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Influence of Molecular Weight of Carriers and Processing Parameters on the Extrudability, Drug Release, and Stability of Fenofibrate Formulations Processed by Hot-Melt Extrusion

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Abstract

The objective of this study was to investigate the extrudability, drug release, and stability of fenofibrate (FF) formulations utilizing various hot-melt extrusion processing parameters and polyvinylpyrrolidone (PVP) polymers of various molecular weights. The different PVP grades selected for this study were Kollidon[®] 12 PF (K12), Kollidon[®] 30 (K30), and Kollidon[®] 90 F (K90). FF was extruded with these polymers at three drug loadings (15%, 25%, and 35% w/w). Additionally, for FF combined with each of the successfully extruded PVP grades (K12 and K30), the effects of two levels of processing parameters for screw design, screw speed, and barrel temperature were assessed. It was found that the FF with (K90) was not extrudable up to 35% drug loading. With low drug loading, the polymer viscosity significantly influenced the release of FF. The crystallinity remaining was vital in the highest drug-loaded formulation dissolution profile, and the glass transition temperature of the polymer significantly affected its stability. Modifying the screw configuration resulted in more than 95% post-extrusion drug content of the FF–K30 formulations. In contrast to FF–K30 formulations, FF release and stability with K12 were significantly influenced by the extrusion temperature and screw speed.

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Graphical Abstract

Keywords

Fenofibrate; PVP grades; processing parameters; hot-melt extrusion; stability

1. Introduction

Hot-melt extrusion (HME) is a continuous, solvent free, and cost-effective method, which makes it a viable processing technology for use in the pharmaceutical industry [1]. One of the most common applications of HME processing is enhancing the solubility of poorly water soluble active pharmaceutical ingredients (APIs) via the preparation of amorphous solid dispersions in numerous polymeric carriers [2–4]. Crystalline APIs are commonly changed to the amorphous phase by the high shear conditions and temperature typically employed in the extrusion process. This generally results in increased solubility of poorly water soluble APIs, particularly in the case of biopharmaceutics classification system (BCS) class II compounds, and subsequently improves their bioavailability [1, 2]. However, the high energy input from the applied shear forces and elevated temperature could lead to drug instability [5, 6]. Therefore, researchers have investigated these stability issues by using carefully selected carriers and processing parameters [7, 8].

The primary processing parameters for HME are barrel temperature, screw speed, feeding rate, and screw design [1]. The extrusion temperature influences the melt viscosity of the material and the extrusion process. Screw speed is also one of the factors that affects the dispersion and the residence time of the material within the barrel [9]. The screws themselves can be configured into various designs by changing the number, orientation, and order of the kneading and conveying elements, as well as altering the overall screw length. These processing parameters play a vital role in the extrusion process and should be chosen based on the physiochemical properties of the API and the carrier, as well as the desired outcome [2].

In this study, various grades of polyvinylpyrrolidone (PVP), commonly referred as povidone, were used as the polymeric carriers. PVP is water soluble and is primarily used for immediate release formulations [9]. Additionally, PVP has been observed to function as

a recrystallization inhibitor [10, 11]. The various grades of PVP are typically characterized by their molecular weight and glass transition temperatures (T_g). For example, Kollidon® 12 PF (K 12), Kollidon® 30 (K 30), and Kollidon® 90 F (K 90) possess average molecular weights of approximately 2500, 50000, and 1250000 g/mol, and T_g s of 90°C, 149°C, and 156°C, respectively [9]. These grades of PVP can be utilized to study the effect of polymer molecular weight on the extrudability, *in vitro* drug release, and stability of an API when processed by HME.

Fenofibrate (FF) is used as an antilipidemic agent for decreasing cholesterol and triglyceride levels in the blood. It is a BCS class II drug, which indicates poor solubility and high permeability. It can be considered as a melt-extrudable API [10, 12] with a melting point of 80.5°C and a low T_g of -20°C [13, 14]. FF can be easily processed by melt extrusion; however, it subsequently exhibits rapid recrystallization behaviors due to its low T_g [10]. Therefore, FF is a good candidate for the investigation of the effects of the molecular weight of the carrier, extrusion processing parameters, and drug loading.

The objective of this study was to investigate the effects of different molecular weights of polymeric carriers and processing parameters on the extrudability, *in vitro* drug release, and stability of FF utilizing HME technology. K12, K30, and K90 were used as the polymeric carriers with three different drug loadings of 15%, 25%, and 35% (w/w) to study the effect of the molecular weight of the carrier. Additionally, design of experiments was utilized to assess the effects of the processing parameters on the extrudability, *in vitro* drug release, and stability of the FF-PVP matrices based on the molecular weight of PVP used.

2. Materials and methods

2.1. Materials

The various grades of PVP (K12, K30, and K90) were generously donated by BASF SE (Ludwigshafen, Germany). FF was obtained from Ria International (East Hanover, NJ, USA). All other reagents used in this study were of analytical grade.

2.2. Methods

2.2.1 Thermogravimetric analysis—A Perkin Elmer Pyris 1 TGA (PerkinElmer Life and Analytical Sciences, CT, USA) was used to conduct the thermogravimetric analysis (TGA). The drug and polymer samples (3–4 mg) were heated over a temperature range of 30–200°C at a heating rate of 20°C/min. The data were analyzed using Pyris manager software (PerkinElmer Life and Analytical Sciences, CT, USA).

2.2.2. Differential scanning calorimetry—A Perkin Elmer Diamond DSC (PerkinElmer Life and Analytical Sciences, CT, USA) was utilized to study the formation of solid dispersions as well as to calculate the percent crystallinity. The drug and polymer samples (3–5 mg) were hermetically sealed in an aluminum pan and analyzed at a heating rate of 10°C/min under an inert nitrogen atmosphere at a flow rate of 20 ml/min over a temperature range of 30–200°C. The data was analyzed using Pyris manager software.

The percentage crystallinity was calculated using the following formula [10]:

$$\text{Crystallinity \%} = [\Delta H_{\text{extrudate}} / (\Delta H_{\text{fenofibrate}} \times w\%)] \times 100$$

where $w\%$ is concentration of the drug in the extrudates ($\% w/w$), and $H_{\text{fenofibrate}}$ is 90 J/g.

2.2.3. HPLC analysis—The dissolution study and the drug content samples were analyzed using a Waters HPLC-UV system (Waters Corp., Milford, MA, USA) with a Phenomenex Luna® RP C18 (250 × 4.6 mm, 5 μm) column and a detection wavelength of 286 nm. The mobile phase was acetonitrile:water:trifluoroacetic acid at a ratio of 700:300:1 (v:v:v) [15]. The flow rate was 1 ml/min and the injection volume was 20 μL . All of the HPLC data were analyzed using Empower V software (Milford, MA, USA).

2.2.4. Hot-melt extrusion—Three different drug loadings (15, 25, and 35% w/w) of FF with three grades of PVP (K 12, K 30, and K 90) were blended in a small V-blender prior to extrusion using a batch size of around 50 gm for each formulation. The blends were melt extruded at the temperatures and screw speeds shown in Table 1. The processing temperatures were selected based on the T_g of each polymer and the plasticizing effect of FF in order to obtain well-solidified extrudates. The screw speed and the feeding rate were adjusted to keep the torque below 70%.

To study the effect of the processing parameters, FF at a drug load of 25% (w/w) was mixed with K12 and K30 individually, and then extruded using a standard and a modified screw design (Figure 1) utilizing the processing parameters shown in Table 2 (FF–K12) and Table 3 (FF–K30). The drug and individual polymers were sieved through an USP #35 mesh to remove any agglomerates and then mixed using a V-Shell blender (MaxiBlend™, GlobePharma, North Brunswick, NJ, USA) for 10 min at 25 rpm. A co-rotating twin-screw extruder (11 mm Process 11, Thermo Fisher Scientific, Pittsburgh, PA, USA) was used for the extrusion process. The drug content uniformity of the physical mixtures and extrudates was analyzed using HPLC. The drug content analysis was evaluated by dissolving an accurate amount of FF from the extrudates or the physical mixtures in 20 ml of acetonitrile, then 1 ml was transferred to another bottle and diluted with 9 ml of acetonitrile. Samples were taken from the diluted solution and centrifuged followed by the analysis using the HPLC. The drug content analysis was performed using six replicates from different position of the extrudates or the physical mixture.

2.2.5. In vitro dissolution studies—The dissolution studies were conducted using a USP type II dissolution apparatus. An amount equivalent to 54 mg of FF was filled into capsules and the capsules were then placed in the dissolution medium within the apparatus for 2 hours. The dissolution studies were performed under sink conditions and the medium was 0.025 M sodium lauryl sulfate (SLS) in 1000 ml of water maintained at $37 \pm 0.5^\circ\text{C}$ and the paddle rotation speed was 75 rpm [16]. At various time points, the samples were withdrawn and an equal amount of fresh medium was added to the ongoing dissolution medium vessel. The % of the drug release was calculated based on the actual post-processing drug content. HPLC was used to analyze the samples and the % of drug release vs. time (min) profile was plotted. The dissolution studies were performed in triplicate.

The similarity factor (f_2) was used to compare dissolution profiles using the following equation [17]:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where:

R_t = percentage of drug dissolved at each time point for the reference;

T_t = percentage of drug dissolved at each time point for the test; and

n = number of dissolution sampling times.

If $f_2 \geq 50$, then the dissolution profiles are to be considered similar.

2.2.6. Scanning electron microscopy—A scanning electron microscope (SEM, JEOL JSM-5600) was utilized to examine the surface morphology of the samples. Samples were mounted on adhesive carbon pads placed on aluminum stubs. The sputter coating of the samples with gold was carried out using a Hummer® 6.2 Sputter System (Anatech Ltd, Springfield, VA). The SEM was operated at an accelerating voltage of 10 kV.

2.2.7. Stability studies—The extrudates were stored in closed glass vials to investigate their physical stability at 40°C/75% relative humidity (RH) for 3 months. Differential scanning calorimetry studies were utilized to determine the crystallinity of FF at 0 and 3 months.

2.2.8. Statistical analysis—Repeated measures two-way ANOVA and Sidak's multiple comparisons test were used to study the statistical significance of the release profiles. For the recrystallization significance analysis, the t-test was used. The data were analyzed using GraphPad Prism version 6.00 (GraphPad Software, La Jolla, California, USA).

3. Results and discussion

3.1. Effect of molecular weight

3.1.1. Extrudability—Most of the formulations were successfully extruded under the employed temperatures and screw speeds (Table 1); however, F3, F6, and F9 could not be extruded. As there was no evidence of degradation at the selected extrusion temperatures based on the preliminary TGA studies (data not shown), the non-extrudability of these formulations (F3, F6, and F9) was attributed to the fact that the binary mixture contain a significant portion (65–85%) of high molecular weight K90, which produced excessively high torque during processing. The extrudates that were successfully extruded were optically transparent when using low drug loadings with low molecular weight carriers, and became increasingly opaque with increasing drug loads and polymer viscosity. The successfully extruded formulations (F1, F2, F4, F5, F7, and F8) were selected for further study to investigate the effect of the molecular weight of PVP on the *in vitro* drug release and stability of FF.

3.1.2. Differential scanning calorimetry—The differential scanning calorimetry (DSC) studies (Figure 2) demonstrated that FF exhibited a melting endotherm at approximately 80.5°C; however, the corresponding drug melting peak was absent in the extrudates with drug loads of 15% (F1 and F2) and 25% (F4 and F5), which confirmed the existence of an amorphous form of FF within the PVP matrices. When the FF loading was increased to 35%, the miscibility between FF and each polymer decreased, and the extrusion temperature played a vital role in the dispersion of FF in the polymeric matrix. Using low extrusion temperatures (90–100°C) with FF–K12 (F7) was insufficient to dissolve the API in the polymer, while applying higher temperatures (120–130°C) to the solid dispersion decreased the percentage crystallinity of FF (F8). It was concluded that the applied processing temperature influenced the dispersion of the API in the carrier for the high drug-loaded formulations, based on the molecular weight of the PVP.

3.1.3. In vitro release—The formation of an amorphous solid dispersion tends to improve the release of poorly water soluble APIs and its characteristics are affected by multiple factors, such as drug loading and the viscosity of the carrier. In the case of low drug loadings (15% and 25%), FF is completely converted to the amorphous phase after extrusion and its release was influenced by the viscosity of the polymers. Generally, the dissolution rate decreases with an increase in the viscosity of the polymer, as reported earlier [18], and this was clearly observed for these formulations (F1, F2, F4, and F5), as shown in Figure 3. The release of 15% FF–K12 (F1) is significantly ($f_2 < 50$ and $p < 0.05$) higher than 15% FF–K30 (F2). Additionally, the release of 25% FF–K12 (F4) is higher than that of 25% FF–K30 (F5) and the difference is statistically significant ($f_2 < 50$ and $p < 0.05$), as shown in Table 4. In the 15% drug loaded formulations, the extrusion temperatures for F1 and F2 are considerably different; however, the temperatures required become highly comparable when the drug load is increased to 25% (F4 and F5). Since the extrusion temperature influences the formation of a molecular dispersion [19], the similarity factor (f_2) between the release profiles of the extrudates with 25% drug loading (F4 and F5) ($f_2 = 42$) is higher than with 15% drug loading (F1 and F2) ($f_2 = 29$), which may be caused by the differences in the extrusion temperatures in the case of each level of drug loading.

When the amount of PVP decreased and the drug load of FF increased to 35%, the effect of the molecular weight of PVP was not significant ($f_2 \geq 50$ and $p > 0.05$), and the remaining FF percent crystallinity begins to play a role in the release profile (Table 4). Due to the relatively lower level of crystallinity of the fresh extrudates (Figure 4), the FF release was increased for FF–K30 (F8) as compared to that of FF–K12 (F7), which has a higher degree of FF crystallinity remaining (Figure 3). The two phases in the dissolution profile of F7 might be the result of the presence of an amorphous portion of FF, which rapidly dissolves, whereas the crystalline portion dissolves slowly.

3.1.4. Stability—As reported earlier, all PVP powders are stable and act as stabilizing agents [18]. The different physical properties of Kollidon® grades (such as T_g) have an influence on the stability of the dosage form. The stability studies (Figure 4) indicated an effect of the molecular weight of PVP on the stability of FF under accelerated stability conditions (40°C/75% RH). This effect was not significant ($p > 0.05$) at 15% drug load as

the polymer and API are miscible at this drug load (Table 4). When the drug loading was increased to 35%, the effect of the polymer T_g on the recrystallization of FF was vital. The molecular mobility was decreased when a high T_g polymer was utilized, which is due to the increased T_g of the mixture [20, 21]. From Figure 4 and Table 4, the percentage of crystallinity after 3 months' storage for FF-K30 (F8) is significantly ($p < 0.05$) lower than that for FF-K12 (F7), which is indirectly proportional to the T_g of the polymers.

The morphological changes after 3 months storage, relative to fresh extrudates, were investigated by SEM. The 35% FF-K12 formulation (F7) indicated the crystalline phase of FF (Figure 5A). In the case of FF-K30 (F8), the SEM images indicated that there was no significant difference between the extrudate before and after three months of storage, which implies the low percentage of recrystallization of FF with K30 in comparison to the other grade (Figure 5B).

From these results, it is concluded that the extrudability of FF was affected by the molecular weight of PVP. Additionally, the release of FF in each grade of PVP was affected by the viscosity of the polymers in the low drug-loaded formulations and the percentage of crystallinity remaining in the higher drug-loaded formulations. The T_g of the polymer played a significant role in recrystallization at higher drug loading. K12 seemed to be the best carrier for the 15% drug load in terms of the rate of drug release and physical stability, while K30 exhibited better drug release and stability in the 35% drug-loaded formulations. Interestingly, 25% drug loading seemed to be a tipping point with respect to both the release profile and the percentage of recrystallization. Based on this finding, 25% drug loading with the successfully extruded PVP grades (K12 and K30) was chosen for further studies to investigate the effect of the processing parameters on the extrudability, *in vitro* drug release, and stability of these formulations.

3.2. Effect of processing parameters

3.2.1. Extrudability—The processing parameters influenced the outcomes of the HME process, and these outcomes varied with the physicochemical properties of the polymers. Using high molecular weight PVP (K30), which has a relatively high T_g and viscosity, required significantly different processing parameters than the low molecular weight (K12), which has low T_g and low viscosity. The processing parameters that were chosen for FF-K12 (Table 2) and FF-K30 (Table 3) directly affected their extrudability. From the DSC analysis of the physical mixtures (data not shown), FF at 25% drug load is immiscible with both grades of PVP (K12 and K30). The immiscibility can affect the post-processing drug content [10]. Altering the processing parameters and the screw design may reduce the effect of immiscibility on the post-processing drug content and uniformity by influencing the mixing and distribution of the drug within the matrix. Increasing the screw speed increases the level of dispersion [9]. In addition, the length of the screw influences the residence time. For the FF-K12 formulations, most of the formulations (P1, P2, P3, P4, P6, P7, and P8) have an acceptable drug content (Figure 6). However, the combination of these factors (modified screw design, low extrusion temperature, and low screw speed) that were used to prepare formulation P5 reduced its post-processing drug content. This may be because the melting point of the drug (80.5°C) and the T_g of K12 (90°C) are close, and the processing

parameters for this formulation did not impart enough shearing force to disperse the API in the molten polymer. This is attributed, in part, to the decreased residence time resulting from the modified screw design.

In the FF–K30 formulations, the difference between the melting point of the drug and the T_g of the polymer (149°C), as well as the viscosities, is relatively large. The de-mixing might occur because they were immiscible. In addition to the de-mixing, increasing the extrusion temperature decreases the melt viscosity of the drug and allowed part of the drug to exit the die in a liquid form faster than that of the polymer making it difficult to collect. This ultimately resulted in a poor post processing drug content of the formulations H3 and H4 (Figure 7). This effect was attributed, in part, by the length of the standard screw configuration, which is longer overall. On the other hand, using low extrusion temperatures and/or decreasing the length in the modified screw design decreased the chance of the phase separation within the barrel and improved the post-processing drug content. The screw speed had no significant effect on the extrudability of FF–K30 formulations, as it exhibited no improvement in the post-processing drug content when the screw speed was changed from 70 rpm (H3) to 100 rpm (H4) (Figure 7). The extrudability results showed that the standard screw design is useful for extruding the low melting point API (FF) with low T_g polymer (K12), and the results were not affected by changing the barrel temperature and/or screw speed. On the other hand, modifying the screw design is favorable for avoiding any loss of post-processing drug content, especially when increasing the barrel temperature for the processing of FF with the high T_g polymer (K30). Based on these findings, the FF–K12 formulations that were prepared using the standard screw design (P1, P2, P3, and P4), and the FF–K30 formulations that were processed using the modified design (H5, H6, H7, and H8) were selected for further studies on the effect of the processing parameters (barrel temperature and screw speed) on the release and stability of FF based on the PVP grade utilized in the formulation.

3.2.2. DSC studies—DSC studies exhibited the absence of the crystalline peak of FF in all of the fresh FF–K30 and FF–K12 extrudates that were selected for additional studies. The absence of the peak indicates the amorphous nature of FF in these matrices, which confirms that the applied processing parameters were able to convert FF from its crystalline form to its amorphous form. The DSC curves for FF–K12 and FF–K30 are shown in Figure 8 and 9, respectively.

3.2.3. In vitro release and stability

3.2.3.1. Effect of barrel temperature: The extrusion temperature influences the molecular dispersion [19] and this effect was vital for the release and stability of FF. Because the melting point of the drug (80.5°C) and the T_g of the K12 (90°C) are close, applying high extrusion temperatures is sufficient to disperse the drug in the molten polymer and results in enhanced release when compared to low extrusion temperatures. The effect of barrel temperature on the release profile of FF–K12 was in the following order: P3 (110°C, 100 rpm) > P1 (90°C, 100 rpm) and P4 (110°C, 130 rpm) > P2 (90°C, 130 rpm), as shown in Figure 10. Regarding the stability of the FF–K12 formulations, applying extrusion temperatures higher than the T_g of the polymer positively affects their stability at both screw

speeds (Figure 11). Statistically, the *in vitro* release profile and the stability of the FF–K12 formulations that were processed at different extrusion temperatures [P4 (110°C) and P2 (90°C)] are only significantly different ($f_2 < 50$ and $p < 0.05$) when the high screw speed (130 rpm) was utilized (Table 5, comparison no. II). This is because the high level of dispersion, which was caused by high shearing as a result of the synergistic effect of increasing the barrel temperature and the screw speed. However, losing the supportive influence of the high screw speed on the shearing and dispersion leads to the non-significant effect of the extrusion temperature on the formulations that were processed at a low screw speed (100 rpm) using different extrusion temperatures [P3 (110°C) and P1 (90°C), Table 5, comparison no. I].

In the case of FF–K30 formulations, owing to the positive influence of the high T_g of the polymer (K30) on the stability, and the elevated extrusion temperatures required to process this polymer, the *in vitro* drug release and the stability (Figure 12 and 13) were not significantly affected by changing the barrel temperature ($f_2 > 50$ and $p > 0.05$) because both of the selected extrusion temperatures (130°C and 150°C) were high enough to make a homogenous solid dispersion (Table 6, comparison no. I and II).

It is concluded that formulations using a low molecular weight PVP (K12) with FF are influenced by the change in the processing temperature, and this influence becomes significant when the formulations are processed at high screw speed. However, formulations using high molecular weight PVP (K30) are not sensitive to the altered changes in the extrusion temperature as it has more stabilization effect and should be processed at a high temperature based on its T_g .

3.2.3.2. Effect of screw speed: It was observed that applying a low screw speed (100 rpm) for the FF–K12 formulation (P1) increased its residence time in the barrel and improved its dispersion, which further enhanced its release and stability as compared to formulation P2 (130 rpm), as shown in Figures 10 and 11. This effect was significant ($f_2 < 50$ and $p < 0.05$) because the applied barrel temperature for P1 and P2 was low (90°C) and not enough to disperse the FF in the matrix (Table 5, comparison no. III). In contrast, using a higher extrusion temperature (110°C) for formulations P3 (100 rpm) and P4 (130 rpm) played an important role in the dispersion of FF in the matrix and was not significantly affected ($f_2 > 50$ and $p > 0.05$) by the screw speed (Table 5, comparison no. IV). This insignificant effect of the screw speed on the release and stability of FF was also observed when using a high molecular weight PVP (K30), because the temperatures that were used for the FF–K30 formulations (130°C and 150°C) were high enough to influence the dispersion regardless of the screw speed (Table 6, comparison no. III and IV), as shown in Figures 12 and 13. It is concluded that the residence time of the formulations, which is a result of the screw speed, played a significant role when the extrusion temperature was not enough to make a homogenous dispersion for the FF–K12 matrix. On the other hand, the high extrusion temperatures required to process the high molecular weight PVP (K30) abolished the significant role of the screw speed on the release and stability of FF.

4. Conclusions

The molecular weight of Kollidon® influenced the extrudability, dissolution profile, and stability of FF, and these were significantly affected by the drug load and the processing parameters. FF can be extruded with K12 or K30, however, it was difficult to be extruded when the higher molecular weight (K90) was used as a polymeric carrier. The polymer's viscosity and the remaining crystallinity influenced the release of the API, while, the stability of the drug was affected by the T_g of the polymer. The modified screw design resulted in increased drug content in the case of FF–K30 formulations when compared to the standard design. Both temperature and screw speed significantly influenced the release and recrystallization behavior of the FF–K12 formulations, while, the release and the stability of FF–K30 formulations were not significantly affected by changing these parameters. The Kollidon® polymers, with their significantly different T_g s, are promising carriers for FF, and the processing parameters can be adjusted to achieve the desired extrudability, release, and stability of FF.

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Figure 1.
Images of A) standard screw design and B) modified screw design.

Figure 2. Differential scanning calorimetry curves of F1 (15% FF-K12), F2 (15% FF-K30), F4 (25% FF-K12), F5 (25% FF-K30), F7 (35% FF-K12), F8 (35% FF-K30) and pure FF. FF: fenofibrate, K12: Kollidon® 12 PF, K30: Kollidon® 30.

Figure 3. Dissolution profiles of F1 (15% FF-K12), F2 (15% FF-K30), F4 (25% FF-K12), F5 (25% FF-K30), F7 (35% FF-K12), and F8 (35% FF-K30) to study the effect of molecular weight of polyvinylpyrrolidone on the release of FF. FF: fenofibrate, K12: Kollidon® 12 PF, K30: Kollidon® 30.

Figure 4. Percentage crystallinity for the fresh extrudates and after 3 months storage for the formulations F1 (15% FF-K12), F2 (15% FF-K30), F4 (25% FF-K12), F5 (25% FF-K30), F7 (35% FF-K12), and F8 (35% FF-K30). FF: fenofibrate, K12: Kollidon® 12 PF, K30: Kollidon® 30.

A) 35% FF-K12 (F7)

B) 35% FF-K30 (F8)

Figure 5. Scanning electron microscopy images of fresh extrudates and after 3 months storage of A) F7 (35% FF-K12) and B) F8 (35% FF-K30). The images on the left side are for the fresh extrudates, and the images on the right side are for the extrudates after 3 months storage. FF: fenofibrate, K12: Kollidon® 12 PF, K30: Kollidon® 30.

Figure 6.

Post-processing drug content for 25% FF-K12 formulations prepared using different processing parameters. P1 (SSD, 90°C, 100 rpm), P2 (SSD, 90°C, 130 rpm), P3 (SSD, 110°C, 100 rpm), P4 (SSD, 110°C, 130 rpm), P5 (MSD, 90°C, 100 rpm), P6 (MSD, 90°C, 130 rpm), P7 (MSD, 110°C, 100 rpm), and P8 (MSD, 110°C, 130 rpm). SSD: standard screw design, MSD: modified screw design. FF: fenofibrate, K12: Kollidon[®] 12 PF.

Figure 7.

Post-processing drug content for 25% FF-K30 formulations prepared using different processing parameters. H1 (SSD, 130°C, 70 rpm), H2 (SSD, 130°C, 100 rpm), H3 (SSD, 150°C, 70 rpm), H4 (SSD, 150°C, 100 rpm), H5 (MSD, 130°C, 70 rpm), H6 (MSD, 130°C, 100 rpm), H7 (MSD, 150°C, 70 rpm), and H8 (MSD, 150°C, 100 rpm). SSD: standard screw design, MSD: modified screw design, FF: fenofibrate, K30: Kollidon® 30.

Figure 8.

Differential scanning calorimetry curves of 25% FF–K12 formulations prepared using different processing parameters. P1 (SSD, 90°C, 100 rpm), P2 (SSD, 90°C, 130 rpm), P3 (SSD, 110°C, 100 rpm), and P4 (SSD, 110°C, 130 rpm). SSD: standard screw design, FF: fenofibrate, K12: Kollidon® 12 PF.

Figure 9. Differential scanning calorimetry curves of 25% FF–K30 formulations prepared using different processing parameters. H5 (MSD, 130°C, 70 rpm), H6 (MSD, 130°C, 100 rpm), H7 (MSD, 150°C, 70 rpm), and H8 (MSD, 150°C, 100 rpm). MSD: modified screw design, FF: fenofibrate, K30: Kollidon® 30.

Figure 10.

Dissolution profiles of 25% FF-K12 formulations prepared using different processing parameters. P1 (SSD, 90°C, 100 rpm), P2 (SSD, 90°C, 130 rpm), P3 (SSD, 110°C, 100 rpm), and P4 (SSD, 110°C, 130 rpm). SSD standard screw design, FF: fenofibrate, K12: Kollidon® 12 PF.

Figure 11.

Percentage crystallinity of 25% FF-K12 formulations prepared using different processing parameters after 3 months storage and the fresh extrudates. P1 (SSD, 90°C, 100 rpm), P2 (SSD, 90°C, 130 rpm), P3 (SSD, 110°C, 100 rpm), and P4 (SSD, 110°C, 130 rpm). SSD: standard screw design, FF: fenofibrate, K12: Kollidon® 12 PF.

Figure 12. Dissolution profiles of 25% FF-K30 formulations prepared using different processing parameters. H5 (MSD, 130°C, 70 rpm), H6 (MSD, 130°C, 100 rpm), H7 (MSD, 150°C, 70 rpm), and H8 (MSD, 150°C, 100 rpm). MSD: modified screw design. FF: fenofibrate, K30: Kollidon® 30.

Figure 13.

Percentage crystallinity of 25% FF–K30 formulations prepared using different processing parameters after 3 months storage and the fresh extrudates. H5 (MSD, 130°C, 70 rpm), H6 (MSD, 130°C, 100 rpm), H7 (MSD, 150°C, 70 rpm), and H8 (MSD, 150°C, 100 rpm).

MSD: modified screw design, FF: fenofibrate, K30: Kollidon® 30.

Table 1

Formulation design and processing conditions used to study the effect of molecular weight of polyvinylpyrrolidone with different fenofibrate loadings.

Formulation	Fenofibrate (% w/w)	Kollidon ® grade	Processing parameters	
			Temperature (°C)	Screw speed (rpm)
F1	15	Kollidon ® 12 PF	100–110	100
F2	15	Kollidon ® 30	135–145	70
F3	15	Kollidon ® 90 F	165–175	40
F4	25	Kollidon ® 12 PF	100–110	130
F5	25	Kollidon ® 30	120–130	70
F6	25	Kollidon ® 90 F	160–170	50
F7	35	Kollidon ® 12 PF	90–100	135
F8	35	Kollidon ® 30	120–130	100
F9	35	Kollidon ® 90 F	145–155	70

Table 2

Experimental design to study the effect of processing parameters (screw design, extrusion temperature, and screw speed) on the 25% fenofibrate-Kollidon® 12 PF.

Formulation	Screw design	Extrusion temperature (°C)	Screw speed (rpm)
P1	Standard	90	100
P2	Standard	90	130
P3	Standard	110	100
P4	Standard	110	130
P5	Modified	90	100
P6	Modified	90	130
P7	Modified	110	100
P8	Modified	110	130

Table 3

Experimental design to study the effect of processing parameters (screw design, extrusion temperature, and screw speed) on the 25% fenofibrate-Kollidon® 30.

Formulation	Screw design	Extrusion temperature (°C)	Screw speed (rpm)
H1	Standard	130	70
H2	Standard	130	100
H3	Standard	150	70
H4	Standard	150	100
H5	Modified	130	70
H6	Modified	130	100
H7	Modified	150	70
H8	Modified	150	100

Table 4

Statistical analysis of the effect of the molecular weight of polyvinylpyrrolidone on the release and stability of FF for each % drug loading.

FF drug load %	Formulations		Drug release (fresh extrudate)		Recrystallization (3 months storage)	
	FF-K12 (Reference)	FF-K30 (Test)	f_2	p-value		p-value
15	F1	F2	29	0.0145 *		0.0917 ^{ns}
25	F4	F5	42	0.0235 *		0.4964 ^{ns}
35	F7	F8	50	0.1642 ^{ns}		0.0085 *

Significant (*): $p < 0.05$, not significant (ns): $p > 0.05$, FF: fenofibrate, K12: Kollidon® 12 PF, K30: Kollidon® 30.

Statistical analysis of the effect of processing parameters (extrusion temperature and screw speed) on the release and stability of FF on the 25% FF-K12. P1 (SSD, 90°C, 100 rpm), P2 (SSD, 90°C, 130 rpm), P3 (SSD, 110°C, 100 rpm), and P4 (SSD, 110°C, 130 rpm). SSD: standard screw design.

Table 5

Comparison No.	Constant parameter	Variable parameter (formulation code)		Drug release (fresh extrudate)		Recrystallization (3 months storage) p-value
		Reference	Test	f_2	p-value	
I ↗	100 rpm	90°C (P1)	110°C (P3)	60	0.1340 ^{ns}	0.0725 ^{ns}
	130 rpm	90°C (P2)	110°C (P4)	35	0.0055 *	0.0018 *
	90°C	100 rpm (P1)	130 rpm (P2)	49	0.0168 *	0.0080 *
IV	110°C	100 rpm (P3)	130 rpm (P4)	71	0.4297 ^{ns}	0.0518 ^{ns}

Significant (*): $p < 0.05$, not significant (ns): $p > 0.05$, FF: fenofibrate, K12: Kollidon® 12 PF.

Table 6

Statistical analysis of the effect of processing parameters (extrusion temperature, and screw speed) on the release and stability of FF for the 25% FF–K30. H5 (MSD, 130°C, 70 rpm), H6 (MSD, 130°C, 100 rpm), H7 (MSD, 150°C, 70 rpm), and H8 (MSD, 150°C, 100 rpm). MSD: modified screw design.

Comparison No.	Constant parameter	Variable parameter (formulation code)		Drug release (fresh extrudate)		Recrystallization (3 months storage) p-value
		Reference	Test	f_2	p-value	
I	70 rpm	130°C (H5)	150°C (H7)	60	0.4488 ^{ns}	0.2448 ^{ns}
	100 rpm	130°C (H6)	150°C (H8)	61	0.6805 ^{ns}	0.1321 ^{ns}
III	130°C	70 rpm (H5)	100 rpm (H6)	54	0.8109 ^{ns}	0.3120 ^{ns}
IV	150°C	70 rpm (H7)	100 rpm (H8)	57	0.5153 ^{ns}	0.6129 ^{ns}

Significant (*): $p < 0.05$, not significant (ns): $p > 0.05$, FF: fenofibrate, K30: Kollidon® 30.