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

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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

Abbreviations

API	Active Pharmaceutical ingredient
FIC	Flow Induced Crystallization
HME	Hot Melt Extrusion
KETO	Ketoprofen
NSAID	Nonsteroidal anti-inflammatory drug
PEO	Poly (Ethylene Oxide)
SD	Solid Dispersion
SIC	Shear Induced Crystallization
T_g	Glass transition temperature
T_m	Melt temperature

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, POLYOX^{TM} 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 (± 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 = 1mm) 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 (±10000 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 (±

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 (ΔT = 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 = 1Hz, γ = 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.

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

Were 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):

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

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

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

226

227 3 **Results & Discussion**

228 3.1 Drug solubility and viscoelastic properties

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

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

239 $$\frac{\eta^*}{\eta_0} = \frac{1}{1+(k\cdot\omega)^{(1-n)}} \quad (3)$$

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

241 Table 2 lists the calculated zero shear rate viscosities obtained from the frequency sweep data.
242 Figure 2 a - c shows the frequency sweep results at 70, 80 and 100 °C respectively. Also the viscosity
243 ratio (η_0 drug mixture / η_0 neat PEO) was calculated for the different test temperatures in order to
244 construct Fig 2d. All samples were showing a similar shear thinning behaviour. As for the typical shear
245 rates encountered in pharmaceutical hot melt extrusion (i.e., 1 - 100 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 modules (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 ($2s^{-1}$) increased the crystallization speed due to the stable nuclei that

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

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

337

338

339 4 **Conclusion**

340 This study showed that APIs alter the flow behavior of a polymer melt formulation. Also, the
341 polymer crystallization is influenced by the API's solid-state (crystalline or dissolved). Crystalline
342 material (theophylline) in the polymer melt act as filler and nucleating agent, inducing polymer
343 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.

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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

	Crossover frequency (rad/s)		
Material	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

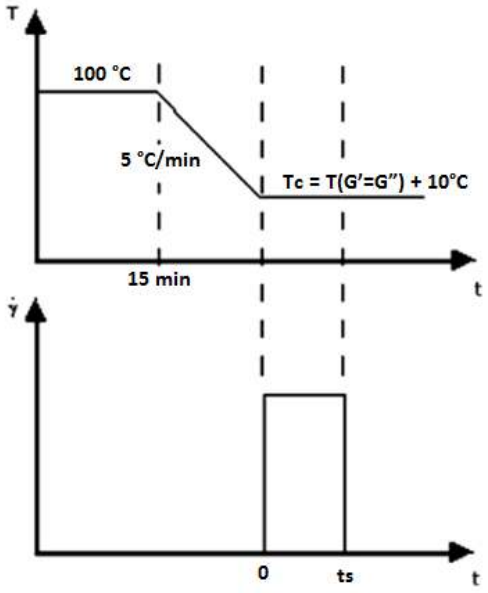
460 Table 3: Crossover frequency as a function of drug content and drug type, determined at various

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

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



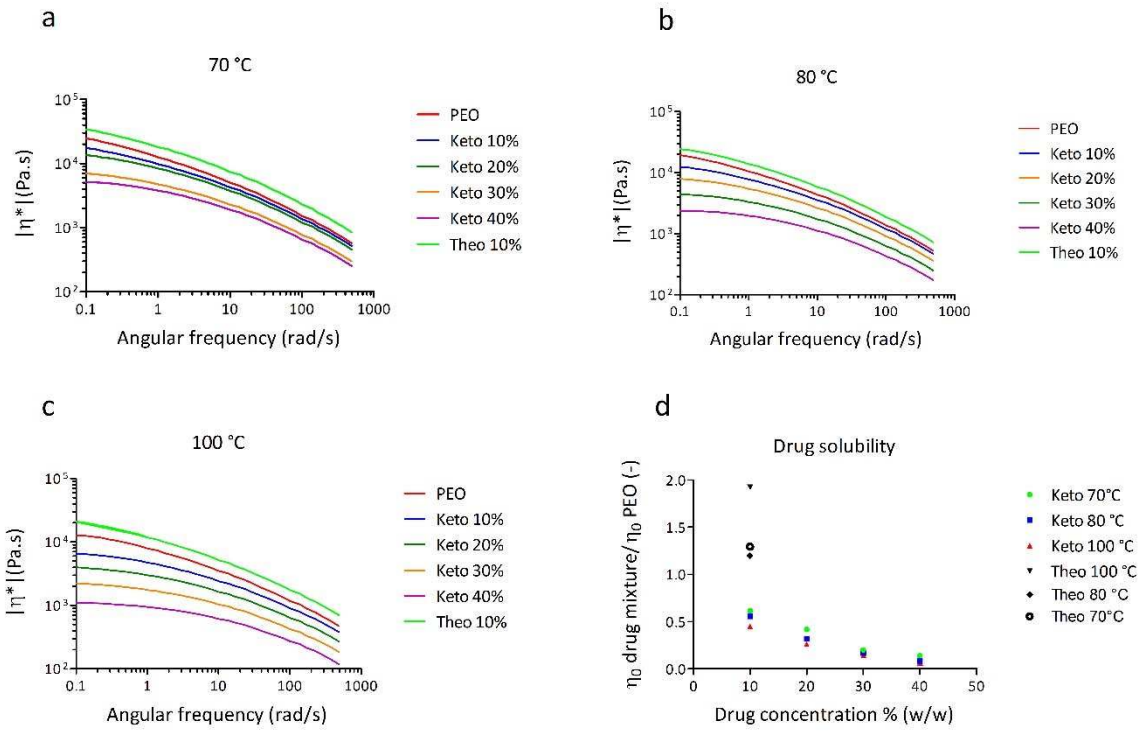
469

470

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

472

473



474

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).

478

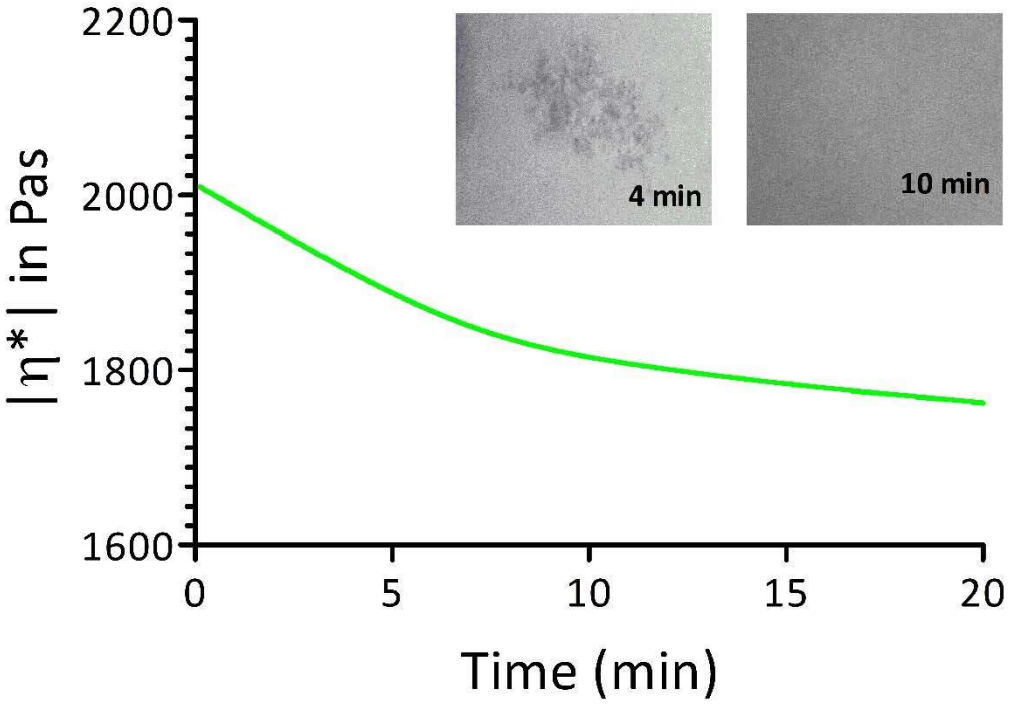


Figure 3: Time sweep (over 20 min at 70°C) of a PEO sample containing 40 % Ketoprofen. Inset: image after 4 and 10 min taken at the same location.

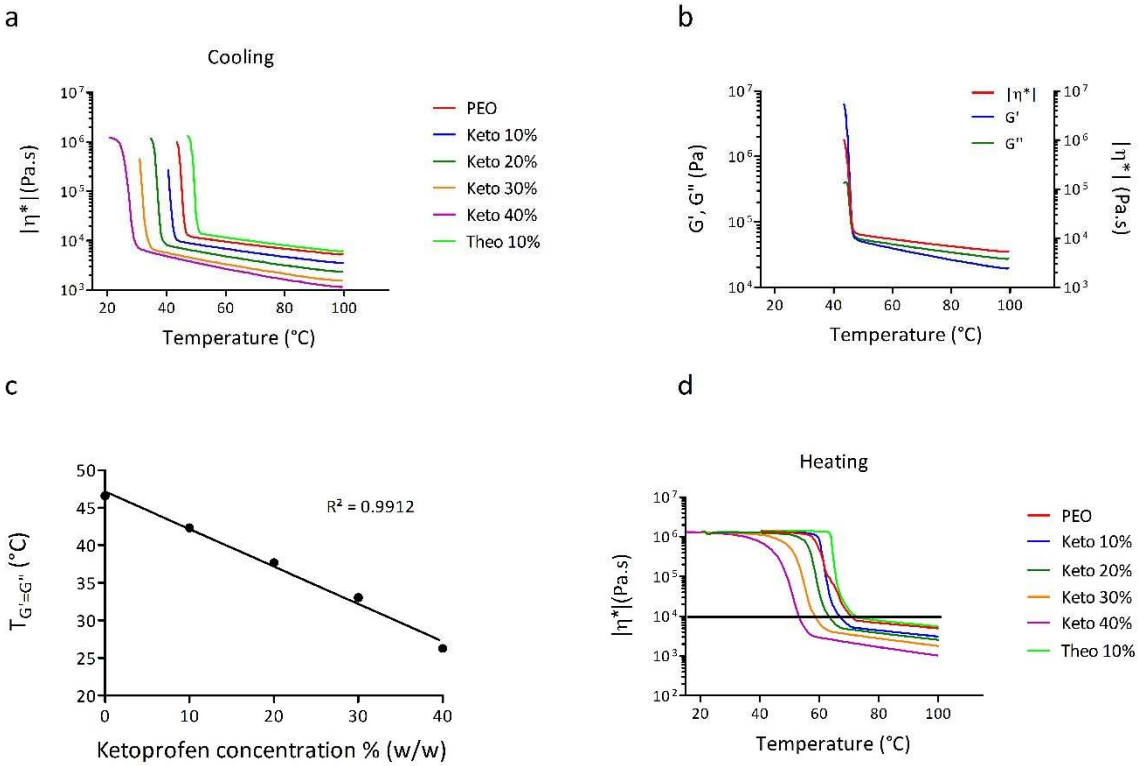


Figure 4: a) Complex viscosity as a function of temperature during cooling experiment b) G', G'' and Complex viscosity as a function of temperature during cooling experiment of pure PEO. c) Crossover temperatures as a function of Ketoprofen concentration % (w/w) in PEO. d) Heating experiment subsequent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

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499

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

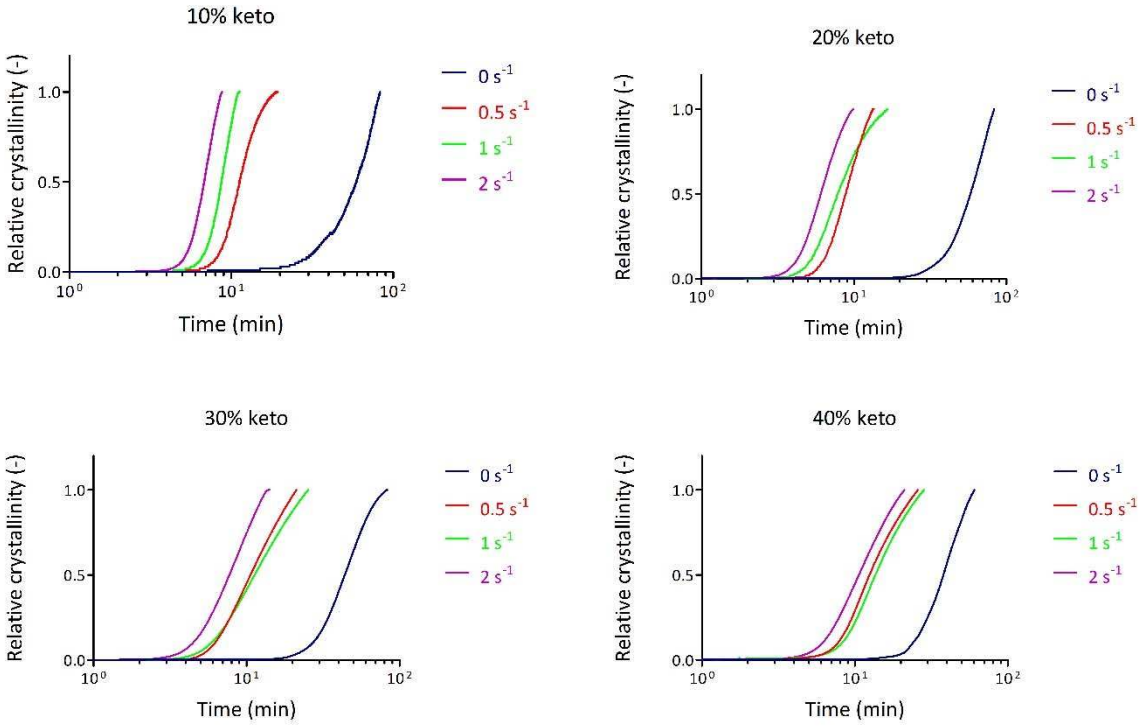

Figure 6: Relative crystallinity as a function of time for FIC experiments of samples containing 10, 20, 30 and 40 % (w/w) ketoprofen in PEO. Applied shear rates: Quiescent (blue), 0.5 s^{-1} (red), 1 s^{-1} (green), 2 s^{-1} (purple).

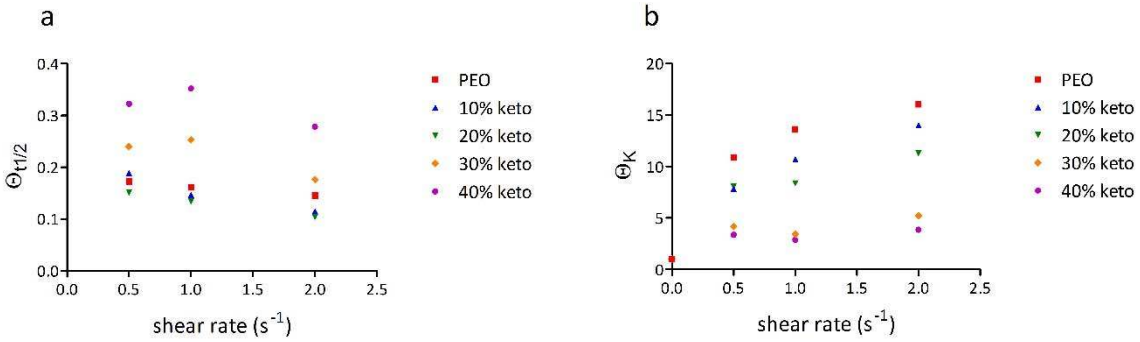

Figure 7: (a) Dimensionless half crystallization time and (b) dimensionless crystallization rate constant as a function of the applied shear rate.

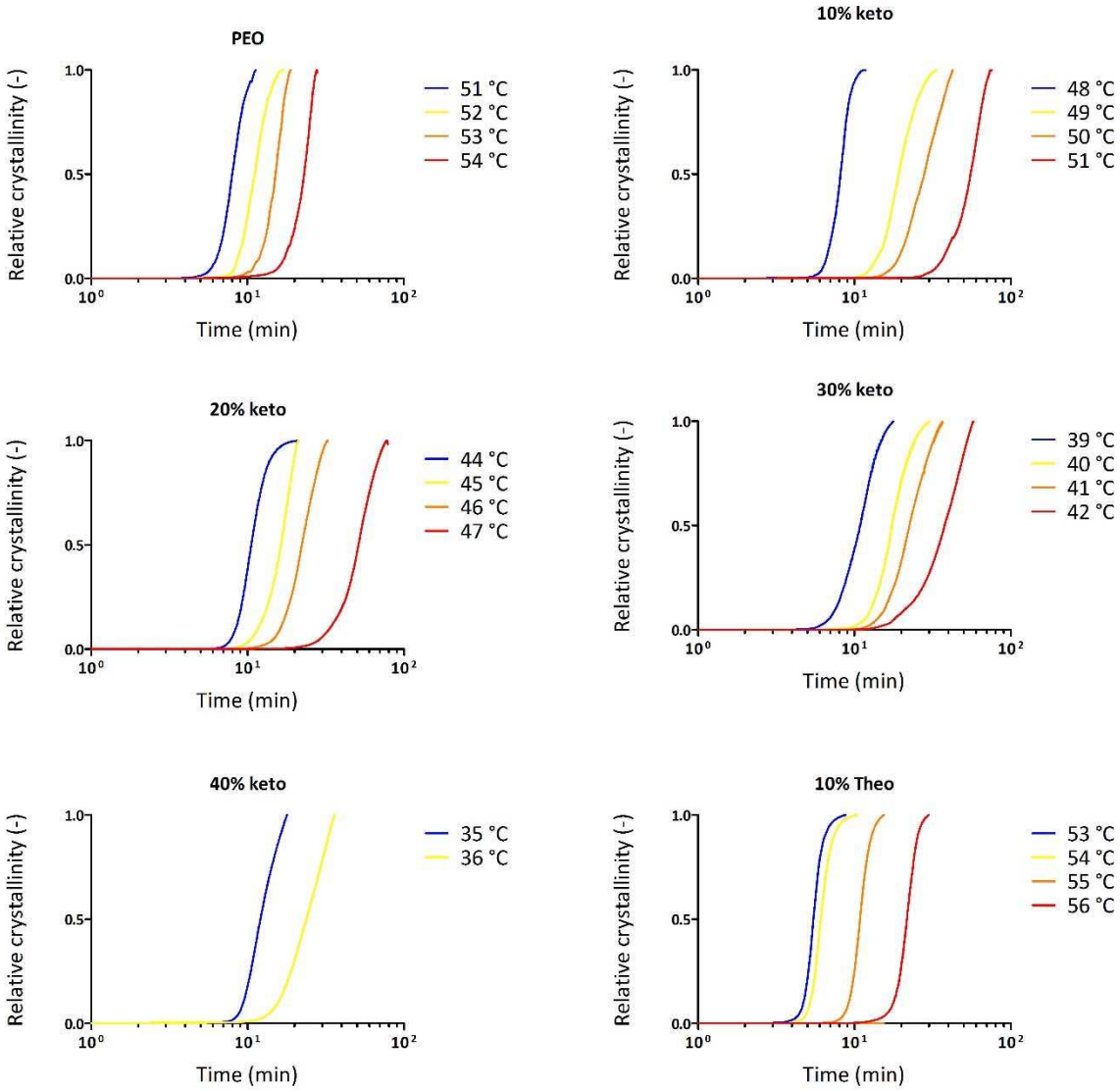

Figure 8: Relative crystallinity as a function of time for the isothermal crystallization experiments.