of Pharmaceutical Excipients, J. Raman spectrosc. **2008**, 40, 297-30.
21. G. Socrates, Infrared and Raman Characteristic Group Frequencies: Tables and Charts, John Wiley & Sons Ltd. , England, **2004**.
22. V.B. Mathot, Calorimetry and Thermal Analysis of Polymers, Hanser Publishers, New York, NY, **1994**.
23. S. Qi, A. Gryczke, P. Belton and D.Q.M. Craig, Characterisation of solid dispersions of paracetamol and EUDRAGIT® E prepared by hot-melt extrusion using thermal, microthermal and spectroscopic analysis, Int. J. Pharm. **2008**, 354, 158-167.