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Application of mixtures of polymeric carriers for dissolution enhancement of fenofibrate using hot-melt extrusion

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ABSTRACT

Hot-melt extrusion was applied to improve dissolution behavior of poorly soluble model drug fenofibrate. Blends of polymers were used as carrier: copovidone (COP), polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol copolymer (PVCL–PVAc–PEG) and hypromellose 2910/5 (HPMC). The ratio of fenofibrate to COP remained constantly 1 + 3 (weighted parts) with varying amounts of PVCL–PVAc–PEG and HPMC. Solid state of fenofibrate was characterized by X-ray diffractometry and differential scanning calorimetry. Dissolution performance was compared to marketed formulations Lipidil and Lipidil-Ter. Stability studies were conducted at 25 °C/60%rH.

The dissolution rate from extrudates was significantly increased when compared to pure fenofibrate powder or physical mixture of the components. A supersaturation of 7.6–12.1 was reached with the pelletized extrudates. All extrudates were superior to marketed formulations. No recrystallization was observed after 26 weeks of storage for fenofibrate-COP extrudates 1 + 3 (weighted parts) with or without polymeric additives. Even so, both degree and duration of supersaturation decreased with increasing storage periods with the exception of fenofibrate-HPMC extrudates.

Of particular interest is the finding that by adding polymers with differing release characteristics to the drug–carrier mixture, the dissolution performance of hot-melt extruded solid dosage forms can be readily adapted to meet specific requirements.

1. Introduction

In the field of drug delivery system development for peroral application, the enhancement of in vivo solubility of newly developed drugs is becoming increasingly challenging as the number of innovative but poorly soluble APIs is rising. BCS class II drugs as defined by Amidon in 1995, are most suitable for bioavailability enhancement through pharmaceutical formulation (Amidon et al., 1995). In literature, various approaches have been described, one of them being the manufacture of solid dispersions. In 1961, eutectic mixtures were introduced as a novel way for solubility enhancement by Sekiguchi and Obi (1961). Goldberg et al. pursued the subject further, suggesting that solid solutions of a drug in a carrier are superior to eutectic mixtures as the particle size is drastically reduced (Goldberg et al., 1965). A detailed classification of solid solution and solid dispersion systems and a summary of methods of manufacture was given by Chiou and Riegelman (1971). Since then, many more methods for solid dispersion or solution manufacture have been introduced one of them being hot-melt extrusion. Coming from the plastics industry, it was first used for pharmaceutical formulation in 1971 by El-Egakey et al. and refined in later years by various research groups (Breitenbach, 2002; El-Egakey et al., 1971; Repka et al., 2008). It was shown that the dissolution behavior of the hot-melt extruded solid dosage form depends on the physicochemical characteristics of the carrier applied. Thus, the choice of carrier plays an important role for a successful formulation. The suitability of various polymers as carrier for hot-melt extrusion has been investigated in literature, e.g. polyethylene glycol, polyvinylpyrrolidone or sugar alcohols for immediate release and methacrylic acid copolymer (Eudragit® L 100; Evonik Roehm GmbH, Darmstadt, Germany) or ethylcellulose for sustained release solid dosage forms (Repka et al., 2008).

The key objective of this study was to improve the solubility of poorly water soluble model drug fenofibrate by manufacturing a solid dispersion via hot-melt extrusion. In the past, a great amount of research was performed to improve the dissolution rate and bioavailability of fenofibrate preparations and to develop a fenofibrate solid dosage form which may be applied

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independent of food uptake. A great variety of methods was used, e.g. micronization (Munoz et al., 1994), stabilization of micronized fenofibrate through a coating process (Guichard et al., 2000), self-microemulsifying drug delivery systems (SMEDDS) (Patel and Vavia, 2007) and, more recently, solid dispersions. Hot-melt extrusion has been found to be a very promising, reliable and possibly continuous process technology for pharmaceutical solid dispersion preparation. It has been successfully applied by numerous research groups for solubility enhancement of poorly soluble drugs, one of them being fenofibrate. In previous work, it was shown that a solid dispersion of fenofibrate and a suitable polymeric carrier may enhance its solubility (Sheu et al., 1994; Vogt et al., 2008). He et al. employed polyvinylpyrrolidone vinylacetate copolymer and basic butylated methyl methacrylate copolymer (Eudragit® E; Evonik Röhm, Darmstadt, Germany) as carriers in hot-melt extruded solid dispersions of fenofibrate (He et al., 2010). Kanaujia et al. (2011) used polyvinylpyrrolidone and polyvinylpyrrolidone vinylacetate as carriers for fenofibrate. Djuric and Kolter (2010) applied polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (PVCL–PVAc–PEG, Soluplus®; BASF SE, Ludwigshafen, Germany) as polymeric carrier.

In 2007, Prodduturi et al. used polymeric blends as carrier for clotrimazole in hot-melt extruded films: It was observed, that the unfavorable characteristics of a hot-melt extruded film produced with only one polymer could be improved by adding another polymer with opposed properties. The polymers used were hydroxypropyl cellulose and polyethylene oxide, the first of these exhibiting a better release profile but worse mechanical properties (Prodduturi et al., 2007).

The aim of this work was to further explore the possibilities of polymeric mixtures. The key objective was to ascertain whether the findings of Prodduturi et al. (2007) may be transferred to other polymeric carriers to compensate their deficiencies when functioning as single polymeric carriers. Emphasis was laid on the influences of the polymeric additives on the release profile of the extrudates. In addition, the stability of the hot-melt extruded formulations regarding dissolution behavior and crystallinity was to be investigated.

2. Materials and methods

2.1. Materials

Copovidone (COP, Kollidon® VA 64) and polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (PVCL–PVAc–PEG, Soluplus®) were kindly donated by BASF SE, Ludwigshafen, Germany. Hypromellose (HPMC) 2910/5 was used as supplied by Colorcon GmbH, Idstein, Germany. Fenofibrate was purchased from Smruthi Organics Ltd., Solapur, India.

Two commercial products served as comparison: a fenofibrate formulation, where micronized API is dispersed onto a hydrophilic polyvinyl pyrrolidone network (Guichard et al., 2000) (formulation J, Lipidil-Ter®) and a micronized fenofibrate formulation (formulation K, Lipidil®). The comparators were used as obtained by Solvay Arzneimittel GmbH (Hannover, Germany).

Table 1
Composition of drug–polymer blends. The ratio fenofibrate to COP remained constantly 1 + 3 (weighted parts). The amount of additional polymers was varied as described.

Formulation	Fenofibrate	COP	PVCL–PVAc–PEG	HPMC
A	1	3	–	–
B	1	3	1	–
C	1	3	1.5	–
D	1	3	–	0.6
E	1	3	–	1
F	1	3	1	1
G	1	–	3	–
H	1	–	–	3

For dissolution experiments, polyethylene (PE) filters with a pore size of 10 μm (Poroplast®, Durst Filtertechnik GmbH, Besigheim-Ottmarsheim, Germany) and syringe filters consisting of a regenerated cellulose membrane with a pore size of 0.45 μm were used (Spartan® 30, Whatman GmbH, Dassel, Germany). To avoid a draw-in of large particles into the syringe (Omnifix®, B. Braun Melsungen, AG, Melsungen, Germany), PE filters were connected to the manual sampling manifold (Erweka, GmbH, Heusenstamm, Germany). Sodium chloride and 25% hydrochloric acid, both of analytical grade, and polysorbate 80 (Tween® 80) of reagent grade according to Ph. Eur. (all Merck KGaA, Darmstadt, Germany) were used for dissolution medium preparation. To prepare the HPLC mobile phase, acetonitrile in gradient grade quality for HPLC analysis and extra pure phosphoric acid 85% were used (Merck KGaA, Darmstadt, Germany). High purity, Milli-Q filtered water was used throughout the experiments (Millipore Corporation, Billerica, MA, USA).

2.2. Methods

2.2.1. Sample preparation

Substances were weighed according to Table 1 and blended for 15 min using shaker-mixer Turbula® T2C (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland). Of each mixture, a batch size of 500–750 g was prepared. These physical mixtures were either hot-melt extruded as described above or analyzed directly using the following methods. Pure fenofibrate powder served as comparison throughout the studies.

2.2.2. Hot-melt extrusion

Hot-melt extrusion was performed using PRISM PharmaLab 16 (Thermo Fisher Scientific, Karlsruhe, Germany) which is a co-rotating twin screw extruder with a screw diameter of 16 mm and an L/D ratio of 40:1. The screw configuration is illustrated in Fig. 1. The barrel is divided into 10 zones, for 9 of these the temperature

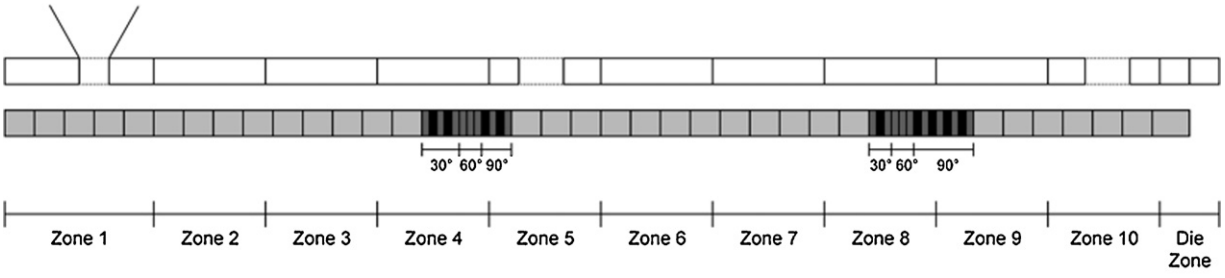

Fig. 1. Configuration of the extruder barrel and screws. Light gray areas represent conveying elements, dark gray and black areas represent mixing elements with a 0° and 90° offset, respectively. Mixing elements are aligned to result in kneading areas with displayed advance angles.

Table 2
Hot-melt extrusion process settings.

Formulation	Barrel zone temperature (°C)										Screw speed (rpm)	Feed rate (kg/h)
	2	3	4	5	6	7	8	9	10	Die		
A	60	100	110	110	110	110	110	110	110	105	75	0.4
B	60	100	110	115	115	115	115	115	115	110	100	0.4
C	60	100	110	115	115	115	115	115	115	110	100	0.4
D	60	110	125	135	135	135	135	135	135	135	150	0.4
E	60	110	145	150	150	150	150	150	150	145	150	0.4
F	60	100	125	135	135	135	135	135	135	130	100	0.4
G	50	100	115	115	115	115	115	115	115	115	100	0.4
H	90	150	165	165	165	165	165	165	165	165	150	0.4

can be set individually. Barrel zone 1 is the feeding zone and cannot be heated. The die plate temperature is also defined by the user. The applied die hole diameter was 3 mm for formulations A–G. For formulation H, both 3 mm and 1 mm diameter were used for comparison. Two venting ports were applied: In barrel zone 5 and barrel zone 10 as displayed in Fig. 1. A vacuum pump was connected to the zone 10 venting port to ensure a more efficient degassing. The chosen setting was −0.5 bar for all extrudates. As the polymers used as carrier components exhibit different physicochemical characteristics, the hot-melt extrusion process parameters had to be adjusted for each fenofibrate–polymer mixture (see Table 2). The temperature settings were chosen such that a semisolid, transparent strand was obtained being neither too brittle nor too soft for down-processing. With formulation H, no transparent strand could be obtained but all other criteria were met. The feeding rate was kept constant while the screw speed was slightly varied depending on the processability of the fenofibrate–polymer mixture. After extrusion of the molten mixture through the die hole, the strand was air-cooled on a conveyer belt (Pharma 16 mm air cooled conveyor belt) and pelletized into pellets with a set length of 1.5 mm (Pharma 16 mm Varicut pelletizer; both Thermo Fisher Scientific, Karlsruhe, Germany).

To assess the effect of pellet size on the release profile of the extrudates, formulation H was extruded using two different die diameters: 1 mm and 3 mm. The hot-melt extrusion process conditions were set as described in Table 2. The pelletizer cutting length was set to 1.5 mm.

The obtained pellets were analyzed directly using the following methods. A milling step was not included as the aim was to keep the manufacturing process as simple and time-saving as possible.

2.2.3. Solubility studies

A shake-flask method was used to determine the saturation concentration of fenofibrate in the dissolution medium. A surplus amount of 200 mg of pure fenofibrate was added to 50 mL of hydrochloric acid medium pH 1.2 containing 0.1% polysorbate 80 which was added to ensure sufficient wetting. The dissolution medium was conditioned at 37.0 ± 0.5 °C. The shaking rate was set to 95 min^{-1}. A 10 μm PE filter was attached to a stainless steel cannula to reduce the draw-in of large particles into the syringe. At set time points, a sample volume of 2 mL was withdrawn and filtered through a 0.45 μm syringe filter. The first milliliter of filtered sample was discarded. Sampling times were 0, 0.5, 2, 4, 8, 24 and 48 h. The samples were diluted 1:1 with acetonitrile and then analyzed via HPLC. All solubility studies were performed in triplicate.

2.2.4. Dissolution studies

Dissolution studies were performed with USP apparatus 2 (DT 80, Erweka GmbH, Heusenstamm, Germany) according to Ph. Eur. specifications on dissolution testing (PhEur, 2012a,b). 500 mL of hydrochloric acid medium pH 1.2 containing 0.1% polysorbate 80 to ensure sufficient wetting were conditioned at 37.0 ± 0.5 °C. Weighted samples corresponding to 145 mg of fenofibrate were used: 580 mg of physical mixture, 145 mg of pure fenofibrate and corresponding amounts of pelletized extrudates. The stirring speed was 75 rpm. At set time points, sample volumes of 3 mL were drawn through a stain-less steel cannula with an attached 10 μm PE filter. The samples were filtered through a 0.45 μm syringe filter. The first milliliter of filtered sample was discarded. The removed sample volume was substituted with the same amount of conditioned dissolution medium. Sampling times were 0, 5, 10, 15, 30, 45, 60, 90 and 120 min. The samples were diluted 1:1 with acetonitrile and analyzed via HPLC. All dissolution studies were performed in triplicate.

The two comparators formulation J and K have a drug content of 160 mg and 200 mg, respectively, per solid dosage form. To ensure equal conditions and comparability during dissolution studies while leaving the solid dosage forms intact, the volume of dissolution medium was adjusted. For formulation J, 552 mL of dissolution medium were used, for formulation K 690 mL.

In some dissolution experiments for fenofibrate-COP extrudates, adequate amounts of HPMC or PVCL–PVAc–PEG were dissolved in the dissolution medium to assess whether the hot-melt extrusion of all components is essential for the observed effect.

Non-sink conditions were chosen, as solid dispersions might lead to a temporary supersaturation of the dissolution medium. Therefore, under non-sink conditions a better differentiation of solid dispersion formulations and comparison of the degree of supersaturation reached is possible.

Dissolution rates and decrease rates of the samples were calculated by linear regression using SigmaPlot Software Version 10 (Systat Software Inc., San Jose, CA, USA).

To assess the stability of supersaturation of the respective formulation, the half-value of the maximal concentration ($c_{max}/2$) was calculated. The time period of the dissolved concentration of fenofibrate above this half-value was determined for each formulation.

2.2.5. High pressure liquid chromatography

A Merck-Hitachi LaChrom HPLC system equipped with a pump L-7100, autosampler L-7200, column oven L-7300, UV–vis detector L-7420 and a Merck-Hitachi interface L-7000 (Hitachi High-Technologies Corporation, Tokyo, Japan) was used to determine the amount of dissolved API in solubility and dissolution studies via HPLC analysis. A modified Ph. Eur. method was used to identify the amount of fenofibrate released. The mobile phase consisted accordingly of 70% acetonitrile and 30% water adjusted to pH 2.5 with phosphoric acid and the column LiChroCART® Superspher® 250-4 100 RP-18 (Merck KGaA, Darmstadt, Germany) was used. The flow rate was maintained at 2.0 mL/min, the detection wavelength was set to 286 nm and the column was tempered at 50 °C. A sample volume of 5 μL was injected. Fenofibrate eluted after 5.3 min.

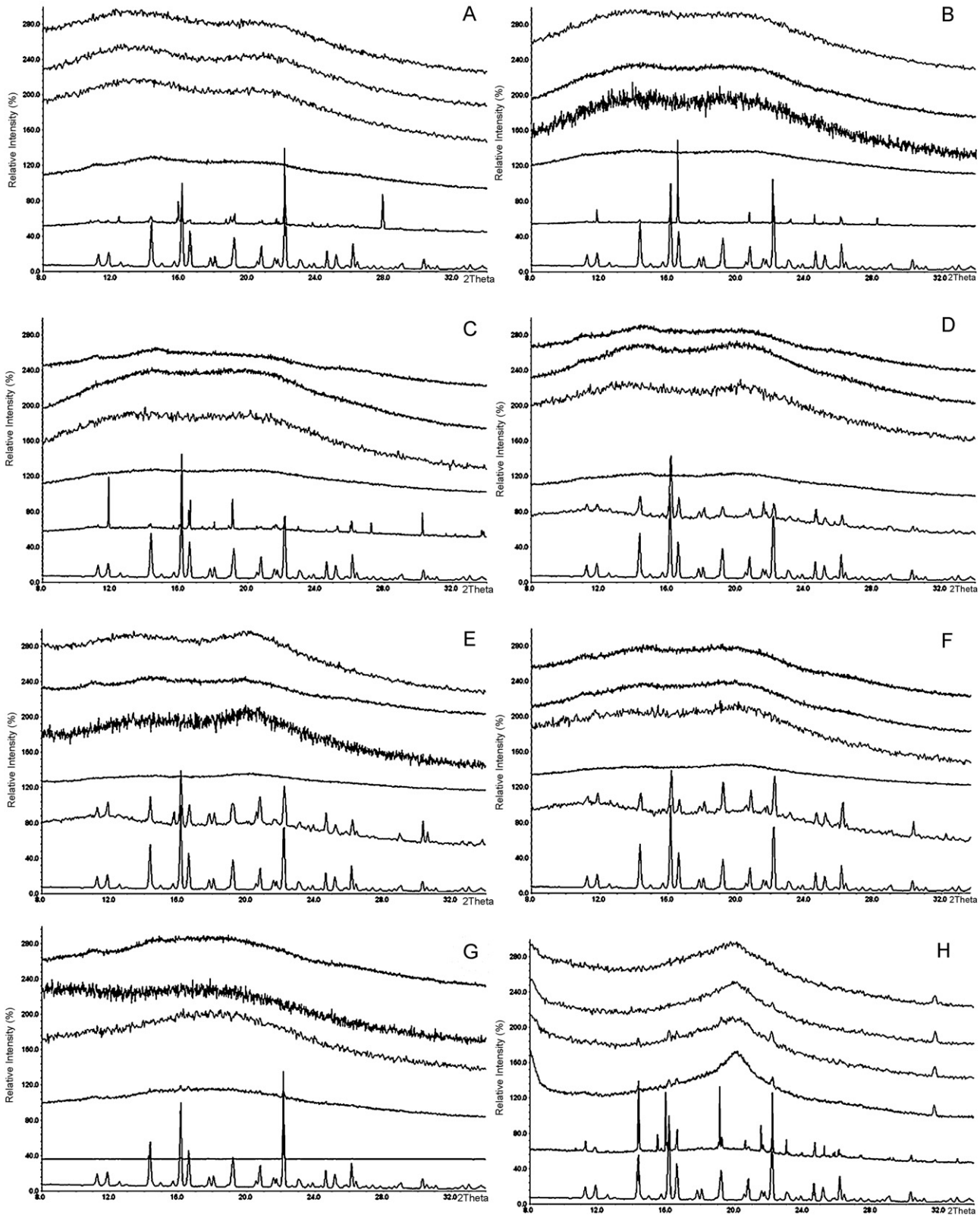

Fig. 2. XRD-diffractograms of formulations A–H depicting, from top to bottom, the following data: sample directly after manufacture, after 4 weeks of storage, after 10 weeks of storage, after 26 weeks of storage, the corresponding physical mixture, pure fenofibrate powder.

Standard solutions were prepared in mobile phase. HPLC method validation was performed: Linearity was verified over a concentration range from 1 μg/mL to 1 mg/mL and the precision of the method was confirmed.

2.2.6. X-ray crystallography

A transmission diffractometer StadiP (STOE & Cie GmbH, Darmstadt, Germany) was used to investigate crystallinity in pelletized extrudates and physical mixtures. A Ge (1 1 1) monochromator and

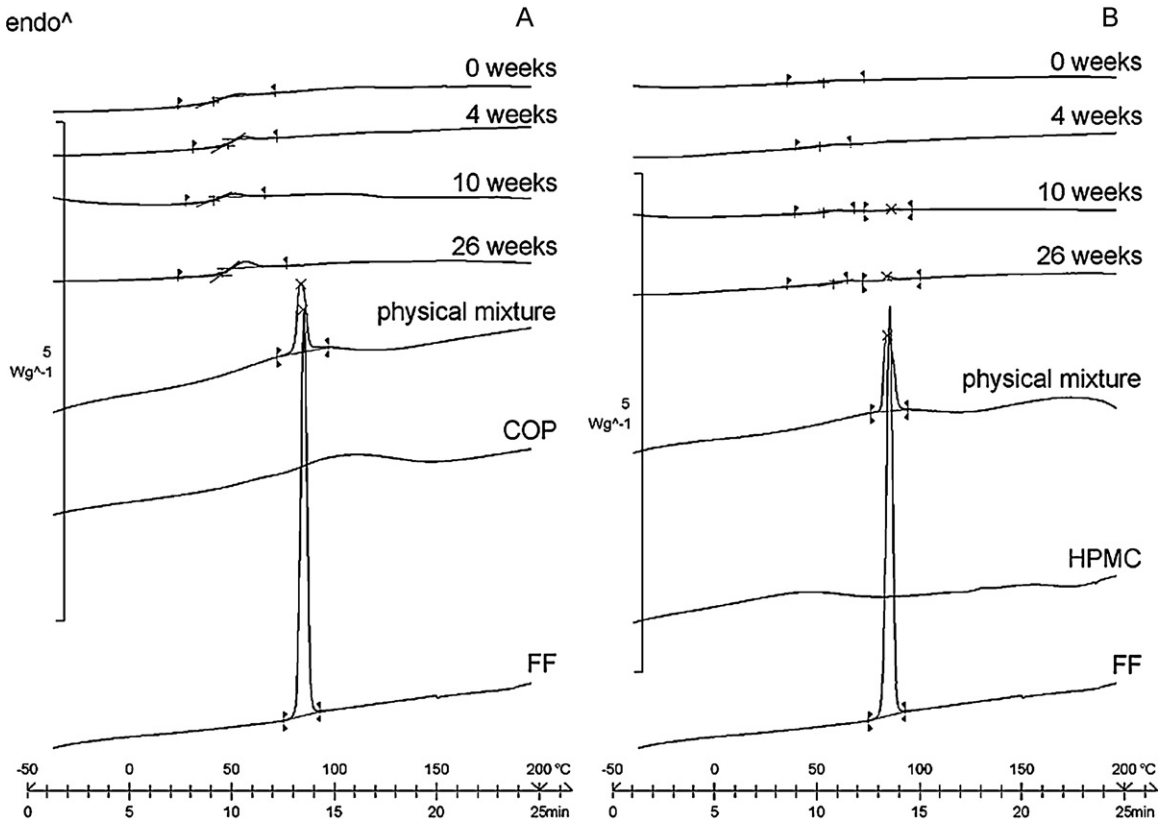

Fig. 3. DSC thermogram of the first heating cycle of (A) formulation A (FF + COP = 1 + 3 weighed parts) and (B) formulation H (FF + HPMC = 1 + 3 weighed parts).

Cu Kα radiation were employed. The generator accelerating voltage was 40 kV, the plate current 40 mA. The samples were measured in the 2θ-range from 1° to 64.95° with a step size of 0.05° and a dwelling time of 15 seconds. In this work, the range depicted in the diffractograms is limited to 0–34° as the characteristical patterns of crystalline fenofibrate are located in this region.

2.2.7. Differential scanning calorimetry

It is commonly known that small sized crystals might be not detected by XRD even if their concentration in the sample is above the limit of detection (Munson, 2009). For this reason, DSC was applied as a second method to detect crystallinity. About 15 ± 5 mg of sample in a 100 μL aluminum pan were measured with a DSC 821e (Mettler-Toledo GmbH, Giessen, Germany). A scan rate of 10 K/min and a nitrogen gas flow of 50 mL/min were applied. The measurement was conducted in a temperature range of −50 to 200 °C.

2.2.8. Stability testing

Stability testing was performed according to ICH Guideline "Stability testing of new drug substances and products Q1A(R2)" (ICH, 2003) to assess the effects of temperature, humidity and time on the product. The samples were stored under long-term storage conditions (25 °C/60%rH) for 4, 10 and 26 weeks in polyethylene (PE) double pouches.

To assess the effects of humidity on the dissolution performance of the extrudates, some of the samples were stored under moisture protection in Activ-Vials® (CSP Technologies, Inc., Auburn, Alabama, USA) for 4 weeks.

2.2.9. Particle size analysis

The particle size distribution of fenofibrate was determined by laser light diffraction using a Mastersizer 2000 with a Hydro 2000SM sample dispersion unit (Malvern Instruments Ltd., Worcestershire, United Kingdom). About 200 mg of sample were added to 5 mL of silicone oil. The stirring rate was 2000 rpm. Each sample was measured 50 times with a single measurement time of 7.5 s. Values were then averaged.

2.2.10. Karl Fischer titration

The water content of the samples was determined using the Karl Fischer oven method. Samples were analyzed directly after manufacture and after the removal from storage at set time points using Oven Sample Processor 774 and KF Coulometer 756 (Deutsche Metrohm GmbH & Co. KG, Filderstadt, Germany). About 100 mg of pelletized extrudates were accurately weighed into a glass vial and sealed. The sample was then heated to 120 °C. The water released during the heating procedure is transferred through a hollow needle into the Karl Fischer cell and titrated. A coulometric titration method was applied. Lactose monohydrate was used as standard.

2.2.11. Pellet size analysis

The length and diameter of the pellets was determined using a digital caliper ($n = 50$). Each pellet was weighed.

3. Results and discussion

3.1. Solid state

Directly after manufacture of hot-melt extruded formulations A–H, crystalline fenofibrate could not be detected via XRD analysis of the pelletized extrudates (see Fig. 2). This was also confirmed by DSC (see Fig. 3 for exemplary DSC data of formulations A and H). The limit of detection was determined to be 2% for both XRD and DSC. Hence it can be concluded that the amount of crystalline fenofibrate in the extrudates is lower than 2%. Formulations A–F

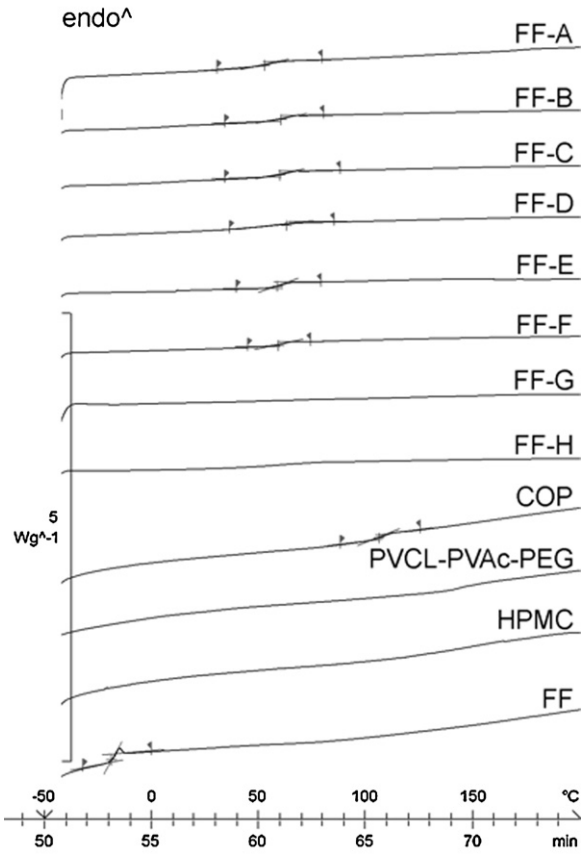

Fig. 4. DSC thermogram of the second heating cycle of hot-melt extruded formulations A–H and the single compounds COP, PVCL–PVAc–PEG, HPMC and pure FF.

were stable over a time period of 26 weeks as no crystalline material was found after removal from storage after 4, 10 or 26 weeks. With formulations G and H, recrystallization occurred during storage as crystalline fenofibrate was detected after a storage period of 26 and 10 weeks, respectively, via XRD and DSC (see Figs. 2 and 3). It can be concluded that COP has a stabilizing, recrystallization inhibiting effect on the extrudates during storage.

Only one glass transition was detected in the second heating cycle of DSC analysis with hot-melt extruded formulations A–F (see Fig. 4). No glass transitions were detected in the second heating cycle of formulations G and H and the single polymers PVCL–PVAc–PEG and HPMC, possibly due to degradation processes. However, these data could be derived from the first heating cycle, leading to the same conclusion as with formulations A–F. The T_g values of all extrudates (T_g values = 30–60 °C) were intermediate between the T_g values of the single components (T_g COP = 105 °C, T_g HPMC = 175 °C, T_g PVCL–PVAc–PEG = 70 °C), indicating the formation of a one-phase system of the amorphous drug in the amorphous carrier. It is concluded, that a glassy solution of the molecularly dispersed drug in the polymeric carrier is present in the hot-melt extruded formulations A–H.

3.2. Dissolution studies

To evaluate the dissolution enhancement achieved through hot-melt extrusion, the release behavior of hot-melt extruded pellets was compared to pure fenofibrate powder and the corresponding physical mixtures of all components.

No degradation of fenofibrate was detected in extrudates directly after manufacture or after 4, 10 and 26 weeks of storage using HPLC analysis. It can therefore be stated, that neither the hot-melt extrusion process nor dissolution studies over a time period of 2–48 h affect the stability of this drug substance.

3.2.1. Dissolution profile of fenofibrate extrudates with one polymeric carrier

With formulation A, which is the fenofibrate-COP 1 + 3 (weighted parts) extrudate with no additional excipients, an immediate release was observed as the maximum concentration was already achieved after 10 min of dissolution (see Fig. 5A). At this sampling point, a dissolved amount of 227 μg/mL of fenofibrate was detected which equates 78% of total API. After 10 min of dissolution, the release from this extrudate was 12.1 times above saturation concentration. After 45 min of dissolution, the amount of dissolved fenofibrate has dropped down to 4.9 times above saturation level. With formulation G, the maximum concentration of 138 μg/mL fenofibrate was achieved after 60 min of dissolution (see Fig. 5G). The dissolved amount of fenofibrate corresponds to a released amount of 48% of total API and is 7.4 times above saturation level. The maximum concentration of fenofibrate achieved with formulation H was 80 μg/mL after 30 min of dissolution (see Fig. 5H). This corresponds to 28% of total API and is 4.3 times above saturation level. For formulations A and H, supersaturation could be maintained for 2 h of dissolution, for formulation G it was maintained for 105 min. However, the level of supersaturation was not stable for all three formulations.

3.2.2. Dissolution profile of fenofibrate extrudates with a mixture of polymers as carrier

Formulations B–F consist of fenofibrate as poorly soluble model drug and COP as main carrier with varying amounts of PVCL–PVAc–PEG and/or HPMC as polymeric additives. The modifications of the dissolution profile by the additional polymers in comparison to fenofibrate extrudates with only one single polymeric carrier were of particular interest.

Differences of the dissolution profiles of the various formulations were found especially in the initial release rate, the maximum released amount of fenofibrate and the level of supersaturation. In comparison to formulation A, the initial release rate decreased if HPMC or PVCL–PVAc–PEG were added to the mixture. While the initial dissolution rate of formulation A pellets was 43.9 μg/min, it was only 2.7–9.1 μg/mL if additional polymers were employed (see Table 3 for results). Furthermore, the maximum concentration of dissolved fenofibrate was reduced by employing additional polymers. While the maximum concentration was 227 μg/mL after 10 min of dissolution with formulation A, it was 212 μg/mL after 45 min for formulation B, 187 μg/mL after 60 min for formulation C, 153 μg/mL after 60 min for formulation F, 145 μg/mL after 30 min for formulation E and 141 μg/mL after 45 min for formulation D (see Fig. 5A–F). An increase in stability of the achieved supersaturation was obtained if polymeric blends were used as carriers: while the concentration of released API remained for approximately 25 min above half of the respective maximum supersaturation concentration with single polymeric formulation A, 50 min with formulation H and 60 min with formulation G, it was approximately 70–100 min for formulations B–E. With formulation H, the half-value of the supersaturation concentration was not reached within the investigated dissolution time of 120 min (see Table 3).

It was observed, that the maximum amount of API dissolved is mainly a result of the application of COP as main polymeric carrier. However, the application of additional polymers strongly influences the curve progression, e.g. the initial release rate and the degree as well as the stability of supersaturation. Even with an added amount of only 0.6 parts of a second polymer as in formulation D, the shape of the dissolution curve was shown to approach the shape of the curve of fenofibrate with the additional polymer as sole carrier (see Fig. 5D and H). When using two additional

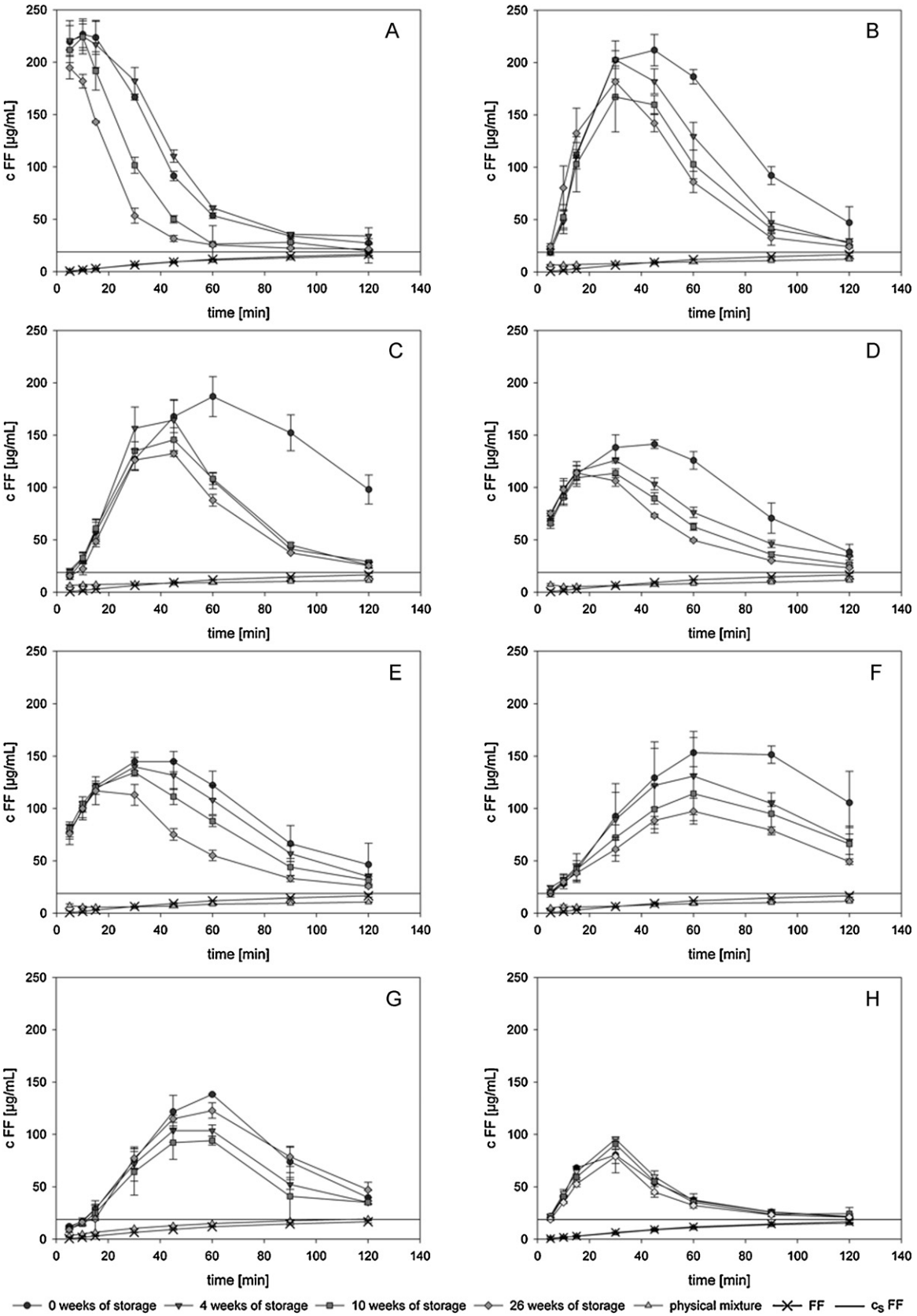

Fig. 5. Dissolution profiles of formulations A–H in comparison to pure fenofibrate and physical mixtures of the corresponding components. Dissolution testing was performed either directly after manufacture or after removal from storage at set time points.

polymers as in formulation F (see Fig. 5F), the effect of the applied polymers on the dissolution profile can be summarized as follows: the maximal achieved supersaturation level was increased by the COP effect and both HPMC and PVCL–PVAc–PEG reduce the initial release rate in comparison to COP-FF extrudate without any additional polymers (formulation FF-A) resulting in a delayed t_{max}. Although the initial release rate is reduced even further if a blend of the three polymers COP, PVCL–PVAc–PEG is used as carrier, the stability of the supersaturation is improved. The decrease rate after c_{max} is equivalent to the decrease rates of PVCL–PVAc–PEG and HPMC if used as single polymers (see Table 3).

It was thus pointed out that the release profile of a polymeric blend extrudate is dependent on the dissolution behavior of the respective single polymers after their extrusion.

Literature data confirm these findings, as COP extrudates are reported to fully dissolve after approximately 20 min in pH 1.1 medium and PVCL–PVAc–PEG after approximately 1 h (Kolter et al., 2010). HPMC is known to absorb water upon contact with the dissolution medium and to swell, thus forming a gel layer. Drug release from HPMC matrix systems is reported to be diffusion and erosion controlled (Tu et al., 2010). Nevertheless, the initial release rates of poorly water-soluble APIs were reported to be enhanced if HPMC is used as carrier in hot-melt extrusion (Six et al., 2003; Verreck et al., 2003).

3.2.3. Comparison to the release profile using a dissolution medium containing additional polymers

When comparing the results of formulations A–F to the dissolution profiles of fenofibrate-COP 1 + 3 (weighted parts) pellets where HPMC and PVCL–PVAc–PEG were added directly to the dissolution medium, it was discovered that the sole presence of the additive during dissolution is not sufficient to explain the observed effects. In fact, there was no significant difference observed between fenofibrate-COP 1 + 3 (weighted parts) extrudates without additives in the dissolution medium and the same formulation with a dissolution medium containing HPMC or PVCL–PVAc–PEG (see Fig. 6A). The dissolution profiles of the corresponding physical mixtures, which can be seen in Fig. 6B, confirm that the extrusion process and the resulting effects, e.g. improved blending of the components, intensified linking of the components' particles and transition of the API into its amorphous state are essential for the monitored effects.

Table 3
Initial dissolution rates, decrease rates and the time period above the half-value of the supersaturation concentration ($c_{max}/2$) of hot-melt extruded formulations A–H in comparison to pure fenofibrate powder.

Formulation	Dissolution rate (μg/min)	Decrease rate (μg/min)	Time above $c_{max}/2$ (min)
A	43.9	−3.9	25
B	6.7	−2.3	70
C	3.8	−1.5	100
D	8.4	−1.6	80
E	9.1	−1.8	80
F	2.7	−1.5	>90
G	2.6	−1.4	60
H	4.4	−1.6	50
Fenofibrate	0.2	–	–

3.2.4. Comparison to the release profile of physical mixtures of the components

The release profile of all formulations was enhanced through hot-melt extrusion. The initial release rate as well as the maximum concentration of dissolved fenofibrate and the achieved level of supersaturation was higher with extruded formulations A–H. The release profile of the physical mixtures of formulations A–H did not achieve supersaturation level (see Fig. 6B). With the physical mixture of formulation G, both the initial release rate and the concentration of dissolved API after 120 min of dissolution were improved, the release level being consistently 3 μg/mL above the results gained with pure fenofibrate powder. This effect can be

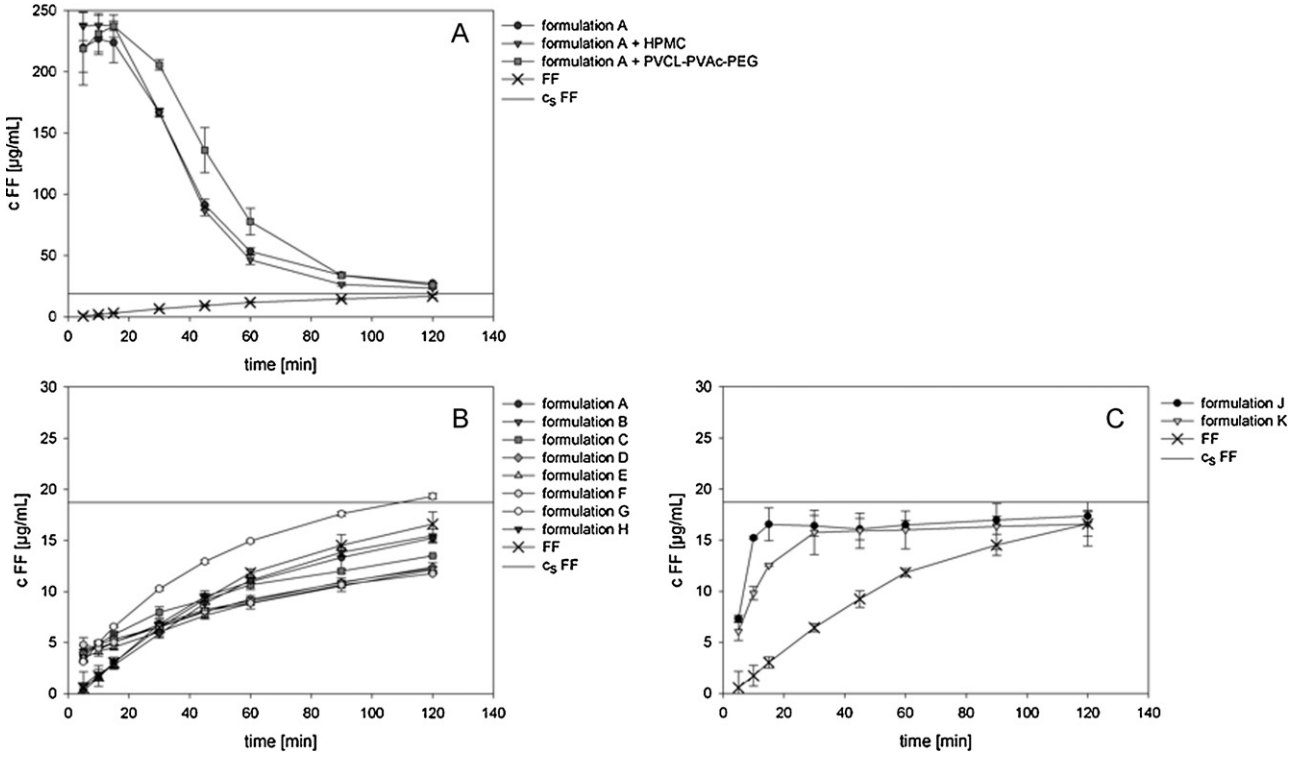

Fig. 6. Dissolution profiles of (A) fenofibrate-COP extrudates 1 + 3 (weighted parts) with the additional polymer directly added to the dissolution medium, (B) the corresponding physical mixtures of formulations A–H and (C) comparators.

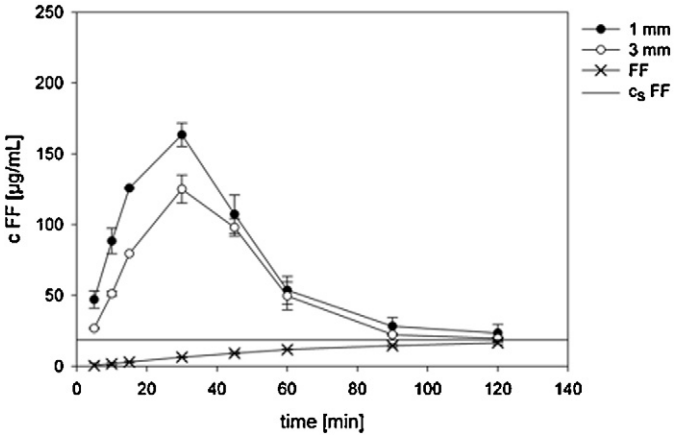

Fig. 7. Dissolution profile of formulation H using two different die diameters in the extrusion process: 1 mm and 3 mm.

contributed to the solubilizing effect of PVCL–PVAc–PEG proposed in literature (BASF SE, 2010). The release profiles of the physical mixtures of formulations A–F and H can be considered to be comparable to the release profile of pure fenofibrate powder.

3.2.5. Comparison with originators

Fig. 6C shows that the initial release rate of the comparators differs: after 5 min, the concentration of dissolved fenofibrate amounts to 7.3 μg/mL for formulation J and to 6.1 μg/mL for formulation K which corresponds to 2.5 and 2.1% of dissolved API. After a dissolution time of 120 min, the concentration of dissolved fenofibrate that was achieved with both comparators has approached the level of saturation concentration. In contrary to this, release from all of the manufactured extrudates surpasses the saturation concentration for at least 105 min (see Fig. 5A–H). Therefore it can clearly be stated that all of the formulations A–H are superior to the investigated comparators regarding the dissolution performance in vitro.

3.2.6. Effect of pellet size on dissolution

As can be seen in Fig. 7, variations in pellet size strongly affect the dissolution profile. A decrease of the pellet diameter by 63% from 2.5 to 0.9 mm results in an increase of initial dissolution by 20.3 μg/mL (5 min) and of c_{max} by 38.4 μg/mL (30 min). The supersaturation level was increased from 6.7 to 8.7 times above saturation concentration. The decrease rate of supersaturation was not affected. Therefore, the results are according to the modified Noyes–Whitney equation describing the dissolution rate of solids to be increasing with increasing surface area (Bruner and Tolloczko, 1900; Dokoumetzidis and Macheras, 2006).

Due to material characteristics of the applied carrier polymers such as viscosity in their molten state, the pellet diameter of formulations A–G was approximately 1.5 mm while the diameter of formulation H pellets was 2.5 mm when extruded with die diameter 3 mm (see Table 4). As can be derived from the data displayed in Fig. 7, a further increase of supersaturation level and c_{max} value has to be expected if the pellet diameter of formulations A–G is decreased.

Table 5
Humidity content of hot-melt extruded formulation C directly after manufacture (0 weeks) or after 4 weeks of storage at 25 °C/60%rH in different packaging materials.

Storage conditions	Humidity content (%)	
	0 weeks	4 weeks
PE double pouches	1.1	1.8
Activ-Vials®		0.7

3.3. Stability upon storage

It was observed that with increasing storage times the level of supersaturation decreased for formulations A–F (see Fig. 5). The release profile of formulation H was shown to be the most consistent over a storage period of 26 weeks as the supersaturation reached was 4.3 directly after manufacture, 5.1 after 4 weeks of storage, 4.8 after 10 weeks and 4.2 after 26 weeks of storage which corresponds to a variation of 8 μg of dissolved fenofibrate per mL. With formulation G, a decrease of supersaturation level was observed from 0 to 10 weeks while the 26 weeks values were above the 4 and 10 weeks dissolution profiles. The high variability of the results of this formulation (standard deviations of 0.1–22.7 μg/mL) is considered to be the reason for this unexpected finding.

As no crystalline material was detected via XRD and DSC for formulations A–F, there is either no recrystallization occurring or the amount of crystalline fenofibrate remains below the determined limit of detection (2%) for the storage period of 26 weeks (see Fig. 3 for exemplary DSC data). Therefore, the pronounced effects of storage time on the dissolution profiles of the samples must be caused by levels of crystallinity even below 2% or by other storage effects, e.g. the humidity content of the extrudates. It was shown with Karl-Fischer titration that the humidity content of extrudates stored in PE double pouches under longterm-storage conditions is continuously increasing: The water content was determined to be approximately 0.4% for formulations A, B and D–H directly after manufacture of the samples. For formulation C, a water content of 1.1% was detected directly after manufacture of the sample. It has increased to approximately 2% after 26 weeks of storage with all formulations.

An increase of humidity content during storage was reported to reduce polymer–polymer interactions and, possibly, polymer–drug interactions through the plasticizing effect of water (Vasanthavada et al., 2004; Wypych, 2004). This is particularly expected for hydrophilic polymers. The molecular mobility is increased, thus promoting recrystallization and the formation of small crystals that might not be detected via XRD or DSC. The longer the storage time, the higher is the humidity content and the more pronounced the possible effect on polymer–polymer and/or drug–polymer interactions.

The comparison of the dissolution profiles of sample FF-C after 4 weeks of storage in different containers (PE double pouches or Activ-Vials® as described in Section 2.2.8) confirms this hypothesis. A drop of the release profile was observed with the samples stored in PE double pouches (see Fig. 8A). This packaging does not provide sufficient humidity protection as the humidity content of the samples was shown to increase within 4 weeks of storage times. If the samples were stored in Activ-Vials®, a decrease of the

Table 4
Pellet sizes of formulation H pellets extruded with die diameters 1 mm and 3 mm.

Pellet properties	Die diameter 1 mm			Die diameter 3 mm		
	Diameter (mm)	Length (mm)	Weight (mg)	Diameter (mm)	Length (mm)	Weight (mg)
Mean value	0.9228	1.5518	1.3618	2.5114	1.3754	8.1796
Deviation	0.0234	0.0316	0.1025	0.1332	0.1201	0.9525

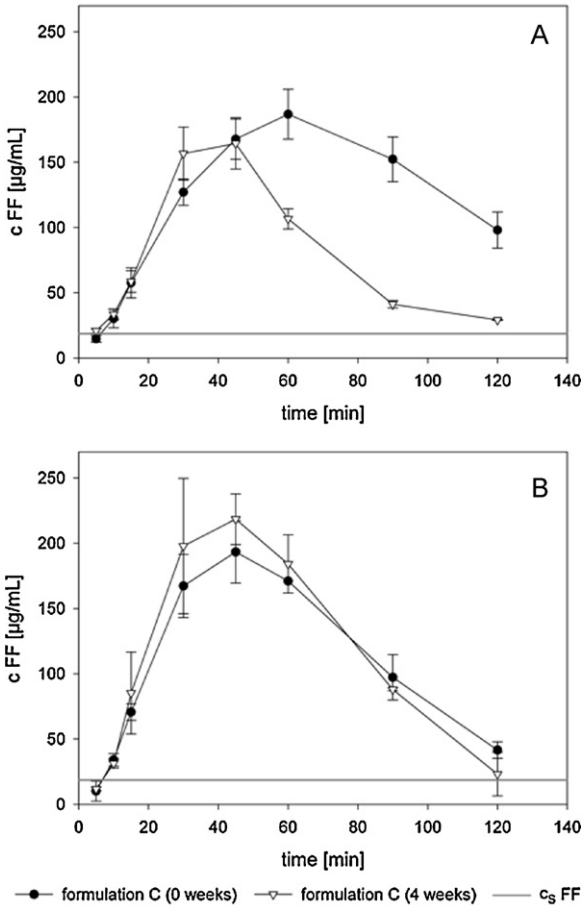

Fig. 8. Dissolution profiles of formulation C pellets directly after manufacture and after storage for 4 weeks in (A) PE double pouches or (B) Activ-Vials® at 25 °C/60%rH.

humidity content of the samples was observed (see Table 5). The reason for this is an active drying of the pellets, as the polymeric desiccant sleeve does not only absorb the water from the surrounding air inside the container, but also from the sample itself. It was demonstrated that an increase of the humidity content of the extrudate does indeed have an influence on the release behavior of the solid dispersion formulation as no drop of the release profile was observed with the sample stored under humidity protection (see Fig. 8B).

It was thus successfully demonstrated that a worsening of the dissolution profile with increased storage times can be avoided by an optimization of the packaging material. An additional impact of other storage effects on the release profile, for example recrystallization of the drug or polymer aging, cannot be excluded.

3.4. Particle size analysis of fenofibrate

The mean particle size of fenofibrate prior to HME was determined to be 230 µm. The melting temperature of fenofibrate was analyzed with DSC: T_m = 82 °C. As the HME process temperatures are clearly above this melting temperature for all formulations (see Table 2), the API is molten during the manufacturing process and the particle size of the pure drug is, therefore, deemed irrelevant.

4. Conclusion

By employing additional polymers with differing physicochemical characteristics to a drug–polymer mixture before extrusion, the dissolution profile can be influenced. If the release data of the drug with the respective polymers as single polymeric carriers are known beforehand, predictions on the dissolution behavior of extrudates with multiple polymeric carriers can be made as the dissolution curves were shown to lie intermediate between the individual results. To ensure a sufficient supersaturation, which is stable during storage time, further research will have to be conducted. Also, in vivo studies are desirable to verify the concept and the relevancy of the results in vivo. Even so, the data shown in this work are promising as the release behavior of the manufactured extrudates can be easily modified and offer the possibility to readily adapt the release profile of a solid oral dosage form to one's needs.

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