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Process monitoring for analysis, understanding and control of pharmaceutical hot-melt extrusion processes: A review

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Abstract

Hot-melt extrusion (HME) is applied as a continuous pharmaceutical manufacturing process for the production of a variety of dosage forms and formulations. To ensure the continuity of this process, the quality of the extrudates must be assessed continuously during manufacturing.

Pharmaceutical extruders are equipped with traditional (univariate) process monitoring tools, observing barrel and die temperatures, throughput, screw speed, torque, drive amperage, melt pressure and melt temperature. The relevance of several spectroscopic process analytical techniques for monitoring and control of pharmaceutical HME has been explored recently. Nevertheless, many other sensors visualizing HME and measuring diverse critical product and process parameters with potential use in pharmaceutical extrusion are available, and were thoroughly studied in polymer extrusion. The implementation of process analytical tools in HME serves two purposes: (i) improving process understanding by monitoring and visualizing the material behaviour; and (ii) monitoring and analyzing critical product and process parameters for process control, allowing to maintain a desired process state and guaranteeing the quality of the end product.

This review provides an evaluation of the process analytical tools applied for pharmaceutical HME monitoring and control, and discusses techniques that have been used in polymer extrusion having potential for monitoring and control of pharmaceutical HME.

1. Introduction

1.1. Hot-melt extrusion (HME)

HME is one of the most widely used processing techniques within the plastic and rubber manufacturing industry and is extensively applied in the food processing industry. It is defined as the process of pumping raw materials with a rotating screw through a die into a product of uniform shape under controlled conditions, such as temperature, feed rate and pressure [1, 2]. HME has potential to be applied in continuous manufacturing for a wide variety of dosage forms and formulations, such as granules, pellets, tablets, capsules, implants, suppositories, stents, transdermal and transmucosal systems and ophthalmic inserts [3, 4]. In hot melt extruded drug delivery systems, (poorly soluble) active pharmaceutical ingredients (APIs) are embedded in a carrier, containing meltable materials and additional excipients. These materials can be polymeric materials or thermodeformable waxes [5].

HME offers several advantages compared to conventional pharmaceutical production processes [1, 3, 4, 6, 7] of solid dosage forms for certain formulations. Formulations produced with HME often exhibit an enhanced bioavailability of poorly soluble drugs, due to dispersion of the API at molecular level in the final dosage forms [8-10]. The molten polymers can function as thermal binders and act as drug depots or drug release retardants, hence allowing sustained, modified and targeted release. An improved content uniformity is obtained by the intense agitation and distributive and dispersive mixing generated by the rotating screw and its selected configuration, resulting in the de-aggregation of suspended particles in the molten polymer. The process is anhydrous, avoiding potential water-mediated drug degradation. Exclusion of solvents in the production process decreases the number of processing steps and eliminates the need for time-consuming drying steps. The extrudates can be cut into tablets, hence eliminating tableting issues caused by poor compressibility of the formulation. An additional significant advantage is that HME is a continuous process. The advantages of continuous production over traditional batch processes are numerous [11-13]: less scale-up issues resulting in a shorter development time, possible automation of the production line, reduction of production costs and waste, a reduced time-to-market, less product variability and improved product quality.

During extrusion, all components in the formulation must be thermally stable at the selected processing temperatures, which could limit the extrusion of thermosensitive APIs and carriers. However, the residence time in a twin-screw extruder is relatively short, and the temperature of each barrel segment can be accurately controlled. Downstream feeding of thermolabile APIs (after the kneading zone) can avoid degradation of these compounds due to high temperatures caused by the shear forces generated by the rotating screw and its screw design that are needed to melt the polymers.

Hence, the exposure of the API to high temperatures is reduced to a minimum. Another drawback of HME is related to the high energy input from the shear forces in the extrusion barrel, leading to higher, uncontrolled and unknown product temperatures, which could induce drug or polymer degradation, having a significant impact on the product quality. This obstacle can be overcome by adjusting the process parameters as well as the screw and die design [2].

1.2. Process and equipment

The equipment for HME comprises an extruder, downstream auxiliary equipment and monitoring tools used for performance and product quality evaluation. The extruder itself (Fig. 1) consists of a feeding hopper, a temperature controlled barrel with one or two screws, a screw-driving unit, a die to shape the final product and a heating/cooling device [2, 5]. A powder blend, typically containing the API, thermoplastic polymers or waxes as a matrix carrier and other functional excipients (e.g. plasticizers, release modifying agents, super desintegrants, thickening agents, antioxidants, thermal lubricants, bulking agents and miscellaneous additives [1, 2]), is fed through the feed hopper into the barrel. This barrel usually contains different zones, each with a specific set barrel temperature. The rotating screw(s) within the barrel transport the powder blend towards the extrusion die. The powder blend will melt primarily due to the heat generated by friction as the material is sheared between the rotating screw(s) and the barrel wall, and additional heat is conducted from the barrel [6]. This melt is then pumped through the die located at the end of the extrusion barrel, and subjected to further downstream processing equipment.

The screw design has a significant influence on the efficiency of the HME process and on the quality of the end product. Screw geometry directly affects the throughput, melting rate, mixing, product temperature and homogeneity of the melt. Different screw configurations allow downstream transport of the material in the barrel towards the extrusion die, conveying, melting, mixing, venting or devolatilization, and pumping and compression of the molten powder blend. Several types of screw elements are required to perform these tasks. Conveying elements provide transport of the melt, either forward or backward. Different mixing elements can also be included in the screw design. Their function, distributive or dispersive mixing, is related to their geometry. Furthermore, they also play a key role in transforming the API from its crystalline to its amorphous form [14]. For a detailed overview of all possible screw elements, readers are referred to the literature [8, 15, 16].

In pharmaceutical HME, twin-screw extrusion is preferred over single-screw extrusion. In twin-screw extrusion, the screws can rotate in the opposite direction (counter-rotating) or in the same direction

(co-rotating), whichever is most favourable. Counter-rotating designs are used when regions with very high shear are required. These extruder types allow potential air entrapment, high pressure generation and low maximum screw speeds and output [1]. Co-rotating screws are often fully intermeshing, indicating that as the screws rotate, the element on one screw wipes the element on the neighbouring screw, causing material to transfer between both screws [6]. They can be operated at high screw speeds and deliver high outputs, and offer better mixing and conveying of the melt. Other benefits related to co-rotating screws are a shorter residence time, less tendency to overheat the materials, and an easier material feed [6, 17].

Several downstream processing devices are available for further cooling, cutting and shaping of the hot melt extruded strands. Cooling of the extrudates can be accomplished with air, nitrogen, in water or simply at room temperature on conveyor belts or rolls. Film extrusion on chilled rolls or calenders has been applied for the manufacturing of films for oral administration [18-24] and transdermal drug delivery [25, 26]. Injection moulding is a downstream process step where the melt is injected into a closed mould under high pressure and temperature conditions after leaving the extrusion die. An overview of the applications of injection moulding for drug delivery is presented in [27]. Another possibility of shaping the extruded strands is by cutting them into small pellets using pelletizers [28-30].

Nowadays, extruders are equipped with standard (univariate) process monitoring sensors. These traditional monitoring options provide information on barrel and die temperatures, feed rate or throughput, screw speed, torque and drive amperage, melt pressure, melt temperature and possibly melt viscosity [1, 31] (Fig. 1). Classical process control based on measurements of these conventional parameters is in many cases not sufficient to account for process-induced variations in material properties, to guarantee stable processing and to monitor and predict the extrudate quality attributes.

This review provides an overview and evaluation (advantages/disadvantages) of the process analytical techniques that have been used for monitoring and controlling pharmaceutical HME, and for improved process visualization and understanding. In addition, process analyzers applied in polymer extrusion that might be valuable for pharmaceutical HME are reviewed and discussed. Several reviews have been published describing the general mechanisms of action of process analytical tools in pharmaceutical production processes. Readers are referred to these publications illustrating near infrared (NIR) spectroscopy [32-38], Raman spectroscopy [32, 35, 36, 39-42], ultraviolet/visible (UV-VIS) spectroscopy [32], fluorescence spectroscopy [32], Terahertz (THz) spectroscopy [32, 36, 39, 43, 44], nuclear magnetic resonance (NMR) spectroscopy [32], ultrasound techniques [45] and rheological techniques [46, 47].

2. Process analytical tools for hot-melt extrusion

Process analytical tools for pharmaceutical HME are needed for two purposes: (i) improving the understanding of pharmaceutical HME by monitoring and visualizing material behaviour during processing (an enhanced understanding of the process and the material behaviour allows optimization of formulations, process settings such as screw configuration etc.); and (ii) monitoring and analyzing critical product and process parameters for process control, allowing to maintain a desired process state, guaranteeing the quality of the end product. An overview of the applied process analytical techniques for pharmaceutical HME discussed in this review can be found in Table 1, together with their purpose, interfacing possibilities, challenges and disadvantages encountered during implementation. Table 2 provides an overview of the reviewed HME process analytical techniques used in polymer extrusion with relevant potential for monitoring and control of pharmaceutical HME. Their purpose, possible benefits and shortcomings for pharmaceutical HME and interface positions are also listed in Table 2. The reported possible drawbacks of each technique applied in pharmaceutical extrusion and polymer extrusion should be taken into account when considering application of these tools for analysis, understanding and control of pharmaceutical HME processes.

2.1. Process analytical techniques applied for pharmaceutical hot-melt extrusion

2.1.1. NIR spectroscopy

Tumuluri et al. [20] applied NIR spectroscopy to predict the clotrimazole quantity in hot-melt extruded polyethylene oxide (PEO) films via a developed partial least squares (PLS) model. A fibre-optic NIR reflectance probe was fixed above the extruded films, behind the extrusion die. Vector normalization of the spectra was performed to reduce the variations in intensity caused by path length variation. Extrusion was performed on a single-screw extruder. The calibration model, containing 9 different PEO films with varying clotrimazole content, regressing the on-line collected NIR spectra versus the actual clotrimazole content as determined with high-performance liquid chromatography (HPLC), yielded a root mean square error of cross validation (RMSECV) of 0.298% (w/w). Four validation samples were predicted within a margin of error of less than 3.5% (w/w). It was shown that the model was more accurate for predictions at higher concentrations.

Saerens et al. [48] implemented a diffuse reflectance NIR probe implemented in the extrusion die of a co-rotating twin-screw extruder (screw diameter = 16 mm) (Fig. 2) to monitor and predict drug content and to evaluate the solid state of the extrudates before exiting the die. A PLS model was built,

regressing the in-line NIR spectra collected during extrusion of physical mixtures containing 20, 30 and 40% (w/w) metoprolol tartrate (MPT) in Kollidon® SR versus known MPT concentrations. The model was validated with new extrusion experiments, resulting in a root mean square error of prediction (RMSEP) of 1.54% (w/w).

Furthermore, a physical mixture with a drug load of 40% MPT (w/w) in Kollidon® SR was extruded at 135°C and at 105°C. The in-line NIR spectra were compared to the NIR spectrum of the physical mixture. The spectra of both extrudates still contained the MPT peaks, though broader, indicating that not all MPT remained in its crystalline form. This broadening of spectral bands was slightly more pronounced at 135°C than at 105°C. Peak shifts throughout the entire spectrum were also visible, expressing the extent of molecular interactions between polymer and drug. At 105°C, these shifts were smaller, suggesting stronger interactions between Kollidon® SR and MPT at 135°C. Furthermore, the polymer-drug interactions were confirmed by the manifestation of a new peak at 6495 cm⁻¹. This peak is attributed to the first overtone of hydrogen bonded hydroxyl groups [49]. At 135°C, this peak was more intense than at 105°C. Saerens et al., hence demonstrated that NIR spectroscopy can be used in-line during HME to monitor the drug concentration and solid state and hydrogen bonds formed during extrusion. The authors chose a formulation with Kollidon® SR as matrix since this formulation does not produce a transparent extrudate, which would cause detection problems when using reflectance NIR spectroscopy.

Smith-Goettler et al. [50] used NIR spectroscopy for real-time predictions of the API loading (% w/w) and surfactant loading. Two transmission NIR probes were mounted in a die adapter on a twin-screw extruder with a screw diameter of 27 mm. The first probe is used to send the laserlight through the melt, and on the opposite side of the melt channel, a second probe captures this signal and sends it to the detector. 20 calibration mixtures for the development of a PLS model and six independent validation mixtures with varying API (0-30.1% w/w) and surfactant (4.8-27.0%w/w) concentrations were extruded with an output varied from 20 kg/h to 35 kg/h. NIR spectra of the extrudates confirmed the conversion of the API to the amorphous state, since bands specific for the amorphous API were found in the spectra of the extrudates. The API loading prediction model yielded an RMSEP of 0.3% w/w. The surfactant loading prediction model yielded an RMSEP of 0.6% w/w. These predictions were then used for fault detection, isolation of suspect material and real-time troubleshooting during HME using the SIPAT software package (Siemens). When a drift in the API loading, due to a change in API lots with different bulk densities, was detected, the molten extrudate stream was diverted to waste. Process parameters regarding the material feeders were investigated, and the material continued to be diverted to waste until the feeder reached steady state. In this research, NIR spectroscopy was hence applied for quantitative monitoring and control of the extrusion process.

McKelvey et al. [51] illustrated the use of transmission NIR spectroscopy to study the impact of process design and scale up on residence time distributions (RTDs) and on composition disturbances caused by feeding issues. RTD measurements as a function of screw speed and feed rate were performed on a co-rotating twin-screw extruder with a screw diameter of 16 mm, by adding a single drop of blue food colouring to the extruder feed inlet and measuring the optical response at the die adapter. This RTD fingerprint was used to assess the ability to scale from the 16 mm to a 27 mm co-rotating twin screw extruder, using the ratio of free volumes in the extruders (3.63) to adjust the feed rate from 2.75 kg/h to 10 kg/h. At the 27 mm extruder, each component of the mixture (compound 'C', a surfactant and polyvinyl pyrrolidone-polyvinyl acetate copolymer) was fed individually, and NIR spectroscopy was used to monitor the composition of this melt during extrusion. A die block adapter was designed to accommodate the transmission optical probes. A predictive model based on feeder input parameters was used to determine the melt composition and was compared to the real-time concentration measurements with NIR spectroscopy. This model can be used to control the feeding system and to isolate bad product. The transmission NIR spectroscopic tool presented here was successful in measuring RTDs and formulation composition at the extrusion die, providing possibilities for scale-up of the process and optimization with limited amounts of material and time.

Troup et al. [52] describe the development and implementation of an in-line transmission NIR measurement system allowing the determination of the composition of a multi-component melt stream at the exit of a twin screw extruder. NIR measurements were performed in a custom built die adapter on a 27 mm twin-screw extruder. Two loss-in-weight mass feeders were used to feed the polymer and drug separately into the extruder. A liquid surfactant was fed into the process using a gear pump. Data from the mass feeders and liquid addition system were also logged. Using a PLS model, NIR spectroscopy allowed the simultaneous prediction of concentration of all three components in the extrudate. The used spectral range was the 1600 – 1800 nm region since all three components have chemical groups with strong absorbance in this region, and since this range is robust to moisture variability. In routine manufacturing, the NIR system was demonstrated to be able to detect process upsets and to continuously ensure product uniformity over the entire manufacturing run.

A different application of pharmaceutical HME is the production of cocrystals. Kelly et al. [53] used NIR spectroscopy to monitor the formation of ibuprofen and nicotinamide cocrystals during extrusion based solvent free continuous cocrystallization. The cocrystallization of ibuprofen and nicotinamide in a 1:1 molar ratio was carried out in a co-rotating twin-screw extruder with a screw diameter of 16mm. A high temperature NIR reflectance probe with a sapphire window was fitted into a threaded port at the end of the extruder barrel. Off-line NIR spectra were taken at several points along the extruder screws to examine the dynamics of the cocrystal formation. This occurred mainly in the latter stages of

the extruder screw, suggesting that cocrystal formation is highly dependent on the length of the screws, residence time and shear caused by the mixing elements across the length of the screw. The effects of three different screw configurations with different mixing intensities (low, medium and high) dependent on the number and angle of mixing elements, the set temperature profiles and the screw speeds were evaluated. Cocrystals showed significant differences to the physical mixture. Once ibuprofen and nicotinamide are bonded together, the vibrations are modified and the peaks shift, giving rise to the appearance of new peaks in the NIR spectrum. The high mixing intensity screw configuration (the screw design comprising the most mixing elements at an angle of 90°) resulted in the most significant spectral changes compared to the spectrum of the physical mixture, particularly between 4980 and 5100 cm^{-1} . Increasing the set temperature at a screw speed of 30 rpm induced similar spectral changes as increasing the mixing intensity of the screw configuration. Relatively small spectral changes were observed when varying the screw speed (20, 30 and 40 rpm) at 90°C using the high intensity screw configuration. A PLS model, regressing the in-line NIR spectra against cocrystal purity as determined from X-ray diffraction (XRD), was developed using a dataset including only the spectra obtained at a set temperature of 90°C with medium and high screw intensity configurations, since temperature is a well known factor influencing the NIR spectral signals. It was expected that calibrations over multiple temperature configurations would not give accurate results. A correlation coefficient of 0.999 for measured and predicted purity was obtained.

NIR spectroscopy has demonstrated to be a versatile process analysis tool for pharmaceutical HME to monitor several critical product characteristics such as quantitative formulation composition, solid state, polymer-drug interactions and the formation of cocrystals (Table 1). Besides the application for monitoring purposes, it was also applied to control API levels adequately. NIR spectroscopy can be applied in both reflectance and transmission mode, depending on the type of formulation used. For transparent formulations, the transmission mode is favoured, since spectra collected in reflection mode contain more noise. Interpretation of the collected NIR spectra can be a challenging task since NIR spectra contain broad, overlapping overtones and combination bands. However, with the proper chemometric techniques, the relevant information can be extracted from NIR spectra.

2.1.2. Raman spectroscopy

Tumuluri et al. [21] used Raman spectroscopy to quantify the drug load in hot-melt extruded films and to evaluate the physical state of these APIs in the formulations. A fibre optic Raman probe was used for on-line analysis and clamped above the film in a 90° angle behind the extrusion die. Clotrimazole and ketoprofen were used as model APIs and extruded in PEO films on a single-screw extruder. Two PLS models were developed regressing the on-line collected Raman spectra against the known API

concentration of each API, respectively. For the ketoprofen films, the Raman shift range 506 – 1616 cm^{-1} was used, and a band representing the C-H bending vibration of PEO at 1480 cm^{-1} was used for normalization. A challenge was the undulation of the film, resulting in different path lengths between extruded film and probe. This was corrected by using the ratio of the active band to the polymer band at 1480 cm^{-1} . The PLS model for the on-line clotrimazole quantification was built using the 176 to 1735 cm^{-1} Raman spectral range with normalization to the PEO peak area 1215 to 1248 cm^{-1} .

Saerens et al. [54] used a Raman probe implemented in the extrusion die of a co-rotating twin-screw extruder (screw diameter = 16 mm) (Fig. 2) to monitor and predict the drug content and to evaluate the solid state of the extrudates before exiting the die. A PLS model was built, regressing in-line Raman spectra collected during extrusion of physical mixtures containing 10, 20, 30 and 40% (w/w) MPT in Eudragit® RL PO versus the known MPT concentrations. The model was validated with independent test extrusion runs, and resulted in an RMSEP of 0.59% (w/w). Furthermore, two physical mixtures containing 10% (mixture A) and 40% (mixture B) MPT (w/w) in Eudragit® RS PO were extruded at temperatures of 140°C and 105°C, respectively. The in-line Raman spectra were compared to the Raman spectrum of the physical mixtures. In both extrudates, peak shifts occurred, indicating interactions through hydrogen bonds between polymer and drug. The shifts were larger in the extrudates of mixture A, indicating stronger interactions. Evidence was found for the formation of hydrogen bonds between the hydroxyl and/or amino groups from MPT and the carbonyl groups belonging to the polymer. The MPT peaks in the extrudates of mixture B are still well defined, sharp peaks, whereas for mixture A, they have broadened extensively, showing the presence of amorphous MPT. Raman spectroscopy allowed differentiation between solid states of the drug and formulation, and was able to accurately predict drug concentration during HME.

Almeida et al. [55] extruded physical mixtures containing MPT and ethylene vinylacetate (EVA) (50:50) on a co-rotating twin-screw extruder (16 mm). Diffuse reflectance NIR spectroscopy and Raman spectroscopy were implemented in the die to evaluate the material behaviour at a molecular level in-line as a function of the process settings (temperature: 90, 110 and 140°C; screw speed: 90 and 110 rpm). Principal component analysis (PCA) was performed on all in-line collected Raman spectra. The first principal component (PC) captured 60% of the spectral variation, induced by differences in polymer/drug solid state caused by the variation in applied extrusion temperatures. An increased process temperature induced a loss in drug crystallinity. Extrusion of the physical mixtures at 90°C and 110°C provided Raman spectra characterized by sharp MPT bands, indicating that (the majority of) the MPT was crystalline. When the extrusion temperature was increased to 140°C, broadening of the MPT peaks in the spectrum confirmed the melting of the drug. Raman spectra collected during extrusion at 90°C showed a small peak shift of the $\nu(\text{C-O})$ stretch vibration peak to

lower frequencies, indicating interactions between the drug and polymer, even at this temperature. The acetate group peak of EVA ($\nu(\text{CH}_3\text{COO})$) broadened, confirming the manifestation of interactions between MPT and EVA. The shift of the $\nu(\text{C-O})$ stretch vibration peak increased at an extrusion temperature of 110°C , and disappeared at 140°C , indicating that MPT lost its crystallinity. Additionally, the $\nu(\text{O-H})$ and $\nu(\text{N-H})$ stretch vibrations shifted to lower frequencies, as did the peak of the EVA acetate group. This proved the increase in intensity of interactions (hydrogen bonds) between the drug and polymer, induced by a higher processing temperature. Increasing the screw speed did not result in peak shifts in the Raman spectrum. Besides Raman spectroscopy, diffuse reflectance NIR spectroscopy was also applied for the in-line monitoring of the extrusion process. PCA of the NIR data led to similar conclusions as the Raman spectra. NIR spectroscopy confirmed the formation of hydrogen bonds by the manifestation of an extra peak at 6500cm^{-1} , attributed to the first overtone of the hydrogen bonded hydroxyl. NIR and Raman spectroscopy hence provided complementary information concerning the manifestation of hydrogen bonds between polymer and drug in this formulation.

Only one application of spectroscopic in-barrel monitoring has been illustrated [56]. To improve the understanding of material behaviour in the barrel, a Raman probe was implemented in each section of the barrel. MPT concentration (10 and 40% w/w in Eudragit® RSPO), extrusion temperature (100, 120 and 140°C) and screw speed (80 and 160 rpm) were varied to examine their influence on polymer/drug solid state throughout the entire barrel. When extruding the formulation with 40% (w/w) MPT, broadening of MPT peaks indicated melting of MPT between sections 2 and 3, caused by the first kneading zone (Fig. 3). Decreasing the concentration to 10% w/w showed an additional spectral difference (i.e., peak shifts indicating interactions between MPT and carrier) between sections 5 and 6, due to formation of a solid solution. At a 10% (w/w) MPT load, increasing the extrusion temperature did not influence the solid state or the barrel section where the final solid state is obtained. At a drug load of 40% (w/w), the solid state of the end product was reached further down the barrel when extrusion was performed at a lower barrel temperature. Doubling the screw speed when processing a 10% MPT formulation (w/w) did not affect the product solid state. In contrast, at 40% (w/w) drug load, the section where the final product solid state was obtained, was situated earlier in the barrel when applying a higher screw speed. To conclude, the Raman spectra provided real-time information about polymer/drug behaviour throughout the entire extrusion barrel, facilitating process visualisation and understanding. Twin-screw extrusion is a starve-fed process where most screw elements are not completely filled with material. This presents a challenge in positioning the Raman probe, since the distance between probe and measured material varies throughout processing. This variation in distance creates an undesired source of spectral variability which has to be filtered out.

Kindermann et al. [57] used Raman spectroscopy for the monitoring of the formation of polyelectrolyte complexes composed of poorly water-soluble acid drugs (naproxen and furosemide) and basic polymethacrylates (Eudragit® E PO) by an acid base-reaction during HME. Physical mixtures of naproxen and Eudragit® E PO were pre-blended in a mixer and subsequently hot-melt extruded with a co-rotating twin-screw extruder (screw diameter = 27 mm). A Raman spectrometer was equipped with an extruder-compatible probe. The authors do not mention the exact location of implementation of the probe. Raman spectroscopy was used to characterize the drug-polyelectrolyte interaction. The Raman band at 1684 cm^{-1} represented the symmetric stretch vibration of the carbonyl group of naproxen. This band was found in the pure naproxen and in the physical mixture, but disappeared in the spectra of the extrudates, confirming the acid-base-reaction and complex formation in the melt.

Similar to NIR spectroscopy, Raman spectroscopy can be used as a process analytical tool to monitor component concentrations, solid state and intermolecular interactions that might occur during extrusion (Table 1). Both techniques are complementary, and depending on the formulation used for extrusion, one technique will be more suitable than the other. Raman spectra are influenced by fluorescence and colour in the formulation, which might cause difficulties due to a high background signal. These can however be (partly) overcome by changing the type of laser.

2.1.3. Monitoring of torque and power consumption

Schilling et al. [58] determined the influence of the plasticizer citric acid on the processability of Eudragit® RS PO during single-screw extrusion. The process parameters screw speed and motor load were monitored as a function of citric acid (CA) content and the preset temperature in the die. The quotient of the maximum applicable screw speed divided by the measured load at a given temperature was calculated for each CA level. This quotient was then interpreted as an index of processability of the formulation at the preset die temperature. Improved processability due to plasticization was reflected by high quotients at lower temperatures. Improved processability of a powder blend by plasticization of the polymer yielded a higher screw speed and a lower motor load at a predefined temperature. A temperature of 140°C was needed to extrude the pure polymer with a screw speed of 20 rpm, while blends containing citric acid monohydrate (CA MH) could be processed at temperatures from 110°C to 130°C . The screw speed/motor load quotient significantly increased when the CA MH was increased from 0 to 10, 15, 20 and 25% (w/w). This indicated a decrease in melt viscosity and made extrusion at lower temperatures possible. The absence of a statistically significant difference between 25 and 30% (w/w) CA MH suggested that the plasticizing effect plateaued at this

concentration, coinciding with the solubility limit of CA MH in Eudragit® RS PO. Finally, it was found that CA MH facilitated the extrusion process more efficiently than its anhydrous form.

Torque can be easily measured during HME and are correlated with several important product parameters that cannot straightforwardly be monitored during extrusion, such as the rheological behaviour of the material, plasticizing effects of components in the melt, grinding processes during extrusion and the velocity of material through the extruder. These parameters can easily be monitored during HME without the requirement of barrel and/or die modifications, and without the need for additional sensors.

2.2. Monitoring of polymer melt extrusion

The polymer processing industry has developed and applied numerous process analytical tools to improve HME process understanding, monitoring and control, to enhance product quality and to allow real-time fault detection. In addition to the use of conventional monitoring techniques and spectroscopic techniques such as NIR and Raman spectroscopy, the literature describes applications of ultrasonic techniques, rheological techniques, advanced temperature sensors, dielectric sensors, NMR spectroscopy, fluorescence spectroscopy, UV-VIS spectroscopy and THz spectroscopy. The following section provides an overview of process monitoring techniques that have been applied in polymer extrusion which could be relevant for pharmaceutical HME process monitoring and control. A summarized overview can be found in Table 2, together with the analysis possibilities of each technique, the position in the extruder where the technique should be/can be implemented for its purpose and possible challenges, disadvantages and shortcomings of the analytical technique.

2.2.1. Spectroscopic techniques

2.2.1.1. NIR spectroscopy

Hansen and Vedula [59] used in-line NIR spectroscopy to monitor the comonomer (vinyl acetate (VA)) concentration in a system of EVA copolymers simultaneously with the polymer melt flow index (MI) for this system. In NIR absorption spectra, variations in chemical composition are dominant effects, whereas the rheological flow effects are only subtle variations in the NIR spectra. The anisotropic nature of flow depends on the molecular orientation and the orientation distribution of flowing polymer melt, which are related to molecular weight, chain length, entanglement and branching of the polymer chain. Differences in molecular orientation and orientation distribution affect the NIR absorbance spectra and induce spectral shifts, hence providing information about physical properties that directly correlate with molecular weight parameters such as MI. For EVA random copolymers, these rheological properties are not related to the comonomer ratio for VA concentrations lower than 30%. This indicates that primary effects (composition of the melt) and secondary effects (MI) on the absorbance spectrum are independent. Dual transmission fibre optic probes were mounted in a flow cell attached to a single-screw extruder. The authors developed two PLS models, a first one containing three principal components which is used for MI predictions, and a second PLS model with only one principal component for VA concentration measurements. The standard error of prediction (SEP) values for the two models were 0.46 for MI (ln MI (g/10 min)) predictions and 0.62 wt% for VA predictions. These models were then applied for in-line monitoring of MI and VA concentration. All predicted values for both responses were found between the actual laboratory value \pm SEP,

indicating that NIR spectroscopic measurements can predict the VA content and MI of the melt during extrusion.

In a second study [60], Vedula and Hansen developed a PLS-1 model to predict the complex viscosity ($\ln(|\eta^*(\omega)|)$) and the VA monomer content of molten EVA copolymers. Dual transmission fibre optic probes were mounted in a flow cell attached to a single-screw extruder. The PLS-1 model, where the NIR spectra were regressed versus the complex viscosities measured at different frequencies (ω) comprised four components. The first PC (explained 31.5% of the variation related to the rheological response) accounted for the spectral variation caused by varying VA content, and a second (63.4%) PC described the spectral variation caused by the rheological response. The standard error of calibration (SEC) and SEP values were 0.38 and 0.8 respectively. Most new predicted measurements are found within the detection limits for predictions as decided by the SEP values. A limitation for this type of measurements is the melt temperature, which has a large effect on rheological properties. These experiments were all performed at the same temperature, assuring only a small variance in melt temperature in the flow cell (1-3°C). A further improvement of the calibration models from both studies might be achieved by including temperature as an independent variable in the X matrix.

Nagata et al. [61] developed an in-line density sensor using NIR spectroscopy. The transmission NIR spectra of molten polyethylene (PE) in flow were collected using a fibre-optic device attached to a single-screw extruder. The PE density depends on the number of polymer chain branches and their length. The degree of branching could be estimated by measuring the composition ratio of methyl group (-CH₃, at the ends of branches and main chains) to methylene (-CH₂-, in polymer chains) group. In attempts to correlate the density with the NIR spectra, the correlation coefficient R² between polymer densities and scaled absorbances of 14 polymer grades were calculated, and the highest R² (0.9853) was found at 1170nm. Using this model, it was hence possible to monitor the PE density in-line at the extrusion die.

Witschnigg et al. [62] developed an NIR method where the results of on-line extensional rheometry (on-line measurements of drawing force performed by on-line Rheotens equipment), Young's modulus (calculated out of tensile tests) and interlayer distance (determined by small angle x-ray scattering) are correlated with NIR spectra. A mixture of 90% polypropylene (PP), 5% organoclay and 5% compatibilizer (w/w) was extruded in a co-rotating twin-screw extruder, which had a bypass system to create a melt string for on-line rheotens measurements. The NIR probe was implemented right before the die. Two different screw geometries (1 and 2) were applied during experiments. Screw geometry 1 contained three kneading zones, whereas only 1 kneading zone was present in geometry 2. For geometry 1, a PLS model with 5 components regressing the NIR spectra versus the Young's modulus

was developed resulting in an RMSECV of 30 MPa. For geometry 2, a four component PLS model was built resulting in an RMSECV of 94 MPa. For the correlation with drawing force, 2 component PLS models were developed resulting in an RMSECV of 2.64 mN for geometry 1 and an RMSECV of 1.98 mN for geometry 2. Concerning the correlation of NIR spectra with the interlayer distance, a PLS model with 1 component and an RMSECV of 0.013 nm was developed for geometry 1 and for geometry 2, a PLS model with 2 components resulted in an RMSECV of 0.019 nm. The measurements were not performed at different aggregate states (melt state vs. semicrystalline solid state), since this creates differences in NIR spectra that would affect the chemometric models. Variations in NIR spectra caused by changing the solid state of the extrudates might interfere with the variations attributed to Young's modulus, drawing force and interlayer distance. Nevertheless, the authors demonstrated that NIR spectra can be used with sufficient precision for in-line quality monitoring. However, in this publication it is not mentioned how changes in Young's modulus, interlayer distance and drawing force affect the in-line collected NIR spectra.

In pharmaceutical HME, NIR spectroscopy is mainly applied to monitor the concentration of melt components, and in some cases to determine the solid state and occurring intermolecular interactions within the melt. In polymer extrusion applications however, NIR spectra showed to correlate well with Young's modulus, interlayer distance and drawing force.

2.2.1.2. UV-VIS spectroscopy

Wang et al. [63] applied the UV-VIS spectroscopy technique to monitor the process induced degradation of poly (L-lactic acid) (PLLA) during extrusion. Extrusion was performed on a co-rotating twin-screw extruder, equipped with a special measurement slit die that contained the UV-VIS transmission probes. The influence of the processing parameters barrel temperature, screw speed and throughput was investigated. Samples were also collected for off-line analysis (molar mass, melt viscosity and in vitro biodegradation). The residence time distribution was determined by adding a red coloured pellet to the feeding during stationary state. A reference spectrum was taken, and subtracted from all the UV-VIS spectra collected during experiments. These difference spectra (ΔA) exhibited a maximum at 310 nm for all processing conditions, indicating the wavelength range of the most significant spectral changes due to degradation. ΔA increased with increasing processing temperature and screw speed as well as with decreasing throughput. This means that an increase in ΔA is accompanied by decrease in average molar mass and an increase in specific mechanical energy. UV-VIS absorption of the melt can be used to get an estimate of the molar mass of the extrudates of dry PLLA, regardless of variations in extrusion parameters. To evaluate the effects of processing parameters of PLLA on the biodegradation rate of the extrudates, an in vitro biodegradation

experiment at elevated temperature was performed for selected extrudates. Higher in vitro weight loss was related to higher UV-VIS absorption of the extruded materials, which is correlated with lower molar mass of the extruded materials. The authors demonstrated that UV-VIS is very sensitive to colour changes of the PLLA melt, and a clear correlation between increasing absorption and a decrease in molar mass of the extrudates was found, which can be used as a measure of polymer degradation.

Gilmor et al. [64] developed an in-line colour monitoring system: the colour of the melt during changeover from one pigmented PE to another was continuously measured directly in an extruder using a fibre-optic assisted charge coupled device spectrometer. The fibre-optic reflection probe was inserted into the die of a single-screw extruder. Residence time distributions were calculated from the in-line reflectance data, without requiring knowledge of the absolute concentration values in the melt.

UV-VIS spectroscopy is a process analytical technique that can be applied in pharmaceutical HME to monitor residence distribution times of the melt, to detect polymer and/or drug degradation, to detect impurities in the melt and to quantitatively analyse the melt compounds. It is a simple, straightforward technique, which can be implemented through the use of fibre optic cables. The most important advantage of UV-VIS spectroscopy compared to NIR and Raman spectroscopy is its much lower detection limit. UV-VIS spectral bands are highly overlapping, therefore chemometric analysis and proper preprocessing of the obtained spectra is required.

2.2.1.3. Fluorescence spectroscopy

Migler and Bur [65] incorporated a bis(-pyrene) propane (BPP), a temperature-sensitive fluorescent dye in the polymer resin at dopant levels. By monitoring relevant spectral features of this dye, its temperature can be measured. And through a focusing technique (confocal fluorescent optics), the temperature can be measured as a function of distance into the resin. On-line temperature profiles were measured in a circular die at the exit of a twin-screw extruder. These measurements are based on the dependence of I_e/I_m (e = eximer, m = monomer) with temperature for BPP in polyethylene. In a succeeding study, Bur et al. [66] added different temperature sensitive fluorescent dyes to the polymer melt during single-screw extrusion processing to overcome the inadequacies of thermocouple and infrared radiometer transducers. The fluorescence spectrum, collected in a slit die rheometer attached to the extruder, reflects the resin temperature in its neighbourhood. The temperature measurement is based on the calibration curve where the ratio I_{464}/I_{473} is plotted versus temperature for atmospheric pressure. A pressure compensation factor was added later on. Additionally, Bur et al. [67] relocated

the fluorescent confocal sensor and positioned it over the top of the mixing section of a 63.5 mm diameter single-screw extruder to monitor the temperature gradient in the channel, as a function of screw speed, screw design and melt flow rate. Temperatures were found to be lowest in the centre of the channel and increased at the barrel wall and at the root of the screw for the conventional screw with only transporting elements. As expected, the channel temperatures increased with increasing screw speed. For the mixing screw, the temperature was lowest at the barrel wall and highest at the root of the screw. In summary, this sensor is capable of measuring melt temperatures and temperature gradients within the melt.

Carneiro et al. [68] determined the RTD along a kneading block via on-line monitoring of the light emission of a fluorescent tracer (perylene) in a slit die attached to a single-screw extruder and at several locations along a co-rotating twin-screw extruder. RTD measurements are often used to monitor and control process attributes such as consistency, extent of polymer degradation and degree of mixing. Three devices were developed to accommodate the probe: a slit die for single-screw extrusion, a sampling device with rotating valve for partial measurements within twin-screw extrusion which can be inserted between any 2 consecutive barrel sections and a transparent barrel modified to accommodate the probe (Fig. 4). First, the probe position (horizontal or vertical) and the influence of screw speed were evaluated on a single-screw extruder. The authors found that increasing screw speed reduced the RTD and by changing the probe position, different fractions of the melt stream are monitored. Secondly, concentration versus time curves were generated to characterize the RTD at several locations along the barrel of a twin-screw extruder, and direct comparison with off-line data produced good results. Finally, experiments were performed on a co-rotating twin-screw extruder with a transparent barrel to visualize the flow within a mixing block with staggered kneading disks in a twin-screw extruder. Video images revealed that, in contrast with the kneading block, the conveying elements upstream of the kneading block were only partially filled, causing unstable and weak signals. Therefore, measurements were performed exclusively on the kneading block. The determination of partial RTD is particularly relevant in compounding operations, or when processing thermally sensitive materials, since it provides information that can be used to optimize the operating window or to improve the screw configuration. In this work, an on-line technique, based on the light emission of a perylene fluorescent tracer, was developed for the measurement of RTD along the extruder axis. On-line readings were compared with off-line measurements, and a good agreement was found. Two other examples of RTD monitoring with fluorescence spectroscopy are presented by Barnes et al. [69] and Fang et al. [70].

Fluorescence spectroscopy has been mainly applied to monitor residence times via the use of fluorescent tracers in the melt. The RTD of a formulation provides information on the mixing history

of the melt. A lower RTD indicates a decrease in degree of mixing in the extrusion barrel. In addition, fluorescent tracers allow more accurate melt temperature measurements. These applications might be of interest in pharmaceutical HME, especially for monitoring of extrusion processes during formulation development. The addition of fluorescent tracers will provide insight in residence times and temperature gradients throughout the melt, and the exposure time of an API to high temperatures can be estimated. This will enhance the understanding of material behaviour within the barrel, and will allow the optimization of screw designs.

2.2.1.4. Terahertz (THz) spectroscopy

Krumbholz et al. [71] demonstrated the potential of an in-line monitoring method using a fibre-coupled THz spectrometer, to study the influence of temperature and pressure on molten PP. Measurements were performed in a custom-made die at the end of a planetary gear extruder. The temperature and pressure of a PP melt were varied independently. No influence of melt pressure on the terahertz parameters (absorption coefficient and refractive index) was found. Also, no effect on the absorption coefficient was obtained when changing the melt temperature. However, when the temperature was increased, the refractive index decreased. The refractive index of a melt can be calculated from the time delay of the THz pulse propagating through the melt. It is directly related to the additive content of a compound. When extruding polymer-filler compounds, a linear relation between the refractive index of the compound and its volumetric additive content was established. Though a THz spectrometer is a very complex and expensive system, these first measurements with a newly developed probe supply promising results for refractive index measurements. The refractive index of a melt depends on the melt composition, but is also related to the melt density, allowing the monitoring of melt density as well.

2.2.1.5. Dielectric spectroscopy

Perusich and McBrearty [72] applied dielectric spectroscopy to make composition measurements of the comonomer concentration along polymer chains. Dielectric spectroscopy imposes an electric field across the flowing polymer and measures the resultant alternating current produced from the movement and energy associated with dipole orientation and ionic conduction. These measurements are related to the physical and chemical structure of the polymer. The dielectric permittivity or capacitance was found to be proportional to the polymer sidechain composition. A short sidechain required a high measurement frequency (short relaxation time), whereas a longer sidechain, needed a much lower frequency (longer relaxation time) to orient the sidechain to a measurable extent. Two

types of extruders were used. First, a 22 mm single-screw extruder where the sensor assembly was positioned at the exit of a static mixer section downstream from the screw. And second, a twin-screw extruder without static mixer, and with the sensor positioned downstream from the screw directly upstream from the die. The melt composition of a variety of polymer melt systems was measured with an in-line dielectric sensor. In-line measurements were performed on Elvax®, an EVA copolymer. Once the polymer reached the die, the measured capacitance increased dramatically, and after 10 min a plateau was achieved. The absolute plateau value was a direct function of the applied frequency. The measured capacitance was found to be proportional to the VA content of Elvax®. Bur et al. [73] used the same setup on a twin-screw extruder to perform permittivity and conductivity measurements of resin melts to quantify filler concentrations. Sensitivity to polymer/filler composition can arise because of permittivity contrast between polymer and filler or because of changes in conductivity caused by changes in filler concentration. The authors found that the interelectrode separation distance was crucial for the measurement quality. By increasing the separation, the fringe field will extend beyond the surface, and the capacitance of the cell will decrease and affect the sensitivity of the measurements.

Dielectric measurements are used to analyze the physical/chemical structure of organic materials through the measurement of their dielectric properties. Since the dielectric loss factor is affected by dipolar alignment and by ionic mobility, it provides information on both physical transitions as well as changes in viscosity in a material. Thus, in addition to the monitoring of comonomer content and filler concentrations, dielectric spectroscopy could also be applied to perform rheological measurements in the melt [73]. For example, wall slip may be preceded by extensional stress, orienting the material and producing anisotropic dielectric properties. Migration of polymer additives at high shear stress can be detected as well. These measurements can easily be performed in-line, and therefore present an interesting addition to the existing analytical techniques applied in pharmaceutical HME.

2.2.1.6. Optical detectors

Pinheiro et al. [74] measured the morphology of immiscible blends containing PP and polyamide 6 (PA 6) in a co-rotating twin-screw extruder. The disperse phase particle size and concentration were determined in-line with an optical device developed by Mélo and Canevarolo [75, 76], placed at a slit die with transparent windows at the extruder exit. A polychromatic, visible light source illuminates the entire surface of the glass window and a photocell. The detector's signal depends on the volume concentration and size of the disperse phase. The normalized detector's signal follows a linear correlation with particle concentration of four calibration standards (Al_2O_3 0.5 and $2.0\mu\text{m}$ and TiO_2 0.5 and $2\mu\text{m}$). Mixtures of Al_2O_3 with different particle sizes (0.5 and $2\mu\text{m}$) at different ratios showed that

the signal increases linearly with an increase in the concentration of 0.5 μ m. The detector captures the average value of a set of particles once the signal is linear with the weight average particle size. The signal also increased with increasing PA 6 content (disperse phase) because of the higher light scattering. The results showed that this detector is an accurate device for the assessment of parameters such as particle size and concentration.

The same device was applied by Canevarolo et al. [77] to assess the melting behaviour during polymer extrusion in a co-rotating twin-screw extruder. Melting of two polyamide tracers was studied by changing the barrel temperature and keeping all other operating conditions constant. Increasing the barrel temperature led to a fast growth of the normalized intensity due to melting of the tracer, eventually saturating once all tracer was molten. This type of detector can be applied in pharmaceutical HME during both the formulation development stage and during pharmaceutical production. It can be applied as a monitoring device, to determine the optimal process settings to obtain a completely molten or dissolved API at with minimal energy input but it is also relevant for process control during manufacturing, to monitor and control the state of the melt.

2.2.1.7. Nuclear magnetic resonance (NMR) spectroscopy

Gottwald and Scheler [78] designed a surface NMR probe to monitor extrusion processes. Surface NMR gives access to molecular mobility, correlated to temperature, composition and homogeneity. Two main obstacles are the temperature, which decreases the magnetic field strength and the ferromagnetic materials in the extruder which deform the static field. The device was located next to the die of a single-screw extruder (30 mm diameter) and measurements were performed on a sheet of soft poly (vinyl chloride) (PVC). The probe withstood the harsh conditions although the melt was in direct contact with its surface. The detected signal of PVC melt could be clearly distinguished from the background signal. Based on these results, the authors plan to modify an extruder element to fit the NMR probe, allowing the in-line monitoring of any NMR-detectable parameter, rheological information and component composition. In pharmaceutical processes, NMR is used to monitor interactions between drug and excipients during production, to characterize the different polymorphic forms of an API, and for the identification and characterization of APIs. It is sensitive for small amounts of API in the formulation.

2.2.2. Ultrasonic techniques

Sun et al. [79] monitored the RTD at the melting, mixing and pumping zones as well as at the die exit of a twin-screw extruder (30 mm diameter) by mounting the ultrasonic probes on the extruder barrel over the screw elements and at the die. In order to relate the measured ultrasonic signal to the RTD, the relationship between the signal strength and the CaCO_3 concentration (the ultrasonic tracer) was calibrated, which was linear in the tested concentration range. Secondly, the RTD was measured by injecting a pulse of tracer and monitoring the ultrasonic signal strength. The change of the strength of the ultrasonic signal reflected from the rotating screw was caused by a change in acoustic impedance of the filled material, the scattering loss by the filler and the change in the absorption of acoustic energy due to the presence of the filler.

Lee et al. [80] also performed RTD measurements based on the ultrasonic response of CaCO_3 in PE. Measurements were performed at the die exit (slit die) of a co-rotating twin-screw extruder. The RTD was also evaluated at different filler concentrations, screw speeds, feeding rates and screw configurations. Increasing the screw speed or feed rate reduced the mean residence time and the variance of the residence time, whereas increasing CaCO_3 concentration increased the mean residence time and variance of residence time. Both were also increased by the presence of reverse screw elements in the configuration. The in-line determination of RTD by ultrasound during extrusion was successfully realized.

Wang and Min [81] developed an ultrasound in-line monitoring system to investigate the melting behaviour of linear low density PE (LLDPE) and PVC compounds in the barrel of an intermeshing counter-rotating twin-screw extruder (30 mm diameter). Monitoring of the ultrasound wave attenuation allowed the characterization of the melting process and uniformity across the screw channels. Various melting phenomena were described depending on the selected materials, processing conditions and screw configurations. Materials are periodically scanned by ultrasound in the flight region and in a C-chamber (Fig. 5). Melting in the flight region finishes much faster than in the C-chamber for both LLDPE and PVC, due to the combination of heat conduction and viscous energy dissipation. The melting in the C-chamber always starts at the pushing side of the flight and then spreads to the trailing side. Melting level and uniformity increase with the increase of pressure in the material. During the extrusion of LLDPE and PVC compounds, dispersed or dissipation melting phenomena are dominant under most processing conditions. The ultrasound in-line monitoring method efficiently investigated the melting phenomena of various polymer systems fed in powder form or pellet form.

Abu-Zahra [82] measured the density of a polymer melt using ultrasound shear waves propagating at a frequency of 2.25MHz. At a solid-liquid interface, the amount of ultrasonic shear wave energy reflected back into the solid is dependent on the operating frequency and properties of the fluid (viscosity and density) and of the solid (density and shear modulus). The acoustic impedance of the polymer melt is calculated using the measured reflection coefficient of the polymer melt interface boundary. This ultrasound measurement is independent of the attenuation in the polymer melt and the thickness of the melt stream. A special die adapter was mounted between the extruder barrel and die of a 19 mm single-screw extruder, containing a shear ultrasound sensor. Different mixtures of PVC with varying levels of blowing agent and acrylic processing aid were extruded. Statistical correlation between the density measured by energy ration of shear ultrasound waves and the laboratory density measurements was 96% at constant processing conditions. The main assumption was that a change in the melt density will be directly manifested by a change in the extrudate density, which is accurate for most polymer extrusion applications. The difference between this application of ultrasound monitoring and the three previous examples is the use of ultrasound shear waves instead of longitudinal waves. In longitudinal waves, the oscillations occur in the direction of wave propagation, whereas the particles in shear waves oscillate at a right angle to the direction of wave propagation. At a solid-liquid interface, the amount of shear wave energy reflected back into the solid depends on the operating frequency and on properties of the fluid (viscosity and density) and the solid (density, shear modulus). A relation between the melt density and the energy ratio of shear ultrasound waves can be established. The longitudinal wave reflection method is used to measure the time of flight of ultrasonic waves and the ultrasound velocity in polymer melt. These data are then used to calculate the density. Longitudinal waves can be generated in liquids, as well as solids because the energy travels through the atomic structure by a series of compressions and expansion movements, whereas shear waves require an acoustically solid material for effective propagation, and therefore, are not effectively propagated in liquids.

In polymer extrusion, ultrasound techniques have been used to monitor melt temperature and pressure, changes in material type, effects of process settings on rheological characteristics of the melt and filler concentration [83]. Besides qualitative and quantitative monitoring of the polymer melt, ultrasonic sensors can be used to monitor the barrel and screw integrity at the melting, mixing and pumping zones of the extruder via barrel or flange. This application was discussed by Jen et al [84]. Extrusion of low density PE (LDPE) was performed on a 30 mm co-rotating twin-screw extruder and on a 50 mm counter-rotating twin-screw extruder. Four types of high pressure ultrasound transducers were developed and used at the melting, mixing and pumping zones of the extruder to monitor the screw and barrel wear.

2.2.3. Rheological techniques

Chiu et al. [85] developed a new in-line viscometer that can directly test melt viscosity as a function of shear rate. The viscometer contains a stress sensor and a shear rate sensor which were installed between the screw and the die of a single-screw extruder. During extrusion of LDPE, different temperatures and screw speeds were applied, and a decreasing viscosity with increasing temperature was detected, due to the shear thinning behaviour of LDPE. The in-line results were compared to measurements with an off-line capillary rheometer, where the viscosity results were lower when the shear rate was lower than 600 s^{-1} , and higher when the shear rate was higher than 600 s^{-1} , possibly due to the instability of both the flow meter and the stress sensor. Further research and adaptations are required to improve the accuracy of this device.

Covas et al. [86] presented new equipment for monitoring the evolution of relevant characteristics of polymer systems along the screw axis. A sampling device was constructed, allowing the extraction of material from the screw channel. First, an on-line capillary rheometer was connected to the sampling device. When the material extracted from the barrel is pushed through the die, the torque is recorded, wall shear stress is determined and wall shear rate is calculated. The tool can also be applied for the online measurement of melt flow index/melt volume flow rate. This equipment was used to measure the rheological response of a 12% (w/w) PP-based carbon fibre composite after melting in an intermeshing co-rotating twin-screw extruder. The coherence between online and offline shear data was clear. Large deformations and relatively high shear rates associated with the flow in a capillary rheometer may affect the morphology of the material and consequently its rheological response. Therefore, an online oscillatory rheometer was manufactured to determine the linear viscoelastic behaviour and the non-linear properties of melts extracted from the screw channel. On-line monitoring along the axis of an extruder can provide a wealth of data that contribute to the understanding of the physical and chemical phenomena occurring inside the barrel.

In a subsequent study, Covas et al. [87] also developed an on-line rotational rheometer, enabling the determination of morphology development and reaction kinetics along the screw axis (Fig. 6). The rheometer is very accurate when compared to commercial laboratorial instruments, an average deviation in linear viscoelasticity results between the new device and two off-line rheometers varied between 3 and 8% for various melts and blends. Results also showed that the on-line rheometer was much more accurate in capturing structural evolutions of the materials along the extruder than analysis performed off-line on samples collected on-line for complex multiphase systems.

Mould et al. [88] monitored the dynamic rheological response of PP in a co-rotating twin-screw extruder using a new version of the on-line rotational rheometer developed by Covas et al. [87]. The technique was validated with off-line measurements at room temperature and at high temperatures, and on-line, and the validation step was considered successful. The usefulness of the instrument was first demonstrated with PP, and G' (storage modulus) and G'' (loss modulus) decreased along the extruder. Then, PP grafted with maleic anhydride (PP-g-MA) was extruded, and a decrease of the rheological moduli was anticipated, due to chain scission during grafting. The on-line rheometer confirmed the shift of the moduli to lower values. Next, a PP/PP-g-MA system was extruded with 8.8% (w/w) montmorillonite organoclay, to produce a nanocomposite. As expected, G' and G'' shifted to higher moduli values, the elasticity increased and evolution along the barrel was clearly observed. The results were in-line with observations reported in literature, and evidenced the sensitivity and reliability of the apparatus.

Rajan et al. [89] monitored the thermal degradation of poly (oxymethylene) (POM) during extrusion on a co-rotating twin-screw extruder. The degradation is indicated by the emission of formaldehyde (FA) gas, which was monitored off-line with acetyl acetone colour measurements and by a reduction of viscosity. The online viscosity of the melt was measured by the difference in melt pressure when the melt was forced through a slit die at constant volume flow rate. When the throughput decreased and the screw speed increased, an enhanced thermal degradation was found. A good correlation between the viscosity measured in the slit die and the offline FA measurements was observed. The thermal degradation of POM is successfully monitored by means of online viscosity measurements.

With the use of on-line extensional rheometry on a co-rotating twin-screw extruder and off-line rotational rheometry, Kracalik et al. [90] tested different nanocomposites and investigated the effect of screw speed and geometry on the elongational and viscoelastic properties. In extensional rheometry, the extruded strand is elongated by rotating wheels. The rotation speed is increased to the time when the molten string breaks, to measure the melt strength level. The fast assessment of the melt strength measured by extensional rheometry correlates with a high accuracy with dynamic rheological data measured by rotational rheometry. $\cot \delta$ (G'/G'' ratio), which reflects the rigidity of the melt can be correlated with the melt strength level. The main benefit of extensional rheometry is the simplicity without the need for expensive equipment.

During extrusion, the raw materials are subjected to shear, increased temperatures and pressure conditions resulting in physicochemical changes within the mixture. The rheological response of a material to an imposed stress is sensitive to composition, morphology, degree of mixing and temperature. For process control purposes, it is important to obtain rheological properties of the melt

that has experienced the complete history within the extruder, since these physicochemical changes are highly sensitive to the processing history. However, monitoring the rheological characteristics of the melt at several locations throughout the barrel will improve understanding of the process, and will provide useful information for optimization of screw configuration and operating conditions.

2.2.4. Other process analytical techniques

Chen et al. [91] determined the differences in melting behaviour between a PP/polystyrene (PS) 80:20 and a PP/PS 20:80 blend in a twin-screw extruder under identical operating conditions. Therefore, a perturbation method was used together with temperature and pressure measurements along the channel of a co-rotating twin-screw extruder. A glass window was fitted in one of the nine barrels of the extruder, and a spacer plate was installed upstream of the barrel with the glass window. Three pressure transducers, one RTD probe and three thermocouples were mounted in the spacer plate. In the perturbation method, a material mass pulse is added to the extruder feed to generate a disturbance to the steady-state operation. The pressure, temperature, residence time and drive motor power are monitored. The time history of the pulse material in the channel can be tracked with the RTD data, and can be combined with information from the motor power signals to detect the location of reactions in the extrusion channel. The melting process was visualized through the glass window using a high-speed video recording device. Once measurements at one position were completed, the barrel was moved to the next position. Three distinct regions for the melting of the PP/PS blends were determined: the partially filled region, the transition region and the fully filled region. The location of the transition region was determined from visualization results, temperature and pressure information and the pulse signals. Solid polymer pellets melted through an erosion mechanism in all three regions. The end of the melting process was identified using the visualization results, and the pressure profile. With these techniques, the melting profile of materials in the barrel can be visualized. In pharmaceutical HME, the glass window in the barrel might also be applied to visualize other phenomena such as dispersion and distribution of API within the melt.

Abeykoon et al. [92] evaluated five different melt temperature measurement techniques on a single-screw extruder. The point/bulk temperature of the die melt was measured with a 1 mm diameter non-insulated wall mounted thermocouple, a 3 mm diameter semi-insulated wall mounted thermocouple, a 0.5 mm diameter insulated wall mounted thermocouple and a Methotrexate infrared (IR) sensor. Melt temperatures at different radial locations of the die were measured using a thermocouple mesh (TCM) with seven junctions placed between the adapter and die. LDPE was selected for the experiments. The three wall mounted thermocouples provided poor results in capturing variations in temperature. The IR sensor showed a better performance in detecting thermal variations, but even here the information is

limited to a small volume of the melt flow. The TCM demonstrated that the thermal fluctuations varied significantly across the melt flow cross-section, and these variations increased with screw speed. However, the TCM does interfere with the melt flow, and is difficult to implement. Accurately monitoring the melt temperature remains one of the main challenges in HME. When only the surface temperature is monitored, information on the melt temperature at the screws is not known. A too high temperature in the melt can cause API and excipient degradation and affects the rheological properties of the melt. These consequences can be monitored separately with other process analytical tools described in this review, such as UV-VIS spectroscopy, ultrasonic techniques and rheometers. However, knowing the true temperature of the melt at any point within the barrel will eliminate the need to use several complementary techniques providing the same information.

Commonly used process monitoring devices, such as temperature and pressure sensors, provide limited information on process dynamics inside the extruder barrel. Therefore, Abeykoon et al. [93] performed inferential monitoring of the screw load torque signal by monitoring the motor current. The torque signal was dominated by the solid friction in the barrel and did not correlate well with melting fluctuations. However, torque measurements were proven useful for online identification of solids conveying issues. This technique to monitor polymer behaviour can be adapted in pharmaceutical HME without the requirement of barrel and/or die modifications and without the need for additional sensors.

2.2.5. Combinations and comparison of complementary process analytical techniques

Sun et al. [79] compared RTD measurements with an ultrasound probe and a reflective optical probe. Both probes were implemented at the mixing zone of the screws of a twin-screw extruder, in the same cross section of the barrel. A tracer was added to the polymer melt to monitor the RTD. Dependent on the optical characteristics of the extruded polymer and tracer, the optical probe measured the RTD of either the entire channel volume or that of a surface layer of the volume, whereas the ultrasonic measurements always determined the RTD of the entire channel volume. For certain polymer systems, the ultrasound generated by the probe has a larger penetration depth than the light. The ultrasonic technology uses signals reflected from the screw, whereas the optical probe detects signals scattered by the tracer in the surface layer of the screw channel. The ultrasonic probe was proven to be more appropriate for measuring the RTD of the entire channel volume, and both techniques could provide complementary information to improve understanding of the extrusion process.

Abu-Zahra [94] attached a special die adapter to a 19 mm diameter single-screw extruder. An ultrasound transducer and a dielectric sensor were mounted in this die. PVC was extruded with varying levels of chemical blowing agent (AZO)4 and processing aid (K400). Ultrasound measurements are correlated to the melt density and the dielectric properties of the melt provide information on the mechanical viscosity. Both complementary techniques allow the simultaneous monitoring of the rheological properties density and viscosity of the melt.

3. Conclusions

So far, monitoring of pharmaceutical HME processes remains limited to conventional monitoring of the process settings and parameters (barrel and die temperatures, feed rate or throughput, screw speed, torque and drive amperage, melt pressure and melt temperature) and the application of NIR and Raman spectroscopy to monitor the API concentration and the solid state of the melt. However, the quality of an extrudate cannot simply be assessed by monitoring its drug load and solid state. Promising steps towards a thorough process understanding have been taken recently, but further monitoring of component degradation, rheological properties of the melt and their effect on processing efficiency and accurate melt temperature measurements are required to guarantee the quality of the extrudates and to predict the physical and chemical characteristics of the extrudates before starting the downstream processing.

Various sensors are available for observation of critical process and product parameters during extrusion, as reported in literature related to polymer extrusion. The implementation of the different process analytical techniques evaluated in this review will lead to a thorough process understanding and will allow monitoring of the critical process and product parameters. This monitoring will eventually lead to optimization of the HME process and the formulations, and provide the possibility for improved process control in routine manufacturing.

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Table 1. Process analytical tools applied in pharmaceutical hot-melt extrusion

<i>Process analytical tool</i>	<i>Interface</i>	<i>Purpose</i>	<i>Reported challenges/disadvantages/shortcomings</i>	<i>References</i>
NIR spectroscopy: reflection	die	monitoring of drug concentration	not possible to monitor a transparent formulation (low signal/noise ratio)	[48]
	post die	monitoring of drug concentration	variations in path length cause variations in signal intensity, normalization is required	[20]
	die	monitoring cocrystal production	temperature influence on NIR measurements: the correlation improved when temperature variation was excluded from the dataset	[53]
	die	monitoring of solid state and polymer-drug interactions	not possible to monitor a transparent formulation (low signal/noise ratio) [48]	[48, 55]
NIR spectroscopy: transmission	die	monitoring of drug concentration	-	[50-52]
	die	monitoring of surfactant concentration	-	[50-52]
	die	monitoring of RTD	-	[51]
	die	identification of feeding disturbances	-	[50-52]
Raman spectroscopy	die	monitoring of drug concentration	difficulties with collecting spectra from a non-transparent melt [48], resulting in a high background signal	[54]
	post die	monitoring of drug concentration	film undulation caused differences in path length resulting in variations in signal intensity, normalization is required	[21]
	die	monitoring of solid state and polymer-drug interactions	difficulties with collecting spectra from a non-transparent melt [48], resulting in a high background signal	[54, 55]
	die	monitoring complex formation by an acid-base reaction	-	[57]

	barrel segments	monitoring of solid state and polymer-drug interactions	sapphire probe window provides peaks in Raman spectrum when window is not completely covered by sample	[56]
Motor load	motor	monitoring of surfactant concentration	-	[58]

Table 2. Process analytical tools applied in polymer extrusion

<i>Process analytical tool</i>	<i>Interface</i>	<i>Purpose</i>	<i>Reported challenges/disadvantages/shortcomings</i>	<i>References</i>
NIR spectroscopy: transmission	die	monomer concentration	-	[59]
	die	complex viscosity	-	[60]
	die	density by monitoring polymer chain branches	-	[61]
NIR spectroscopy: reflection	die	drawing force and Young's modulus	Different aggregate states will affect the chemometric models negatively.	[62]
UV-VIS spectroscopy: transmission	die	polymer degradation	The low count rate of the UV-VIS diode array detector leads to a large error, since this area is the wavelength range where the absorption of the optical fibres connecting the probe with the spectrometer becomes dominant.	[63]
UV-VIS spectroscopy: reflectance	die	RTD	-	[64]
Fluorescence spectroscopy	die	melt temperature measurements, temperature gradient measurements	<ul style="list-style-type: none"> - Can only be used in development phase with inert fluorescent dyes. - Effect of pressure on calibration curve must be considered, accurate temperature measurements require simultaneous acquisition of pressure (temperature results need to be compensated). - Only a small sample volume is allowed (specific probe and lens design). - Radial measurements need to be possible (specific probe and lens design). - Selection of fluorescent dyes: dyes need to be stable at high temperatures, spectra should show significant changes with varying temperature, dyes should be soluble in polymer resin and should be chemically inert. - Effect of shear on temperature measurements: sensor needs 	[65, 66, 68]

			to be located beyond the end of screw (low shear rate flow region).	
	die	RTD	Global RTD measurements in single screw extrusion are delicate, as the tracer must be incorporated at the feed opening under very specific conditions (to avoid material accumulation, starve feed conditions and the distribution of the dye in different screw turns, a minimal concentration though easily detectable should be used) [68].	[68-70]
	barrel	RTD	-	[68]
	mixing zone	melt temperature measurements, temperature gradient measurements	- Calibration should involve pressure data. - Temperature spikes in data are associated with shear heating, these spikes need to be filtered out to calculate average temperatures.	[67]
	kneading block	RTD	Video images revealed that, in contrast with the kneading block, the conveying elements upstream of the kneading block were only partially filled, causing unstable and weak signals. Therefore, measurements were performed exclusively on the kneading block.	[68]
Terahertz spectroscopy	die	refractive index measurements related to additive compound content	- Complexity of the system, high costs, very sensitive to vibration → a new, partially fibre coupled terahertz spectrometer was developed. - Die adaptations were required: silica plates that can withstand pressures only up to 26 bar and temperatures only up to 260°C. - The recording time needs to be reduced: only the amplitude value at a fixed time position is used as an indicator. - The pressure and temperature of the melt need to be observed in order to correct the experimental data.	[71]
Dielectric spectroscopy	die	comonomer concentration, sidechain composition	At higher temperatures, the analysis becomes more difficult since ions, permanent dipoles and induced dipoles may all have a significant influence at an elevated temperature.	[72]
	die	filler concentrations	Measuring cells are not sensitive for the melt in the centre of the	[73]

			ring, cells should therefore be as narrow as possible.	
	die	melt viscosity	The sensor utilizes a fringe field to monitor the polymer melt, so the field of the measurement is limited to the depth of penetration of the fringe field. Therefore, the dielectric parameters are measured at the surface of the melt stream.	[94]
Optical probes	die	particle size and concentration of dispersed phase	-	[74]
	die	melting behaviour	-	[77]
	mixing zone	RTD	Dependent on the optical characteristics of the extruded polymer and tracer, the optical probe measured the RTD of either the entire channel volume or that of a surface layer of the volume.	[79]
NMR spectroscopy	die	temperature, composition, homogeneity	<ul style="list-style-type: none"> - Increasing temperature decreases the magnetic field strength. - Ferromagnetic materials in the extruder might deform the static field. - Low sensitivity, but can be overcome by increasing the experiment time for signal accumulation. 	[78]
Ultrasonic techniques: longitudinal waves	melting, mixing, pumping zones	barrel integrity at melting, mixing and pumping zones, screw and barrel wear	-	[84]
	melting, mixing, pumping zones	RTD	-	[79]
	die	RTD	-	[79, 80]
	barrel	melting phenomena dependent on screw configurations	The channel should be completely filled at measurement position: adaptations in screw configuration/probe location are required.	[81]
Ultrasonic techniques: shear waves	die	melt density	<ul style="list-style-type: none"> - Assumption: a change in melt density will be directly manifested by a change in extrudate density (accurate for most polymer extrusion applications). - The accuracy of the measurements is highly dependent on 	[82]

			<p>the condition of the ultrasound transducer and stability of the process: constant cooling of the transducer was necessary.</p> <ul style="list-style-type: none"> - It is essential to keep the melt temperature and pressure within a narrow range during extrusion: a change in either will affect the acoustic properties of the melt and will interfere with the accuracy of the intended measurements: normalisation procedures should be applied. 	
Ultrasonic techniques: undefined wave type	die	melt density	-	[94]
Rheological techniques:				
Stress and shear rate sensor	die	melt viscosity as a function of shear rate	-	[85]
On-line capillary rheometer	barrel	torque, shear stress, shear rate, melt flow index, linear viscoelastic behaviour	Large deformations and relatively high shear rates associated with the flow in a capillary rheometer may affect the morphology of the material and consequently its rheological response.	[86]
On-line oscillatory rheometer	barrel	linear visco-elastic behavior	-	[86]
On-line rotational rheometer	barrel	morphology development, reaction kinetics, linear viscoelastic behaviour	-	[87]
On-line rotational rheometer	barrel	storage and loss modulus of polymer melts	-	[88]
On-line extensional rheometer	die	melt strength	-	[89]
Slit die	die	thermal degradation of polymer	-	[90]
Perturbation method	barrel sections	melting behaviour of polymer blends	-	[91]

Temperature measurements:				
Thermocouple	die	melt temperature	<ul style="list-style-type: none"> - Slow response time. - Measurements are highly dominated by barrel/die wall metal temperature. 	[92]
IR sensor	die	melt temperature	<ul style="list-style-type: none"> - Temperature information is limited to a small volume of the melt flow. - IR measurements may be affected by polymer type and sensor calibration accuracy. 	[92]
Thermocouple mesh	die	melt temperature	<ul style="list-style-type: none"> - Melt flow may be slightly disturbed by the TCM. - TCM measurements are slightly influenced by shear heating depending on the size of the mesh wires and junctions. - Mesh wires may be damaged under poor melting conditions (e.g. highly viscous or un-melted materials). 	[92]
Monitoring of motor current	motor	friction, torque, identification of conveying issues	Since the screw load torque signal is dominated by the solids conveying torque, it is not sensitive enough to identify unstable melting issues.	[93]

Figures

Figure 1. Hot-melt extrusion equipment and process settings and parameters traditionally monitored during pharmaceutical HME.(1. Feeding system 2. Feeding hopper 3. Temperature controlled barrel with 1 or 2 screws 4. Die 5. Heating and cooling device 6. Screw-driving unit).

Figure 2. Implementation of NIR (left) and Raman (right) spectroscopic probes via fibre optic cables in the extrusion die [48, 54].

Figure 3. Detail of the Raman spectra collected in barrel sections 2 and 3 during extrusion of mixtures with 40% MPT with all screw speed settings at a) 100°C and b) 140°C [56].

Figure 4. Solutions to accommodate the optical probe: (a) slit die used for measurements in a single screw extruder; (b) modified sampling device for partial measurements in a twin-screw extruder; (c) device for partial measurement along a transparent barrel [68].

Figure 5. Ultrasound scanning regions: flight region and C-chamber [81].

Figure 6. General overview of the on-line rotational rheometer (O2R) [87].