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Stability and intrinsic dissolution of vacuum compression molded amorphous solid dispersions of efavirenz

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ABSTRACT

In this study, the stability and intrinsic dissolution of vacuum compression molded (VCM) amorphous solid dispersions (ASDs) of efavirenz (EFV) were investigated in relation to its solubility limits in seven polymers determined by the melting point depression (MPD) method. The extrapolated solubility limits of EFV at 22 °C ranged from 3 to 68% (w/w) with PVOH being the only polymer suggesting immiscibility with EFV according to both MPD and Hansen solubility parameters (HSPs). All ASDs with EFV loadings below or close to their calculated solubility limit did not show any signs of crystallization upon conditioning for 7 months at either 22 or 37 °C and 23 or 75% relative humidity. However, all ASDs with EFV loading above the solubility limit crystallized at high humidity, while the ASDs with cellulose derived carrier polymers proved kinetically stable at low humidity over 7 months. While the EFV intrinsic dissolution rates from the VCM ASDs were partly depending on the polymer dissolution rate, no correlation was observed between EFV matrix crystallization and its miscibility in the polymer. Altogether, the observations of the study underline the importance of combining preformulation miscibility determination and dissolution studies to rationally decide on both stability and viability of ASD formulations.

1. Introduction

With an increasing number of new chemical entities being classified as class II or IV drugs in the biopharmaceutics classification system (BCS), there is a growing demand for formulation strategies aimed at improving aqueous solubility and/or dissolution rate. While salt formation or lipid based formulations might sometimes be preferable, several strategies are based on the concept of eliminating the strong intermolecular interactions of the drug crystal lattice by conversion to its amorphous form (Williams et al., 2013). However, the advantageous dissolution and apparent solubility profile of an amorphous drug will eventually diminish upon storage due to its inherent thermodynamic instability eventually causing the drug to recrystallize. For this reason, amorphous dosage forms are often stabilized as amorphous solid dispersions (ASDs) in which the drug is molecularly dispersed in a water-soluble polymeric matrix (Newman et al., 2012; Andreas Schittrny et al., 2020). As amorphous kinetic stability improves with decreasing molecular mobility, polymers with high glass transition temperature (Tg) have been of particular interest in the field (Van den Mooter et al., 2001). Yet, a prerequisite for obtaining a thermodynamically stable ASD is to ensure drug-polymer miscibility by avoiding drug loadings above the drug solubility limit in the polymer at the given storage conditions (Qian et al., 2010). Therefore, a rational design of new ASDs often starts by determination of drug-polymer solubility which is often carried out by differential scanning calorimetry (DSC) based methods (Bochmann et al., 2019; Knopp et al., 2015; Marsac et al., 2006; Rask et al., 2018). A stable ASD with a therapeutically relevant drug loading is, however, not guaranteeing a viable formulation. This is due to a relatively complex interplay of mechanisms altogether defining the enabling potential of an ASD formulation upon ingestion. Optimally, dissolution of an ASD...
formulation results in drug supersaturation sufficiently maintained at the site of absorption to promote increased bioavailability. However, drug precipitation and/or matrix phase separation might cancel out the potential increase in bioaccessibility. For this reason, initial polymer screening is also based on their functionality as precipitation inhibitors, i.e. their ability to maintain drug supersaturation (Monschke and Wagner, 2020; Palmelund et al., 2016). Yet, these screening methods do not provide information on the risk of matrix phase separation which potentially could preclude supersaturation in the first place (Yang et al., 2016; J.R. Jørgensen et al., 2021). The water content of EFV and each of the polymers was determined using a Discovery thermogravimetric analyzer (TGA) from TA Instruments Inc. (New Castle, DE, USA). Samples of 5–15 mg were prepared in platinum pans and analyzed in triplicates with a temperature ramp of 10 °C/min from ambient to 300 °C with a nitrogen flow of 50 mL/min. The water content, quantified as the initial weight percent loss, was used in order to prepare powder blends of accurate EFV weight ratios based on dry conditions.

2.2. Thermogravimetric analysis

The water content of EFV and each of the polymers was determined using a Discovery thermogravimetric analyzer (TGA) from TA Instruments Inc. (New Castle, DE, USA). Samples of 5–15 mg were prepared in platinum pans and analyzed in triplicates with a temperature ramp of 10 °C/min from ambient to 300 °C with a nitrogen flow of 50 mL/min. The water content, quantified as the initial weight percent loss, was used in order to prepare powder blends of accurate EFV weight ratios based on dry conditions.

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2.3. Solubility of efavirenz in the polymers

Powder blends (100 mg) of EFV and polymer ranging from 70 to 97% (w/w) EFV were gently mixed with a mortar and pestle. The EFV melting onset temperature was determined in duplicates for pure EFV and each powder blend using a Discovery differential scanning calorimeter (DSC) from TA Instruments Inc. (New Castle, DE, USA). Accurately weighed samples (3–5 mg) in Tzero aluminum pans with pinholed hermetic lids were equilibrated to 20 °C and heated to 150 °C at a heating rate of 1 °C/min. The data were then fitted with the Flory-Huggins model (Equation (1)) to extrapolate the EFV solubility in each polymer at ambient temperature as previously described (Knopp et al., 2015; Marsac et al., 2006; Rask et al., 2018):

\[
\Delta H_m \frac{1}{R} \times \frac{T_m - T}{1} = \ln(\chi_{EFV}) + \left(\frac{1}{k} \times (1 - \chi_{EFV}) + \chi \times (1 - \chi_{EFV})^2 \right)
\]

where, \(\Delta H_m\) and \(T_m\) are the enthalpy of fusion and melting temperature of pure EFV, respectively. \(R\) is the gas constant, and \(\lambda\) is the molar volume fraction of polymer to EFV. \(\chi\) represents the Flory-Huggins interaction parameter and \(T\) is the depressed melting temperature of EFV in a powder blend of a given EFV volume fraction, \(v_{EFV}\), which is calculated as:

\[
v_{EFV} = \frac{X_{EFV}}{\rho_{EFV}} + \frac{1 - X_{EFV}}{\rho_{polymer}}
\]

where, \(X_{EFV}\) is the weight fraction of EFV in the powder blend and \(\rho_{EFV}\) and \(\rho_{polymer}\) are the true densities of EFV and polymer respectively.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>EFV</th>
<th>HPMC</th>
<th>HPMCAS</th>
<th>PVOH</th>
<th>PVPVA64</th>
<th>PCL-PVAc-PEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\delta_a)</td>
<td>18.4</td>
<td>18.7</td>
<td>16.2</td>
<td>15.3</td>
<td>17.8</td>
<td>17.4</td>
</tr>
<tr>
<td>(\delta_p)</td>
<td>8.9</td>
<td>9.8</td>
<td>10.9</td>
<td>15.4</td>
<td>6.9</td>
<td>6.2</td>
</tr>
<tr>
<td>(\delta_h)</td>
<td>5.6</td>
<td>11.6</td>
<td>9.0</td>
<td>16.1</td>
<td>12.4</td>
<td>8.7</td>
</tr>
</tbody>
</table>

* HSPs acquired from HSPiP 5th edition. The values for PVOH are based on a degree of hydrolysis of 88%, thus calculated as: 0.88 × polyvinylpyrrolidone + 0.12 × polyvinylacetate.

* HSPs based on HSPiP of HPMCAS 2910 from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AS-MF from Jankovic et al., 2019. 
  - R = -H, -CH₃ or -CH₂CH₂CH₃OH.
  - R = -H, -CH₃, -OCH₂CH₂CH₃, -COCH₂CH₂CH₃OH, -COCH₂CH₂COOH₂, -CH₂CH₂OH, -COCH₂CH₂COOH₂, -CH₂CH₂OH.

- HSPs based on HSPiP of HPMCAS AS-MF from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AD-WF from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AD-WF from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AD-WF from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AD-WF from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AD-WF from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AD-WF from Jankovic et al., 2019. 

- HSPs based on HSPiP of HPMCAS AD-WF from Jankovic et al., 2019.
2.4. Preparation of amorphous solid dispersions

Powder blends (1 g) of EFV and polymer were mixed in an oscillatory ball Mixer Mill MM400 from Retsch (Haan, Germany) using 25 mL stainless steel jars with two 12 mm stainless steel balls for 5 min at 30 Hz. Each EFV-polymer system was prepared with an EFV loading of 20% (w/w) for both stability- and intrinsic dissolution studies. Moreover, samples for the stability study were prepared with EFV loadings of 20% (w/w) points above the calculated EFV solubility limit in each polymer based on MPD-extrapolation at 22 °C. ASD discs were prepared from the ball-milled powder blends using Vacuum Compression Molding (VCM) from MeltPrep (Graz, Austria) in a sample chamber (ø = 5 mm) covered with glass fiber reinforced polytetrafluoroethylene separation foils. Samples with HPMCAS, PVPVA64 or Soluplus were heated to 160 °C for 5 min, while samples containing HPMC or PVKOH were heated to 180 °C in order to obtain transparent ASDs (Temperature log for one of the sample preparations can be found in the Supporting Information (Figure S1)). ASD discs for stability studies were prepared using 10 mg powder blend while ASD discs for intrinsic dissolution studies were prepared using 30 mg powder blend in order to obtain thicker samples. Samples of each ASD composition were confirmed to be amorphous by X-ray powder diffraction (XRPD) using an X’Pert PRO X-ray powder diffractometer equipped with a PIXcel detector from PANalytical (Almelo, The Netherlands). A VCM disc of each EFV-polymer composition was crushed and flattened on aluminum reflection-spinner sample holders alongside with pure EFV, polymer and each powder blend sampled prior to ball milling. Diffractograms were collected using the X’Pert Data Collector software (version 2.2i) from 5 to 30 °20 using a CuKα radiation source (45 kV, 40 mA, λ = 1.54187 Å) with a step size of 0.026 °20 and a scan speed of 0.067 °20/s.

2.5. Stability studies

Three samples were prepared of each ASD disc and stored at controlled temperature and relative humidity (RH). The conditions were established in desiccators with saturated solutions of either potassium acetate (23% RH) at 22 °C or sodium chloride (75% RH) at either 22 °C or 37 °C. Periodic screening of EFV crystallization was carried out by polarized light microscopy (PLM) using a Leica DM LM microscope equipped with cross polarizers from Leica Microsystems (Wetzlar, Germany). Images were acquired using a Media Cybernetics Evolution MP digital camera and Image-Pro Insight software version 8.0 from Media Cybernetics (Rockville, MD, USA).

2.6. Solubility of crystalline efavirenz in FaSSIF

The equilibrium solubility of EFV was determined in triplicates by adding excess crystalline EFV to freshly prepared FaSSIF under stirring at 37 °C. Samples were taken from the suspension after 2, 24 and 48 h and filtered through an Anopore membrane filter (pore size 0.1 μm) from Whatman-Cyntiva (Marlborough, MA, USA). The filtrate was immediately diluted 1:10 with acetonitrile (ACN) and analyzed by high-performance liquid chromatography (HPLC) on a Dionex Ultimate 3000 system from Thermo Fisher Scientific (Waltham, MA, USA). Injection volumes of 10 μL were separated on a Luna C18 column (150 × 4.6 mm, 5 μm, 100 A) from Phenomenex (Torrance, CA, USA) at 30 °C with a flow rate of 1.0 mL/min of the following ACN gradient (v/v) in H2O: 0–0.5 min (68%), 0.5–5.0 min (68–77%), 5.0–5.5 min (77–68%), 5.5–7.0 min (68%). EFV was quantified as the area under the curve of the 247 nm absorbance peak with a retention time of 4.27 min against a standard curve from 10 to 100 μg/mL with a linearity (R2) > 0.999.

2.7. Intrinsic dissolution

ASD discs of 30 mg with 20% (w/w) EFV were used for intrinsic dissolution studies performed with a microDISS Profiler from Pion Inc. (Billerica, MA, USA). Disc holders with an inner diameter of 8 mm were adjusted for the purpose by inserting pieces of silicone tubing with outer and inner diameters of 8 and 5 mm, respectively. The ASD discs, measuring about 2 mm in height, were inserted into the silicone tubing thus only subjecting the circular surface area of the disc (0.196 cm2) to the dissolution medium, as depicted in Fig. 1.

Miniaturized discs (0.071 cm2) of pure crystalline EFV were prepared as reference with a compression pressure of 70 bar. Freshly prepared FaSSIF (10 mL) was used as dissolution medium with a stirring speed of 100 rpm at 37 °C. EFV quantification was performed using 5 mm probe tips with standard curve from 0 to 300 μg/mL achieved by stepwise addition of a concentrated EFV stock solution in DMSO. Calculations were carried out in the range 303–314 nm using the 2nd derivative function in the Au PRO Software version 5.5.2 by Pion Inc. (Billerica, MA, USA). The intrinsic dissolution rates (IDRs) were calculated based on the concentration profiles as:

\[ IDR = \frac{dc}{dt} \left( \frac{V}{A \cdot \nu_{EFV}} \right) \tag{3} \]

where, \( dc/dt \) is the initial steepest slope of the concentration profile, \( V \) is the dissolution medium volume, \( A \) is the surface area of the disc and \( \nu_{EFV} \) is the EFV volume fraction of the disc, as defined previously (Eq. (2)). Additionally, ASD discs were prepared alongside with discs of each polymer to compare the surface morphology between pure polymer and the corresponding ASD discs both before and after 1 h of intrinsic dissolution in FaSSIF. The discs were coated with a layer of gold using a sputter coater 108auto from Cressington Scientific Instruments (Waltham, UK) and visualized by scanning electron microscopy (SEM) using a TM3030 Tabletop microscope from Hitachi (Tokyo, Japan) with an accelerating voltage of 15 kV.

2.8. Data analysis

Data were processed with Microsoft Excel 2016 (Redmond, WA, USA) and OriginPro 2020 by OriginLab Corp. (Northampton, MA, USA) or GraphPad Prism version 9 (San Diego, CA, USA) with data expressed as the mean ± standard deviation (SD) unless otherwise stated. Thermograms were analyzed using TRIOS version 5.1 software by TA Instruments Inc. (New Castle, DE, USA).

3. Results

3.1. Solubility of efavirenz in the polymers

The water content of EFV and each of the polymers was determined as the initial weight loss observed by TGA and used to calculate the exact EFV loading of the MPD samples at dry conditions. DSC measurements of pure EFV resulted in an onset melting temperature of 138.4 °C and an

![Fig. 1. An amorphous solid dispersion (ASD) disc (ø = 5 mm) placed in a disc holder modified with a piece of silicone tube to allow for intrinsic dissolution studies.](image-url)
enthalpy of fusion of 59.6 J/g. Additional data for calculating the EFV solubility in each polymer are reported in Table 2 by fitting the depressed melting points using the Flory-Huggins model (Equation (1)) as shown in Fig. 2.

The extrapolated solubilities of EFV in the dry polymers at 22 ℃ are listed in Table 2 together with the calculated Flory-Huggins interaction parameter, \( \chi \), and the sum of the absolute differences of HSPs (\( \Delta \text{HSP} \)) between EFV and each polymer.

### 3.2. Stability of amorphous solid dispersions

The TGA of EFV showed a weight loss of less than 1% at 180 ℃ (Figure S1) which was chosen as the highest temperature for preparation of ASD discs. ASDs were prepared with an EFV load of 20% (w/w) and 20% points above the calculated solubility limits in each polymer at 22 ℃, as listed in Table 2. The PVH-based ASD was only prepared with one EFV load (20% w/w) as this corresponded well to 20%-points above the calculated solubility limits within 2 weeks upon storage at 37 ℃ and 75% RH. The identical samples stored at 22 ℃ and 75% RH had likewise crystallized within 3 months. However, no crystals were observed for the HPMC- and HPMCAS-based ASDs with high drug loadings when stored at 22 ℃ and 23% RH, while the high drug loaded PVH, PVPA64 and PCL-PVAc-PEG ASDs crystallized within 2 months. For the PVH-based ASD, none of the ASDs with an EFV load of 20% (w/w) crystallized within the duration of the study (7 months) at any of the three storage conditions. EFV crystals appeared with needle-like morphology in all the kinetically unstable samples as exemplified in Figure S3. Similar needle-like crystals from samples of neat EFV appeared within 1 day, 1 week and 2–3 weeks at (37 ℃, 75%), (22 ℃, 75%) and (22 ℃, 25%), respectively.

### 3.3. Intrinsic dissolution

VCM of 30 mg of each of the EFV-polymer powder blends all resulted in transparent ASDs with a diameter of 5 mm and a height of about 2 mm (Figure S4). The equilibrium solubility of crystalline EFV in FaSSIF was determined to be 214 ± 2 µg/mL, thus the intrinsic dissolution studies of the ASDs were carried out under non-sink conditions as depicted in the dissolution profiles in Fig. 3.

The dissolution studies of the PVH- and HPMCAS-based ASDs were repeated an additional three times (n = 6) as significant variations in the dissolution profiles were observed. While one group (n = 3) resulted in supersaturation after about 2 h, the other group (n = 3) showed significantly slower dissolution despite identical sample preparation and initial visual appearance. While the supersaturating PVH samples remained transparent during the dissolution study, the PVH samples with slow dissolution became opaque during the initial 30 min, as seen in Figure S5. Opaqueness was also observed for the PVPA64 ASDs (Figure S6) despite resulting in the second highest IDR about 40 times higher than crystalline EFV. The IDR of EFV in Table 4 are calculated based on the steepest linear slope of each dissolution curve as described in Equation (3). The reference dissolution profile of crystalline EFV can be found in the Supporting Information (Figure S7).

The morphology of the ASD discs was compared with that of pure polymer discs after 1 h of dissolution to evaluate potential matrix phase separation by SEM, as seen in Fig. 4. The most notable difference to the pure polymer disc was observed for the PVPA64 ASD, which had formed a porous interface towards the FaSSIF medium, while the pure PVPA64 disc had completely dissolved. The porosity of the PVPA64 ASD was likely due to the formation of a drug-rich interface similar to what has previously been observed for felodipine ASD tablets with fast polymer release (Saboo et al., 2020). Although to a lesser degree, a similar porous surface could be seen for the HPMCAS ASD, which moreover appeared thicker than the pure HPMC disc. The pure PCL-PVAc-PEG disc had formed a swollen curvature which was not observed for the PCL-PVAc-PEG ASD, while the remaining ASDs, e.g. PVH and HPMCAS (AS-LF, -MF and -HF), appeared similar to the pure polymer discs.

### 4. Discussion

#### 4.1. Relation between solubility limits and stability of amorphous solid dispersions

The \( \Delta \text{HSP} \) relative to EFV roughly divided the polymers in two groups with PVH > 20 MPa\(^{1/2}\) and the remaining polymers < 10 MPa\(^{1/2}\), while the calculated solubility limits of EFV in the polymers ranged from 3 to 68% (w/w), (Table 2). In accordance with \( \Delta \text{HSP} \) and the MPD results, PVH was the only polymer incapable of stabilizing a 20% (w/w) EFV ASD during the stability study (Table 3). In contrast, another study has reported stable PVH-based ASDs for 6 months at 40 ℃ and 75% RH even with an EFV load of 25% (w/w) (Zolotov et al., 2022). Whether this discrepancy is due to a different grade of PVH (Parteck® MXP), sample preparation (HME) and/or analytical validation (XRPD, DSC) is uncertain. Nevertheless, PLM was specifically chosen for stability monitoring in the present study as this method had previously shown a lower limit of detection compared to XRPD and DSC similar to

---

**Table 2**

<table>
<thead>
<tr>
<th>Compound</th>
<th>( M_0 ) (g/mol)</th>
<th>( \rho ) (g/cm(^3))</th>
<th>( \text{H}_2\text{O} ) (w/w)</th>
<th>( \chi )</th>
<th>( \text{EFV Solubility} ) (% w/w)</th>
<th>( \Delta \text{HSP} ) (MPa(^{1/2}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>315.68</td>
<td>1.39(^{a})</td>
<td>0.0 ± 0.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PVH</td>
<td>13,500</td>
<td>1.25</td>
<td>1.0 ± 0.0</td>
<td>( -0.7 ± 0.2 )</td>
<td>3 (2–3)</td>
<td>20.1</td>
</tr>
<tr>
<td>HPMCAS AS-LF</td>
<td>18,000</td>
<td>1.29</td>
<td>1.2 ± 0.0</td>
<td>( -1.2 ± 0.2 )</td>
<td>13 (12–15)</td>
<td>7.6</td>
</tr>
<tr>
<td>HPMCAS AS-MF</td>
<td>18,000</td>
<td>1.19</td>
<td>1.1 ± 0.0</td>
<td>( -1.6 ± 0.3 )</td>
<td>17 (14–19)</td>
<td>-</td>
</tr>
<tr>
<td>HPMCAS AS-HF</td>
<td>18,000</td>
<td>1.29</td>
<td>0.8 ± 0.3</td>
<td>( -1.9 ± 0.2 )</td>
<td>20 (18–22)</td>
<td>-</td>
</tr>
<tr>
<td>HPMC</td>
<td>20,000</td>
<td>1.29</td>
<td>1.4 ± 0.0</td>
<td>( -2.9 ± 1.8 )</td>
<td>28 (12–40)</td>
<td>7.2</td>
</tr>
<tr>
<td>PVPA64</td>
<td>57,500</td>
<td>1.20</td>
<td>2.0 ± 0.5</td>
<td>( -13.1 ± 7.6 )</td>
<td>64 (45–71)</td>
<td>9.4</td>
</tr>
<tr>
<td>PCL-PVAc-PEG</td>
<td>118,000</td>
<td>1.08</td>
<td>2.0 ± 0.4</td>
<td>( -14.7 ± 8.6 )</td>
<td>68 (51–75)</td>
<td>6.8</td>
</tr>
</tbody>
</table>

\(^{a}\) True density as stated from the supplier/manufacturer unless otherwise referenced.

\(^{b}\) Value taken from ref (Lavra et al., 2017).

\(^{c}\) Calculated based on the HSP values listed in Table 1 as: \( |\delta_{\text{d}, \text{EFV}} - \delta_{\text{d}, \text{polymer}}| + |\delta_{\text{h}, \text{EFV}} - \delta_{\text{h}, \text{polymer}}| + |\delta_{\text{f}, \text{EFV}} - \delta_{\text{f}, \text{polymer}}| \).
reported data in the literature (Bhujbal et al., 2021; Moseson et al., 2018; Moseson and Taylor, 2018). According to the manufacturer, the PVOH grade used in the present study has a degree of hydrolysis of 86.5–89.0%, thus attributing to relatively high $\delta_p$ and $\delta_h$ compared to the other polymers. While individual HSPs have not been estimated for the three grades of HPMCAS (AS-LF, -MF and -HF), it is evident that a decrease in $\delta_p$ of the polymer improves its miscibility with a lipophilic drug such as EFV. The acetate/succinate ratios for HPMCAS AS-LF, -MF and -HF are 0.5, 0.8 and 1.7, respectively, making the AS-HF grade the least hydrophilic and the AS-LF grade the most hydrophilic. This resulted in an extrapolated EFV solubility limit at 22 $^\circ$C of 20% (w/w) in HPMCAS AS-HF, compared to 17% and 13% (w/w) for the AS-MF and -LF grades, respectively. Previous calculations of the solubility parameter difference between EFV and the three grades of HPMCAS have likewise indicated an order of EFV solubility as AS-HF $>$ -MF $>$ -LF (Jha et al., 2021). Consequently, there is a higher chance of thermodynamic stability of the HPMCAS AS-HF ASD compared to the AS-LF- and -MF-based ASDs, yet none of the HPMCAS based ASDs with 20% (w/w) EFV

Fig. 2. EFV (w/w) solubility curves in the polymers, derived from the Flory-Huggins lattice theory. Data points represent the mean of two measurements except for PVOH where each data point represents single measurements. The dashed lines represent the 95% prediction intervals.

Table 3
Overview of the stability of ASD samples with either 20% (w/w) EFV or an EFV load of 20 %-points above the solubility limit in the polymer (High) stored at three conditions. Time intervals indicate when EFV crystals have started to appear according to the observation frequency (after 1 day; 1, 2 and 3 weeks; 1, 2, 3, 4, 5, 6, and 7 months) by polarized light microscopy (PLM). A line (–) indicates that no crystals were observed by PLM after 7 months.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>22 $^\circ$C, 23% RH</th>
<th></th>
<th>22 $^\circ$C, 75% RH</th>
<th></th>
<th>37 $^\circ$C, 75% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20%</td>
<td>High $^a$</td>
<td>20%</td>
<td>High $^a$</td>
<td>20%</td>
</tr>
<tr>
<td>PVOH</td>
<td>1–2 months</td>
<td>–</td>
<td>2–3 weeks</td>
<td>–</td>
<td>&lt;1 day</td>
</tr>
<tr>
<td>HPMCAS AS-LF</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2–3 months</td>
<td>–</td>
</tr>
<tr>
<td>HPMCAS AS-MF</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2–3 months</td>
<td>–</td>
</tr>
<tr>
<td>HPMCAS AS-HF</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2–3 months</td>
<td>–</td>
</tr>
<tr>
<td>HPMC</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2–3 months</td>
<td>–</td>
</tr>
<tr>
<td>PVPVA64</td>
<td>–</td>
<td>2–3 weeks</td>
<td>–</td>
<td>2–3 weeks</td>
<td>–</td>
</tr>
<tr>
<td>PCL-PVAc-PEG</td>
<td>–</td>
<td>2–3 weeks</td>
<td>–</td>
<td>2–3 weeks</td>
<td>–</td>
</tr>
</tbody>
</table>

$^a$ The high drug loadings correspond to the following % (w/w) of EFV: HPMCAS AS-LF (33%), HPMCAS AS-MF (37%), HPMCAS AS-HF (40%), HPMC (48%), PVPVA64 (84%) and PCL-PVAc-PEG (88%).
crystallized during the duration of the stability study (7 months). A relatively high uncertainty was observed for the extrapolated EFV solubilities in HPMC, PVPVA64 and PCL-PVAc-PEG compared to PVOH and HPMCAS (Fig. 2). Nevertheless, significantly higher EFV solubility limits are evident for PVPVA64 and PCL-PVAc-PEG despite having similar ΔHSPs relative to EFV compared to HPMC and HPMCAS. However, it is important to not strictly depend on the Flory-Huggins theory and HSPs as these conventionally rely on homogenous systems, which might compromise their applicability with copolymers, e.g. PCL-PVAc-PEG. Yet, recent efforts have demonstrated the possibility of predicting HSPs of copolymers by using the HSPs of the corresponding homopolymers as input data (Camacho et al., 2017; Tsakiridou et al., 2019).

Table 4
Overview of the intrinsic dissolution rates (IDRs) of EFV from 20% (w/w) ASDs and of pure crystalline EFV. Linearity is based on the mean value of each point.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>IDR (µg min⁻¹ cm⁻²)</th>
<th>Regression range (min)</th>
<th>Linearity (R²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVOH¹</td>
<td>591</td>
<td>5–30</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>PVPVA64</td>
<td>146</td>
<td>50–80</td>
<td>0.995</td>
</tr>
<tr>
<td>HPMCAS AS-LF</td>
<td>39</td>
<td>45–75</td>
<td>0.995</td>
</tr>
<tr>
<td>HPMC</td>
<td>19</td>
<td>15–45</td>
<td>0.967</td>
</tr>
<tr>
<td>HPMCAS AS-MF</td>
<td>15</td>
<td>60–90</td>
<td>0.976</td>
</tr>
<tr>
<td>HPMCAS AS-HF</td>
<td>10</td>
<td>30–60</td>
<td>0.948</td>
</tr>
<tr>
<td>EFV crystalline</td>
<td>3.5</td>
<td>5–180</td>
<td>0.996</td>
</tr>
<tr>
<td>PCL-PVAc-PEG</td>
<td>3.5</td>
<td>5–60</td>
<td>0.929</td>
</tr>
</tbody>
</table>

¹ Calculated based on the dark blue profile in Fig. 3.

Fig. 3. Intrinsic dissolution curves of ASD discs (0.196 cm²) of 20% (w/w) EFV in fasted state simulated intestinal fluid (FaSSIF) at 37 °C. The dotted line on the left graph marks the equilibrium solubility of EFV while the right graph is a zoom of the initial 90 min. Data are shown as mean ± standard deviation (n = 3).

Fig. 4. Scanning electron micrographs of pure polymer and ASD discs seen from the top and the side after 1 h of dissolution in FaSSIF at 37 °C. The fibers visible from the side view of the HPMCAS AS-MF ASD are detached glass fibers from the VCM separation foils. Scale bars: 500 µm.
4.2. Intrinsic dissolution of amorphous solid dispersions

Polymer dissolution rate is naturally a key parameter controlling the liberation rate of drug molecules from an ASD, and is likely the main reason that the IDR of the HPMCAS grades follow the order of hydrophilicity and pH dependency. Yet, the dissolution of an ASD does not only depend on the polymer dissolution rate, which is evident when comparing the PVPVA64 ASD disc with the pure PVPVA64 after 1 h in FaSSIF. The dissolution rate of PVPVA64 alone has previously been measured to be 3.49 mg/min/cm² in a phosphate buffer, which is in line with the 30 mg disc (0.196 cm²) being fully dissolved after 1 h in the present study (Sabo et al., 2019). Thus, while the calculated IDR of PVPVA64 ASD is about 40 times higher than for crystalline EFV, the ASD dissolution rate is still far from the potential defined by the polymer dissolution rate. A previously suggested explanation has been a competing process between dissolution and phase separation in the hydrated matrix, with the latter being rate limiting at higher drug loadings, thus causing incongruent release of drug and polymer (Indulkar et al., 2019; Sabo et al., 2019). The increased EFV IDR of the PVPVA64 ASD compared to crystalline EFV is therefore mainly a result of an increased EFV-rich surface area caused by incongruous release. A simple way to possibly increase the IDR of the PVPVA64 ASD would be to decrease the drug loading to eliminate matrix phase separation and instead have a strictly polymer-controlled EFV release. This could likewise be a beneficial strategy for both the HPMC-based ASD (also showing porous surface upon dissolution) and the PVOH-based ASD in order to eliminate the large variation observed in IDR. The limit of congruency (LoC) has been defined as the drug loading above which the dissolution goes from being polymer controlled to being limited by matrix phase separation (Indulkar et al., 2019). While the LoC is partly depending on both drug properties and drug-polymer interactions, LoC for PVPVA64-based ASDs has generally been found to be low (Indulkar et al., 2019; Que et al., 2019; Sabo et al., 2020, 2019). In contrast, less hydrophilic polymers with slow dissolution rates, e.g. HPMCAS and PCL-PVAc-PEG, tend to have higher LoCs and could thus benefit from higher drug loadings than the 20% (w/w) EFV investigated in the present study. One should therefore not exclude PCL-PVAc-PEG as a potential matrix candidate for EFV-based ASDs despite the present IDR. A similar intrinsic-like setup of VCM-based ASDs with 30% (w/w) indomethacin has previously shown similar relative profiles between PVPVA64 and PCL-PVAc-PEG (Shadambarik et al., 2020). Yet, dissolution testing of the milled ASDs markedly improved the indomethacin dissolution rate from the PCL-PVAc-PEG-based ASD making it outrank the PVPVA64-based ASD (Shadambarik et al., 2020). Additional dissolution studies would therefore likewise be necessary in order to determine the true potential of the polymers as matrices for ASDs of EFV. Nevertheless, the present study supplies valuable information for further formulation development of ASDs of EFV by firstly supporting EFV: polymer miscibility backed up with correlating stability studies. Secondly, the IDRs and visualization of ASDs upon dissolution give an indication of which polymer might have the best chance of improving the EFV dissolution rate depending on the desired EFV loading. For instance, if an EFV loading of < 20% (w/w) is preferred then PVPVA64 might be ideal, yet if an EFV loading of > 20% (w/w) is desired then HPMCAS or PCL-PVAc-PEG could likely be a better option. Future studies will aim at investigating in vitro and in vivo performance of the milled ASDs to build upon the current knowledge of these systems.

5. Conclusion

In the present study, MPD and Flory-Huggins fitting analysis were used to determine the EFV solubility limits at room temperature in seven polymers commonly used as matrices for HME of ASDs. The lowest solubility limit of 3% EFV (w/w) was measured for PVOH which was also the only polymer with a ΔHSP > 20 MPa² relative to EFV. The ΔHSPs of the other polymers were all < 10 MPa² relative to EFV while the calculated solubility limits ranged from 13 to 68% (w/w) in the order: HPMCAS AS-LF < HPMCAS AS-MF < HPMCAS AS-HF < HPMC < PVPVA64 < PCL-PVAc-PEG. The expected unsuitability of PVOH as stabilizing polymer in EFV ASDs was confirmed in a following stability study for 7 months at three storage conditions (22 °C, 23% RH), (22 °C, 75% RH) and (37 °C, 75% RH). Here, PVOH was the only polymer incapable of stabilizing a 20% EFV (w/w) ASD prepared by VCM. The other polymers were likewise incapable of stabilizing ASDs when EFV loadings exceeded their respective calculated solubility limits by 20 % points, albeit recrystallization occurring with variable rates. While these results support the relevance of determining drug solubility limits in relation to the physical stability of VCM-based ASDs, it was further investigated whether a correlation could also be linked with potential matrix phase separation upon dissolution. This was evaluated in a custom-made setup for intrinsic dissolution of the VCM-based ASD discs with 20% (w/w) EFV loading. Calculated IDRs ranged from being similar to crystalline EFV to being about 170 times higher from PCL-PVAc-PEG- and PVOH-based ASDs, respectively. A microscopic comparison of ASD discs and pure polymer discs after 1 h in FaSSIF indicated that matrix phase separation was likely the cause of hampered dissolution for some of the ASDs. Yet, no correlation between calculated solubility limits and the occurrence of matrix phase separation was established. Altogether, the findings in the present study might aid in the selection of an ideal polymer matrix for ASDs of EFV and further support the present literature in the general methodology towards rational formulation development of ASDs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2022.122564.

References


Data will be made available on request.


