biblio.ugent.be

The UGent Institutional Repository is the electronic archiving and dissemination platform for all UGent research publications. Ghent University has implemented a mandate stipulating that all academic publications of UGent researchers should be deposited and archived in this repository. Except for items where current copyright restrictions apply, these papers are available in Open Access.

This item is the archived peer-reviewed author-version of: Rheological Characterization of Molten Polymer-Drug Dispersions as a Predictive Tool for Pharmaceutical Hot-Melt Extrusion Processability

Authors: Van Renterghem J., Vervaet C., De Beer T.

In: Pharmaceutical Research 2017, 34(11): 2312-2321

To refer to or to cite this work, please use the citation to the published version:

Van Renterghem J., Vervaet C., De Beer T. (2017) Rheological Characterization of Molten Polymer-Drug Dispersions as a Predictive Tool for Pharmaceutical Hot-Melt Extrusion Processability

Pharmaceutical Research 34(11): 2312-2321

DOI: 10.1007/s11095-017-2239-7

Rheological characterization of molten polymer-drug dispersions as a predictive tool for pharmaceutical hot-melt extrusion processability

Jeroen Van Renterghem¹, Chris Vervaet², Thomas De Beer ¹

¹ Laboratory of pharmaceutical process analytical technology, Ottergemsesteenweg 460, 9000, Ghent, Belgium

² Laboratory of pharmaceutical technology, Ottergemsesteenweg 460, 9000, Ghent, Belgium

*Corresponding author: Jeroen Van Renterghem

Laboratory of Process Analytical Technology, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium

TEL: 0032 9 264 8039

FAX: 0032 9 264

E-MAIL: jeroen.vanrenterghem@ugent.be

Abstract

Purpose: The aim of this study was to investigate (i) the influence of drug solid-state (crystalline or dissolved in the polymer matrix) on the melt viscosity and (ii) the influence of the drug concentration, temperature and shear rate on polymer crystallization using rheological tests.

Methods: Poly (ethylene oxide) (PEO) (100.000 g/mol) and physical mixtures (PM) containing 10-20-30-40% (w/w) ketoprofen or 10% (w/w) theophylline in PEO were rheologically characterized. Rheological tests were performed (frequency and temperature sweeps in oscillatory shear as well as shear-induced crystallization experiments) to obtain a thorough understanding of the flow behaviour and crystallization of PEO-drug dispersions.

Results: Theophylline did not dissolve in PEO as the complex viscosity (η^*) of the drug-polymer mixture increased as compared to that of neat PEO. In contrast, ketoprofen dissolved in PEO and acted as a plasticizer, decreasing η^* . Acting as a nucleating agent, theophylline induced the crystallization of PEO upon cooling from the melt. On the other hand, ketoprofen inhibited crystallization upon cooling. Moreover, higher concentrations of ketoprofen in the drug-polymer mixture increasingly inhibited polymer crystallization. However, shear-induced crystallization was observed for all tested mixtures containing ketoprofen.

Conclusion: The obtained rheological results are relevant for understanding and predicting HME processability (e.g., barrel temperature selection) and downstream processing such as injection moulding (e.g., mold temperature selection).

Keywords: Rheology, solid dispersions, shear-induced crystallization, semi crystalline polymers, hot-melt extrusion

63

64

Active Pharmaceutical ingredient

65

Flow Induced Crystallization

66

Hot Melt Extrusion

67

Ketoprofen

68

Nonsteroidal anti-inflammatory drug

69

Poly (Ethylene Oxide)

70

Solid Dispersion

71

Shear Induced Crystallization

72

Glass transition temperature

73

Melt temperature

74

75

76

77

78

79

80

1 Introduction

Solid dispersions (SDs) are considered as a promising water-solubility-enhancing technique to resolve the poor water solubility of many new and future active pharmaceutical ingredients (APIs) (1–3). SDs are bioavailability-enhancing systems consisting of a polymer as matrix former in which the poorly water soluble API is homogeneously dispersed or dissolved. By selecting a specific combination of polymer and API, SDs can be produced which exhibit immediate release characteristics or controlled and sustained release of the API. In the pharmaceutical industry, hot-melt extrusion (HME) is a continuous and highly flexible manufacturing technology used for the production of solid dispersions (4). HME is carried out using a heated barrel containing one or two rotating screws performing four basic steps in a continuous manner: solid conveying, melting, mixing and shaping of the raw materials (i.e., polymer + API) into a product of uniform shape and density.

Processing of amorphous or semi-crystalline polymers via HME is performed above their respective glass transition temperature (T_g) or melting temperature (T_m). A practical rule of thumb is often applied to process the materials, the barrel temperature is generally set 10 - 20 °C above the T_g or T_m of the polymer (5). It should be noted that the set barrel temperature is different from the actual product temperature due to the transfer of mechanical energy from the screws into the molten drug-polymer mixture and that the product temperature cannot be accurately measured (6). However, this rule of thumb is not always useful: for example, T_g of Soluplus is 72 °C but the processing temperature recommended by the manufacturer is between 120 - 180 °C (depending on the screw configuration) in order to decrease the melt viscosity to within the processable range (i.e., 10000 – 1000 Pa.s). The processability of the drug formulation via pharmaceutical HME is also determined by the rheological properties of the drug-polymer mixture. The rheological properties of polymer melts and composites have long been studied in the plastics industry to allow efficient and optimal production of high quality products (7,8). When polymers are deformed, they exhibit complex rheological behaviour, which is of major importance for their processing and the resulting end product properties. Most polymers used

in the pharmaceutical and plastics industry are thermoplastics. This kind of polymers can be processed because they soften during processing at elevated temperatures. In all processing steps of HME (i.e., solid conveying, melting, mixing, shaping) the rheological properties of the polymer melt are important in the selection of the processing conditions (e.g., barrel temperature, mould temperature). Most polymers also exhibit a shear thinning behaviour; i.e. the viscosity decreases at higher shear rates. This observation is due to the disentanglement of polymer chains during shearing at higher rates. This determination is also relevant from a processing point of view since also the screw speed and screw configuration can influence the flow behaviour.

Furthermore, it is well known that the drug substance can plasticize the polymer melt by increasing the free volume between the polymer chains, hence improving the processability. In practice, this can be easily noticed by a reduction of the torque during extrusion. Also the drug concentration and the physical/chemical drug-polymer interactions are important parameters controlling the processability of the drug formulation. Aho. J. (9) published an overview of the use of rheology for pharmaceutical hot melt extrusion. Not only are rheological data useful for selecting the processing conditions, they are also valuable for solving problems often encountered in extrusion such as die swell and shark skinning which often related to the viscoelastic properties.

In production processes as injection moulding and fiber spinning, high pressures and shear rates are encountered which influence the crystallization kinetics and morphology upon cooling of semi-crystalline polymers (10,11). Shear- or flow-induced crystallization has been studied in the plastics industry to simulate the injection moulding process (12). However, to our best knowledge, shear-induced crystallization has not been studied on pharmaceutical solid dispersion formulations containing semi-crystalline polymers. Also the effect of the drug concentration and drug solid-state upon polymer crystallization during cooling remains unclear. Many fillers in polymer composites (e.g., talk, silica) are known to act as nucleating agents, enabling faster crystallization kinetics (13). In a similar way, drugs could act as nucleating agents or on the other hand inhibit the polymer

crystallization. Jeong et al. showed that differences in polymer crystalline microstructure affect the drug release of papaverine from polycaprolactone microstructures (14). Therefore, it is essential to understand all parameters influencing the final properties of the solid dispersion system (i.e., solid-state, polymer crystallization).

In this study, a thorough rheological characterization of solid dispersions containing semi-crystalline polymers is performed. The rheological characterization is performed to obtain information about: (i) the solubility of the two model drugs (ketoprofen and theophylline) in the polymer matrix, (ii) the viscosity in function of shear rate and temperature and (iii) to understand the influence of shear, temperature, drug solid-state and drug content upon polymer crystallization.

2 Experimental

2.1 Materials

Poly (ethylene oxide) (PEO, POLYOXTM WSR N-10 NF, Mw: 100.000 g/mol, Dow Company) is a water soluble polymer with a glass transition temperature of -67 °C and a melting temperature of 65 °C. Two model drugs were selected based on their different melting points. Ketoprofen (S.I.M.S., Firenze, Italy) is a nonsteroidal anti-inflammatory drug (NSAID) with a low melting point of 94 °C. Theophylline (Theophylline anhydrous powder, BASF, Ludwigshafen, Germany) is a drug used in therapy for respiratory diseases with a high melting temperature ($\pm$ 270 °C). Physical drug-polymer mixtures were made with a mortar and pestle containing 10 - 20 - 30 - 40 % (w/w) ketoprofen and 10 % (w/w) theophylline in PEO.

2.2 Methods

A HAAKE MARS[®] III rheometer (Thermo Scientific, Massachusetts, USA) equipped with a parallel plate geometry (d = 20 mm) and a Peltier temperature module (TM-PE-P) was used for all

experiments, except for the time sweep experiment where the RheoScope module was used. Zero gap determination and loading of the samples were done at the test temperature. Samples were first softened at the heated bottom plate and equilibrated at the measuring gap ($h = 1\text{mm}$) for 15 min to erase all thermal history prior to the measurement. Dynamic oscillatory experiments (i.e., frequency sweeps and temperature sweeps) were performed within the linear viscoelastic region (LVR) at a strain deformation of 2% using the CD-AS mode. Viscoelastic properties were measured using a frequency sweep performed at 70, 80 and 100 °C from 490 - 0.1 rad/s. The data measured during a frequency sweep is the storage (G') and loss (G'') modulus as a function of frequency, and captures information about the material's elastic and viscous behaviour at different time intervals. At their cross over point ($G' = G''$), the viscous and elastic properties of the material are equal. The frequency at the cross over point is also related to the characteristic mean relaxation time of the material since time is the reciprocal of frequency. Furthermore, a time sweep (20 min) was performed on the 40 % ketoprofen mixture at the lowest test temperature (70 °C) using the RheoScope module (Thermo Scientific, Massachusetts, USA). This module allowed simultaneous determination of the rheological parameters (e.g., complex viscosity) and visual examination via microscopy using a 20x magnification lens. This time sweep experiment was performed to verify if all ketoprofen crystals were dissolved in the molten PEO matrix.

Also, temperature sweeps were performed, monitoring η^* , G' and G'' as a function of temperature, on all samples using a constant frequency of 1Hz. Samples were first molten and equilibrated at 100 °C followed by a cooling run from 100 °C at 2 °C/min until crystallization of the polymer was completed. After solidification, a subsequent heating run at 2 °C/min until 100 °C was performed. The drug-polymer mixtures were later extruded using a co-rotating vertical twin screw extruder (PME 5, Xplore instruments, Netherlands) to verify their processability based on the complex viscosity ($\pm 10000\text{ Pa.s}$) measured during the temperature sweep heating run. The physical mixture was manually fed (6g) and extruded at a set barrel temperature based on the temperature sweep data: Keto 10% = 50°C; Keto 20% = 55°C; Keto 30% = 60°C; Keto 40% = 63°C; PEO = 66°C; Theo 10% = 70°C. The residence time ($\pm$

2min) of the drug-polymer mixture in the extruder was controlled using the extruder recirculation channel until a constant current was measured before discharging the extrudate. The screw speed was kept constant at 50 rpm and all data (i.e., barrel temperature, current) was logged via the Micro Compounder software (v10.1).

The temperature at the crossover point from the temperature sweep cooling run ($T_{G'=G''}$) was further used during flow-induced crystallization experiments (FIC). FIC experiments were performed on the PEO mixtures with 0, 10, 20, 30 and 40 % (w/w) ketoprofen using the following protocol (see Fig 1):

- The sample was equilibrated for 15 min at 100 °C followed by a cooling ramp (5 °C/min) to the isothermal crystallization temperature (T_c). During the cooling ramp, the measuring gap was kept constant (1 mm) using the thermo gap option in the Rheowin software (version 4.61).
- The isothermal crystallization temperature (T_c) is set at $T_{G'=G''} + \Delta T$. T_c was determined for all samples to evaluate the influence of shear at an equal temperature difference ($\Delta T = 10$ °C) above the nominal crystallization temperature (i.e., $T_{G'=G''}$). ΔT was determined during preliminary tests such that no crystallization was observed during the shear step.
- If shear was part of the experiment, a shear rate of 0.5, 1 or 2 s^{-1} was applied for 192, 100 and 52 seconds (t_s) respectively at T_c for a total shear strain (γ) of 94. Since the HAAKE MARS® III rheometer is a stress controlled rheometer, the shearing time was determined to obtain approximately the same total shear strain.
- A dynamic time sweep ($f = 1$ Hz, $\gamma = 2\%$) was performed after the steady shear step until PEO was crystallized.

Following the FIC experiments, the crystallization kinetics of the samples were analysed using the commonly applied Avrami equation (Eq. 1) as described in (13) to understand the influence of the drug concentration and the shear rate on the polymer crystallization.

$$X(t) = 1 - \exp(-kt^n) \quad \text{or} \quad X(t) = 1 - \exp[-(Kt)^n] \quad (1)$$

Where n being the Avrami exponent and k is the crystallization rate constant, which is dependent on nucleation and crystal growth. Since the units of k are dependent on n , also K can be defined as $k = K^n$.

$X(t)$ is the relative crystallinity calculated from the rheological data via the method proposed by Khanna (15):

$$X(t) = \frac{\eta^*(t) - \eta_{min}^*}{\eta_{max}^* - \eta_{min}^*} \quad (2)$$

Herein, η_{min}^* and η_{max}^* are the respective minimum and maximum values determined at the plateau values of the S-shaped curves over the experimental time range. Since η_{max}^* is determined arbitrarily (due to the torque limit of the rheometer), it should be stressed that this determination of relative crystallinity is not exact but the time scales are the same, allowing to determine the influence of the shear rate on crystallization. Determination of n and k involved calculation of the respective slope and intercept from the linearized Avrami plot, where $\log[-\ln(1-X(t-t_0))]$ is a function of $\log(t-t_0)$. In this equation, t_0 is defined as the induction time. In other words, some time may pass between reaching the isothermal crystallization temperature and the initial start of crystallization. This time is defined as the induction time (t_0). This time must be subtracted from the absolute time when performing the Avrami fit (16).

Furthermore, quiescent isothermal crystallization experiments were performed on the samples containing ketoprofen and theophylline using various T_c 's. These experiments are similar to the FIC

experiments but without a shear flow applied at T_c . These experiments are listed in table 1. The relative crystallinity of the samples was calculated in the same way as for the FIC experiments.

3 Results & Discussion

3.1 Drug solubility and viscoelastic properties

The solubility of a drug substance in the polymer matrix can be measured by a rheological method suggested by Suwardie and Yang (17)(18). This method relies on the plasticizing ability of a dissolved drug substance which disrupts the polymer structure, hence decreasing the viscosity of the drug-polymer system. On the other hand, crystalline material in the polymer matrix will act as a filler and increase the viscosity of the drug-polymer mixture. Previous studies have shown that the drug concentration and the particle shape are both important factors influencing the viscosity of drug-polymer suspensions (19,20). In this study, the miscibility/solubility of ketoprofen ($T_m = 94\text{ }^{\circ}\text{C}$) and theophylline ($T_m = \pm 273\text{ }^{\circ}\text{C}$) in PEO was investigated at various temperatures (70, 80 and $100\text{ }^{\circ}\text{C}$).

In order to obtain the zero shear rate viscosity (η_0), the complex viscosity η^* as function of angular frequency (ω) was fitted with the Ellis model between 0.1 - 490 rad/s (Eq. 3, with $n < 1$).

$$\frac{\eta^*}{\eta_0} = \frac{1}{1 + (k \cdot \omega)^{(1-n)}} \quad (3)$$

where k is associated with the relaxation time and n with the power law index.

Table 2 lists the calculated zero shear rate viscosities obtained from the frequency sweep data. Figure 2 a - c shows the frequency sweep results at 70, 80 and $100\text{ }^{\circ}\text{C}$ respectively. Also the viscosity ratio (η_0 drug mixture / η_0 neat PEO) was calculated for the different test temperatures in order to construct Fig 2d. All samples were showing a similar shear thinning behaviour. As for the typical shear rates encountered in pharmaceutical hot melt extrusion (i.e., $1 - 100\text{ s}^{-1}$), the shear rate had a strong

influence on the viscosity of these materials. As can be seen from Fig 2(a-d), the sample containing 10 % theophylline in PEO showed a higher complex viscosity at all test temperatures compared to neat PEO. Therefore, the viscosity ratio at the highest temperature (100 °C) is higher than 1 as illustrated in Fig 2d. On the other hand, Fig. 2d shows a lower viscosity ratio as function of ketoprofen concentration, even at temperatures below the melting point of ketoprofen (i.e., 70 and 80 °C). This indicated that ketoprofen is dissolving in the polymer matrix. Schachter et al. (21) have shown using solid-state NMR that the carboxylic group of ketoprofen and the ether oxygen of PEO form hydrogen bonds even below the melting temperatures of both crystalline drug and polymer. These interactions are strongly facilitating the dissolution of ketoprofen molecules in the PEO melt.

Furthermore, the 40% ketoprofen mixture was further analysed using the Rheoscope module to verify whether all ketoprofen crystals were dissolved at the lowest test temperature (70 °C). A time sweep over 20 minutes (Fig. 3) showed that the complex viscosity was decreasing, indicating dissolution of ketoprofen in the polymer matrix. While ketoprofen crystals could still be observed in the PEO phase 4 minutes into the experiment (Fig. 3 inset left), these particles were completely dissolved after 10 minutes (inset right).

Besides solubility information, dynamic frequency sweeps are commonly used to provide information about the viscoelastic properties of polymer melts. Herein, the crossover point ($G' = G''$) provided information on the solid- or viscous-like behaviour of the materials at various temperatures. The crossover frequencies (rad/s), listed in Table 3, show that the crossover point of all materials increased at higher test temperature. The resulting faster relaxation time is due to the higher molecular mobility of the material at elevated temperatures. These data also showed that a higher ketoprofen content increased the molecular mobility of the mixture (i.e., shorter relaxation times). The viscosity ratio also reduced at higher temperatures, indicating that the plasticizing ability of ketoprofen is higher at elevated temperature. On the other hand, theophylline does not change the viscoelastic properties with increasing temperature to the same extend as ketoprofen.

3.2 Temperature sweep

Fig 4a shows the rheological data during the cooling phase as this provided information about the crystallization of PEO upon cooling from the melt. Crystallization of PEO is clearly influenced by the drug solid-state in the melt. At a temperature of 100 °C, ketoprofen was completely molten and hence plasticized the PEO matrix. Upon cooling from the melt, the material behaved more like a liquid since the loss modulus (G'') is higher than the storage modulus (G') (see Fig. 4b). However, upon cooling, G'' increased at a slower rate than G' . Eventually PEO crystallized and behaved more like a solid when $G' > G''$. The temperature at the crossover point was arbitrarily defined as the crystallization temperature ($T_{G'=G''}$). Ketoprofen tended to inhibit the crystallization of PEO since the $T_{G'=G''}$ decreased linear as a function of ketoprofen concentration as shown in Fig. 4c. This phenomenon can be explained by the hindering of local arrangements of PEO chains within a crystal lattice. On the other hand, theophylline increased the crystallization temperature ($T_{G'=G''} = 50$ °C), indicating that theophylline acted as a nucleating agent. Nucleating agents are often inducing the formation of more and smaller crystal structures. This phenomenon has been described for many composite materials in the plastics industry (10,22).

Furthermore, Fig. 4d shows the heating experiment subsequent to the cooling experiment. Again, higher ketoprofen concentrations reduced the complex viscosity of the solid dispersions upon heating from the solidified material compared to the pure polymer, indicating the plasticizing effect of ketoprofen upon the molten material. Another interesting observation is that the viscosity drop during melting of the polymer is sharper for the drug-polymer mixtures compared to the neat polymer, suggesting that a more uniform distribution of polymer crystals was formed during the cooling run for the drug-polymer mixtures. Gupta et al. (23,24) described that the melt viscosity processing range for pharmaceutical hot-melt extrusion should be between 10000 - 1000 Pa.s. The horizontal line in Fig 3d highlights this upper viscosity limit (10000 Pa.s). It should be stressed that the temperature sweep is measured at a frequency of 1 Hz (6.28 rad/s), which is low from a processing point of view. However,

using this method, the minimal required processing temperature can be determined for pharmaceutical HME. To confirm the latter method, extrusion experiments were performed using temperatures close to the upper viscosity limit (10000 Pa.s). Smooth extrudates were produced at the set barrel temperatures (Fig 5).

3.3 Shear-induced and isothermal crystallization

Figure 6 shows the plots of the relative crystallinity as function of absolute time from the moment the experiment reached the isothermal crystallization temperature. These plots clearly show that the applied shear flow induced the crystallization of PEO. This phenomenon is well described in literature (10,25,26). By applying a flow in an undercooled melt (i.e., $T_g < T_{test} < T_m$), nuclei are induced and the crystal growth rate is enhanced.

Furthermore, the Avrami parameters were calculated and are listed in table 4. To elucidate the influence of the applied shear rate and the drug loading on the crystallization kinetics, the dimensionless half crystallization time ($\Theta_{t1/2} = t_{1/2shear}/t_{1/2quiescent}$) and the dimensionless rate constant ($\Theta_K = K_{shear}/K_{quiescent}$) are plotted in function of the various applied shear rates (Fig 7 a-b). From Fig 7a, it can be seen that the samples containing less ketoprofen (i.e., 10-20 %) showed a similar decrease in the half crystallization time ($\Theta_{t1/2} < 1$) compared to neat PEO in function of the applied shear rate. On the other hand, samples containing 30-40 % ketoprofen in PEO showed a different crystallization behaviour. The half crystallization time is longer using a shear rate of 1 s^{-1} compared to 0.5 s^{-1} (see Fig 6). This can be due to the faster relaxation times of the material containing high ketoprofen concentrations (as observed during the frequency sweep experiments). Fowler et al. (27) has shown that plasticizers can decrease the crystallization growth rate. Vleeshouwers et al. (11) reported that not only the applied shear rate but also the shearing time (t_s) can affect the crystallization rate. For all samples, the highest shear rate (2 s^{-1}) increased the crystallization speed due to the stable nuclei that

are formed when shearing at higher rate. In Fig 7b, the dimensionless rate constant increases more as a function of the applied shear rate for pure PEO and the lower drug concentrations (10 and 20%) than for the higher ketoprofen concentrations (30 and 40%). This indicates that the pure polymer and the lower drug concentrations are more susceptible to shear flow to enhance polymer crystallization compared to the 30 and 40% ketoprofen mixture. From these results, it can be concluded that in order to induce stable nuclei, not only the applied shear rate, but also a sufficient shearing time is needed when the material is highly plasticized.

Fig 8 shows the curves of the relative crystallinity as a function of time for the isothermal crystallization experiments. It is evident that the temperature has a strong impact on the crystallization speed. For example, the half crystallization time for the 10% (w/w) ketoprofen mixture was reduced by 11 minutes when lowering T_c from 49 to 48 °C. Also the ketoprofen concentration has a profound influence on the crystallization speed, e.g. the half crystallization time at 48 °C for the 10% ketoprofen mixture was 8.24 min vs. 51 min for the 20% ketoprofen mixture tested at 47 °C. From a processing point of view, a highly plasticized mixture will need much lower mould temperatures to solidify after injection into the mould. On the other hand, as the sample containing theophylline was 50% crystallized after 5.46 min at 53 °C, the presence of crystalline theophylline particles accelerated the crystallization of PEO compared to neat PEO ($t_{1/2}$ = 23 min at 54 °C).

4 Conclusion

This study showed that APIs alter the flow behavior of a polymer melt formulation. Also, the polymer crystallization is influenced by the API's solid-state (crystalline or dissolved). Crystalline material (theophylline) in the polymer melt act as filler and nucleating agent, inducing polymer crystallization. On the other hand, a dissolved drug (ketoprofen) inhibited the polymer crystallization

due to a plasticizing effect. Depending on the drug content, the shear flow induced polymer crystallization in a different manner as polymer crystallization of highly plasticized material (30-40% API) was less affected by shear flow than a mixture with less dissolved API (0-10-20%). A thorough characterization of the melt flow behaviour showed predictive potential for the processability of solid dispersions via pharmaceutical hot-melt extrusion (e.g. barrel temperature selection) and injection moulding (e.g. mould temperature selection) and should be part of the characterization toolbox for future melt processed products. Future research should include injection moulding of a formulation containing drug and semi crystalline polymer to study the effect of the extrusion and mould temperature upon the product characteristics: drug and polymer crystallinity, crystalline microstructure and drug release.

5 Acknowledgments

Ruth Cardinaels is kindly acknowledged for her help in setting up the rheological experiments.

6 References

- Repka MA, Battu SK, Upadhye SB, Thumma S, Crowley MM, Zhang F, et al. Pharmaceutical applications of hot-melt extrusion: Part II. *Drug Dev Ind Pharm*. 2007;33:1043–57.
- Vo CL-N, Park C, Lee B-J. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. *Eur J Pharm Biopharm* [Internet]. Elsevier B.V.; 2013 Nov [cited 2014 Oct 14];85(3 Pt B):799–813. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24056053>
- Kim MS, Kim JS, Park HJ, Cho WK, Cha KH, Hwang SJ. Enhanced bioavailability of sirolimus via preparation of solid dispersion nanoparticles using a supercritical antisolvent process. *Int J Nanomedicine*. 2011;6:2997–3009.
- Crowley, Michael M. ZF. Pharmaceutical Applications of Hot-Melt Extrusion: Part I Review Article. 2008;9045(November 2015).
- Chokshi RJ, Sandhu HK, Iyer RM, Shah NH, Malick a W, Zia H. Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion process as a means to manufacture solid dispersion/solution. *J Pharm Sci* [Internet]. 2005 Nov [cited 2014 Dec 12];94(11):2463–74. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16200544>
- Thiry J, Krier F, Evrard B. A review of pharmaceutical extrusion: Critical process parameters and scaling-up. *Int J Pharm* [Internet]. 2015 [cited 2017 Apr 27];479(1):227–40. Available from: <http://www.sciencedirect.com/science/article/pii/S0378517314009338>
- Durmus A, Kasgoz A, Macosko CW. Linear low density polyethylene (LLDPE)/clay

nanocomposites. Part I: Structural characterization and quantifying clay dispersion by melt rheology. *Polymer* (Guildf) [Internet]. Elsevier Ltd; 2007;48(15):4492–502. Available from: <http://dx.doi.org/10.1016/j.polymer.2007.05.074>

8. Scaffaro R, Dintcheva NT, Nocilla M a., La Mantia FP. Formulation, characterization and optimization of the processing condition of blends of recycled polyethylene and ground tyre rubber: Mechanical and rheological analysis. *Polym Degrad Stab*. 2005;90(2 SPEC. ISS.):281–7.
9. Aho J, Boetker JP, Baldursdottir S, Rantanen J. Rheology as a tool for evaluation of melt processability of innovative dosage forms. *Int J Pharm* [Internet]. Elsevier B.V.; 2015;494(2):623–42. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25666026>
10. Housmans JW, Peters GWM, Meijer HEH. Flow-induced crystallization of propylene/ethylene random copolymers. *J Therm Anal Calorim*. 2009;98(3):693–705.
11. Vleeshouwers S, Meijer HEH. A rheological study of shear induced crystallization. *Rheol Acta*. 1996;35(5):391–9.
12. Zuidema H. Flow Induced Crystallization of Polymers Application to Injection Moulding. 2000;42–4.
13. Papageorgiou GZ, Achilias DS, Bikiaris DN, Karayannidis GP. Crystallization kinetics and nucleation activity of filler in polypropylene/surface-treated SiO₂ nanocomposites. *Thermochim Acta*. 2005;427(1–2):117–28.
14. Jeong JC, Lee J, Cho K. Effects of crystalline microstructure on drug release behavior of poly(ϵ -caprolactone) microspheres. *J Control Release*. 2003;92(3):249–58.
15. Khanna YP. Rheological mechanism and overview of nucleated crystallization kinetics. *Macromolecules* [Internet]. 1993;26(14):3639–43. Available from: <http://pubs.acs.org/doi/abs/10.1021/ma00066a024>
16. Lorenzo AT, Arnal ML, Albuerne J, Müller AJ. DSC isothermal polymer crystallization kinetics measurements and the use of the Avrami equation to fit the data: Guidelines to avoid common problems. *Polym Test*. 2007;26(2):222–31.
17. Suwardie H, Wang P, Todd DB, Panchal V, Yang M, Gogos CG. Rheological study of the mixture of acetaminophen and polyethylene oxide for hot-melt extrusion application. *Eur J Pharm Biopharm* [Internet]. Elsevier B.V.; 2011 Aug [cited 2014 Nov 24];78(3):506–12. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21439374>
18. Yang M, Wang P, Suwardie H, Gogos C. Determination of acetaminophen's solubility in poly(ethylene oxide) by rheological, thermal and microscopic methods. *Int J Pharm* [Internet]. Elsevier B.V.; 2011;403(1–2):83–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20974240>
19. Kaully T, Siegmann A, Shacham D. Rheology of highly filled natural CaCO₃ composites. I. Effects of solid loading and particle size distribution on capillary rheometry. *Polym Compos* [Internet]. Wiley Subscription Services, Inc., A Wiley Company; 2007;28(4):512–23. Available from: <http://dx.doi.org/10.1002/pc.20308>
20. Harzallah O, Dupuis D. Rheological properties of suspensions of TiO₂ particles in polymer solutions. 1. Shear viscosity. *Rheol Acta*. 2003;42(1–2):10–9.
21. Schachter DM, Xiong J, Tirol GC. Solid state NMR perspective of drug-polymer solid solutions: A model system based on poly(ethylene oxide). *Int J Pharm*. 2004;281(1–2):89–101.
22. Nam JY, Sinha Ray S, Okamoto M. Crystallization behavior and morphology of biodegradable polylactide/layered silicate nanocomposite. *Macromolecules*. 2003;36(19):7126–31.
23. Parikh T, Gupta SS, Meena A, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - III: Polymethacrylates and

polymethacrylic acid based polymers . J Excipients Food Chem. 2014;5(March):56–64.

24. Gupta SS, Meena A, Parikh T, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - I : Polyvinylpyrrolidone and related polymers. J Excipients Food Chem. 2014;5(March):56–64.
25. Duplay C, Monasse B, Haudin JM, Costa JL. Shear-induced crystallization of polypropylene: Influence of molecular weight. J Mater Sci. 2000;35:6093–103.
26. Sonwai S, Mackley MR. The effect of shear on the crystallization of cocoa butter. JAOCS, J Am Oil Chem Soc. 2006;83(7):583–96.
27. Fowler JN, Chapman BR, Green DL. Impact of plasticizers and tackifiers on the crystallization of isotactic poly(1-butene). Eur Polym J [Internet]. Elsevier Ltd; 2010;46(3):568–77. Available from: <http://dx.doi.org/10.1016/j.eurpolymj.2009.11.013>

Sample	Isothermal crystallization temperature (°C)
PEO	51 - 52 - 53 - 54
10% keto	48 - 49 - 50 - 51
20% keto	44 - 45 - 46 - 47
30% keto	39 - 40 - 41 - 42
40% keto	35 - 36
10% theo	53 - 54 - 55 - 56

453

454 Table 1: Isothermal crystallization temperatures used for the various samples.

455

Material	η_0 (Pa.s) at 70 °C	η_0 (Pa.s) at 80 °C	η_0 (Pa.s) at 100 °C
PEO	42667	30270	17490
Keto 10%	26281	16857	7877
Keto 20%	17803	9734	4580
Keto 30%	8587	5097	2507
Keto 40%	6042	2602	1175
Theo 10%	55245	36301	33659

456

457 Table 2: Zero shear viscosity (η_0) of drug polymer mixtures at various test temperatures.

458

Material	Crossover frequency (rad/s)		
	70 °C	80 °C	100 °C
PEO	20.75	29.63	53.49
Keto 10%	42.03	59.75	124.0
Keto 20%	42.21	68.78	153.7
Keto 30%	58.98	93.44	223.6
Keto 40%	66.80	120.9	307.2
Theo 10%	29.36	40.41	58.27

459

460 Table 3: Crossover frequency as a function of drug content and drug type, determined at various
461 test temperatures via frequency sweep experiments.

462

Sample	shear rate	n	k (min ⁻ⁿ)	K (min ⁻¹)	t1/2 (min)
PEO	0	2.9	4.17E-06	0.014	73.9
	0.5	4.1	3.03E-04	0.138	12.6
	1	3.9	9.27E-04	0.170	11.9
	2	3.1	7.19E-03	0.205	10.6
Keto 10%	0	2.4	7.30E-05	0.021	59.5
	0.5	2.5	1.12E-02	0.165	11.2
	1	2.9	1.40E-02	0.225	8.7
	2	2.5	4.50E-02	0.293	6.8
Keto 20%	0	2.3	1.73E-04	0.023	58.2
	0.5	2.3	1.97E-02	0.185	8.8
	1	1.9	4.37E-02	0.190	7.8
	2	2.2	4.93E-02	0.258	6.1
Keto 30%	0	2.0	9.29E-04	0.031	43.8
	0.5	1.5	4.60E-02	0.128	10.5
	1	1.6	2.74E-02	0.105	11.1
	2	1.8	3.45E-02	0.160	7.7
Keto 40%	0	2.1	8.01E-04	0.034	38.2
	0.5	1.9	1.73E-02	0.115	12.3
	1	2.0	9.62E-03	0.098	13.5
	2	1.4	6.39E-02	0.132	10.6

463

464 Table 4: Calculated Avrami parameters from the FIC experiments for neat PEO and samples
465 containing 10, 20, 30, 40 % (w/w) ketoprofen in PEO.

466

467

468

469

470

471 Figure 1) Schematic presentation of the shear-induced crystallization experiment.

472

475 Figure 2: Complex viscosity as a function of angular frequency at 70, 80 and 100 °C for pure PEO
 476 and PEO samples containing Ketoprofen and Theophylline (a-c). Viscosity ratio as a function of drug
 477 concentration (% w/w) (d).

479

480

481

482

483 Figure 3: Time sweep (over 20 min at 70°C) of a PEO sample containing 40 % Ketoprofen. Inset:

484 image after 4 and 10 min taken at the same location.

485

486

487

488

489

490

491

492 Figure 4: a) Complex viscosity as a function of temperature during cooling experiment b) G' , G'' and
 493 Complex viscosity as a function of temperature during cooling experiment of pure PEO. c) Crossover
 494 temperatures as a function of Ketoprofen concentration % (w/w) in PEO. d) Heating experiment
 495 subsequent to the cooling experiment. Horizontal line indicates the 10000 Pa.s upper viscosity limit for
 496 hot melt extrusion processability. Measurements performed at 2°C/min, 1 Hz, $\gamma = 2\%$.

497

498

499

500

501

502

503

504 Figure 5: Extrudates collected shortly after extrusion, from top till bottom: Keto 40%, Keto 30%,
505 Keto 20%, Keto 10%, PEO, Theo 10%.

506

Figure 6: Relative crystallinity as a function of time for FIC experiments of samples containing 10, 20, 30 and 40 % (w/w) ketoprofen in PEO. Applied shear rates: Quiescent (blue), 0.5 s^{-1} (red), 1 s^{-1} (green), 2 s^{-1} (purple).

516

517

518

519 Figure 7: (a) Dimensionless half crystallization time and (b) dimensionless crystallization rate
520 constant as a function of the applied shear rate.

521

522

523

524

525

Figure 8: Relative crystallinity as a function of time for the isothermal crystallization experiments.