Phase behavior of ASDs based on hydroxypropyl cellulose

Christian Luebbert a,*, Edmont Stoyanov b, Gabriele Sadowski a,c

a amofor GmbH, Otto-Hahn-Str. 15, D-44227 Dortmund, Germany
b Nisso Chemical Europe GmbH, Berliner Allee 42, D-40212 Düsseldorf, Germany
c TU Dortmund University, Laboratory of Thermodynamics, Emil-Figge-Str. 70, D-44227 Dortmund, Germany

ARTICLE INFO

Keywords:
Amorphous solid dispersion
Solubility
Miscibility
PC-SAFT
Long-term stability
Hydroxypropyl cellulose

ABSTRACT

Novel polymeric carriers for amorphous solid dispersions (ASDs) are highly demanded in pharmaceutical industry to improve the bioavailability of poorly-soluble drug candidates. Besides established polymer candidates, hydroxypropyl celluloses (HPC) comes more and more into the focus of ASD production since they have the availability to stabilize drug molecules in aqueous media against crystallization. The thermodynamic long-term stability of HPC ASDs with itraconazole and fenofibrate was predicted in this work with PC-SAFT and compared to three-months enduring long-term stability studies. The glass-transition temperature is a crucial attribute of a polymer, but in case of HPC hardly detectable by differential scanning calorimetry. By investigating the glass transition of HPC blends with a miscible polymer, we were for the first time able to estimate the HPC glass transition. Although both, fenofibrate and itraconazole reveal a very low crystalline solubility in HPC regardless of the HPC molecular weight, we observed that low-molecular weight HPC grades such as HPC-UL prevent fenofibrate crystallization for a longer period than the higher molecular weight HPC grades. As predicted, the ASDs with higher drug load underwent amorphous phase separation according to the differential scanning calorimetry thermograms. This work thus showed that it is possible to predict critical drug loads above which amorphous phase separation and/or crystallization occurs in HPC ASDs.

1. Introduction

Amorphous solid dispersions (ASDs) play a major role as enabling formulations for poorly water-soluble new chemical entities (Vasconcelos et al., 2007; Chiu and Riegelman, 1971; Dhirendra et al., 2009). In such formulations, the active pharmaceutical ingredient (API) is molecularly dispersed in a polymer, that helps preventing the API from crystallization during long-term storage and facilitates the dissolution in aqueous media.

The polymer matrix shall on the one hand stabilize the amorphous form of the API and thus prevent API crystallization during storage, and on the other hand, it shall provide stabilizing dissolution properties in order to maintain high API concentrations in gastrointestinal fluids during dissolution (Konno et al., 2008; Anderson, 2018).

For formulators, it is of high interest to identify an optimal polymeric excipient for ASD formulations, e.g. by using completely new synthetic polymers (e.g. Soluplus®, a polyvinyl caprolactam-co-polivinyl acetate-co-polyethylene glycol graft copolymer or the polymethacrylates and poly methacrylic acid based Eudragit® grades (Shamma and Basha, 2013)), or by utilizing polymer mixtures combining the advantages of different polymers (Monschke and Wagner, 2020; Lehmkemper et al., 2018a; Janssens et al., 2008).

Popular polymeric excipients like polyvinyl pyrrolidone (PVP) or the copolymer poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA64) show high API solubilities and are thus theoretically able to stabilize the amorphous API during storage very well (Prudic et al., 2014a; Prudic et al., 2014b; Lehmkemper et al., 2017a; Tao et al., 2009; Sun et al., 2010). However, they are disadvantageous with respect to hydrophilicity (high amount of water absorbed at humid storage conditions leading to a destabilization and API crystallization (Qi et al., 2013; Saboo and Taylor, 2017; Chen et al., 2018a; Luebbert and Sadowski, 2017)) and their low potential to stabilize high API concentrations in aqueous media during dissolution (weak parachute effect) (Schittry et al., 2020). Cellulosic polymers like hydroxypropyl methylcellulose acetate succinate (HPMCAS) are popular in ASD applications since they better stabilize the API against recrystallization in aqueous media (Monschke and Wagner, 2020; Sun and Lee, 2015) (precipitation inhibitor). Unfortunately, API solubilities herein often are very low (Lehmkemper et al., 2017b; Tian et al., 2013) and thus those ASDs might crystallize within their shelf life. A promising polymer family fulfilling both stabilizing criteria might be hydroxypropyl celluloses (HPC), which
were recently also considered as polymeric carriers in ASDs (Monschke and Wagner, 2026; Rashid et al., 2015; Sarode et al., 2014a). Despite the potential as growth inhibitor of crystal nuclei during storage and dissolution in aqueous media, HPC revealed higher ASD storage stabilities compared to PVPVA64 ASDs at lower storage temperature and elevated humidity (Sarode et al., 2014b).

In this work, we investigate the stabilization potential of HPC for application in ASDs. HPC is a modified cellulose already applied for several tablet-coating applications or as tablet binder (Picker-Freyer and manufacturing processes. (Sarode et al., 2014a; Osawa et al., 2014). It is soluble in many organic solvents and in water and thus applicable in spray-drying manufacturing processes.

The glass transition temperature ($T_g$) and the API solubility in the polymer are two major aspects for achieving long-term stable ASDs (Anderson, 2018; Tian et al., 2013; Huang and Dai, 2014). A storage below the ASDs $T_g$ enhances its kinetic stability via a reduced molecular mobility and thus API-crystallization velocity (Theil et al., 2017). An API load in the ASD above its solubility might cause crystallization (Tao et al., 2009; Tian et al., 2013), the occurrence of amorphous phase separation might lead to a local enrichment of amorphous API and accelerated crystallization (Saboo and Taylor, 2017; Marsac et al., 2010; Yang et al., 2013; Six et al., 2003; Luebbert et al., 2017). Both, crystallization and amorphous phase separation are highly unwanted as they alter the ASDs dissolution performance (Saboo et al., 2020; Purohit and Taylor, 2015; Tian et al., 2016; Chen et al., 2016). PC-SAFT has shown in recent studies its strength in predicting amorphous phase separation in complex pharmaceutical systems (Luebbert et al., 2017; Dohrn et al., 2020; Dohrn et al., 2021). The impact of moisture on ASD stability (amorphous phase separation and crystallization) was successfully investigated recently (Luebbert and Sadowski, 2017; Luebbert et al., 2018a). Anderson gave a detailed review on the different existing computational methods and stressed that ‘ASDs are typically hydrogen-bonded systems’. The hydrogen bonds are explicitely considered by the association term within PC-SAFT (Anderson, 2018).

The $T_g$ is an essential attribute of a polymer since it determines the mobility of molecules at given storage temperature conditions. However, only inconsistent information on the $T_g$ of pure HPC is available, values between 19 °C (Rials and Glasser, 1988) and 124 °C (Sakellariou et al., 1985) are reported in literature. These differences can not only be explained by different molecular weight grades or analytical techniques, but instead show the difficulty in determining the $T_g$ of HPC. For a more detailed review on the different glass transitions, the reader is referred to Nyamweya and Hoag (Nyamweya and Hoag, 2000).

The $T_g$ of fast crystallizing APIs (Baird et al., 2010), organic solvents or even gases is often hard to determine due to spontaneous crystallization and a highly-unstable amorphous state. In such cases, the $T_g$ may be estimated by mixing the compound in different ratios with a second compound and extrapolating the $T_g$’s of mixtures with different compositions to the pure-component’s $T_g$ (Nyamweya and Hoag, 2000).

The long-term stability of an ASD with respect to crystallization and amorphous phase separation is predictable by thermodynamic phase diagrams. Numerous works have recently been published studying the phase behavior of ASDs with the polymers PVP, PVPVA64, Soluplus®, HPMC or HPMCAS, Eudrargit® or poly (lactic-co-glycolic acids) (Lehmkemper et al., 2018a; Prudic et al., 2014a; Prudic et al., 2014b; Tao et al., 2009; Tian et al., 2013; Luebbert et al., 2017; Prudic et al., 2015; Lehmkemper et al., 2018b; Kapourani et al., 2019). However, to the best of our knowledge, no study evaluated so far the phase behavior of HPC ASDs. Therefore, we investigate in this work the potential of different HPC grades to stabilize the amorphous state of APIs by thermodynamic modelling using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). The predicted phase diagrams were validated via twelve-weeks-enduring long-term studies of spray-dried ASDs, during which the crystallization was monitored weekly.

2. Materials and Methods

2.1. Materials

Four different molecular weights (grades) of the polymer HPC (HPC-UL with 20,000 g/mol, HPC-SSL with 40,000 g/mol, HPC-5L with 100,000 g/mol, and HPC-L with 140,000 g/mol) were provided by Nisco Chemical Europe GmbH (Düsseldorf, Germany). The APIs fenofibrate (98% purity) and itraconazole (99% purity) were obtained from VWR International GmbH (Darmstadt). The solvents for DVS analysis (ethanol, acetone, and cyclohexane) were obtained in chromatographic grade from VWR International GmbH (Darmstadt). PVPVA64 was provided by BASF SE (Ludwigshafen, Germany). Water required for sorption experiments was filtered and deionized prior use.

2.2. Experimental Methods for characterizing the thermodynamic properties of pure HPC

The so-far unknown $T_g$ of pure HPC was assessed indirectly since no glass-transition temperature is observable in differential scanning calorimetry (DSC) measurements of pure HPC. According to the supplier of HPC, the polymer PVPVA64 is fully miscible with HPC and shows in a DSC thermogram a clearly distinguishable $T_g$ of 109 °C. PVPVA64 and HPC were spray dried in ratios of 10 wt%, 25 wt%, 50 wt%, 75 wt%, and

| Nomenclature | Greek characters |
|--------------|-----------------|
| $a$ | Helmholtz energy J mol$^{-1}$ |
| $h$ | molar enthalpy J mol$^{-1}$ |
| $c_p$ | Heat capacity J (mol K)$^{-1}$ |
| $M$ | molar mass g/mol |
| $m$ | segment number - |
| $k_b$ | Boltzmann constant J K$^{-1}$ |
| $k_{ij}$ | binary interaction parameter - |
| $N_{assoc}$ | number of association sites - |
| $R$ | ideal gas constant J (mol K)$^{-1}$ |
| $p$ | pressure bar |
| $T$ | temperature K or °C |
| $T_g$ | glass-transition temperature K or °C |
| $u$ | dispersion energy J |
| $w_i$ | mass fraction wt% |
| $x_i$ | mole fraction mol% |
| | $\gamma$ activity coefficient - |
| | $\varepsilon_{ABi}$ | association energy J |
| | $\rho$ | density kg m$^{-3}$ |
| | $\kappa_{ABi}$ | association volume - |
| | $\sigma_{seg}$ | segment diameter Å |
| $i,j$ | component |
| int | intersection |

**Subscripts**

- assoc. associating
- disp dispersion
- hc hard chain
- L liquid
- res residual
- S solid
- V vapor
90 wt% (Büchi B290 spray dryer, Flawil, Switzerland). The inlet temperature of the spray dryer was set to 80 °C, the feed rate of the spray-dried solution was set to 7 ml/min and nitrogen was fed with a volume flow of 550 l/h to the atomizer nozzle. In total, 500 mg of solid (PVPVA64 and HPC) were weighted with an accuracy of ±0.1 mg in the desired PVPVA64/HPC ratio, dissolved in 50 ml ethanol and spray dried. A secondary drying was conducted afterwards for two days under vacuum conditions.

The Tg of pure HPC was then estimated by extrapolating the Tg’s of the mixtures with the Gordon-Taylor-Eq. (Gordon and Taylor, 1952) to that of pure HPC. All DSC measurements were performed with a Q2000 (TA Instruments, Newcastle, USA) temperature-calibrated with pure indium. The DSC cell was purged with a stream of 50 ml/min nitrogen. A heat (2 K/min) -cool (10 K/min) -heat (2 K/min) procedure was performed for each sample, heating was carried out in modulated heating-only mode (oscillation amplitude 0.318 K, oscillation period 60 s) and the glass transition was determined in the second heating ramp to ensure that eventually remaining residual solvent or moisture was removed. The DSC thermograms were evaluated with the Software TA Universal Analysis (TA Instruments, Newcastle, USA).

The sorption of solvents with different polarity in HPC-UL was measured to determine PC-SAFT pure-component parameters for HPC-UL (Lehmkenper et al., 2017; Reschke et al., 2014). The solvents acetone, ethanol, and cyclohexane were selected as solvents for the dynamic vapor sorption (DVS) analysis. HPC-UL samples were exposed to 15%, 30%, 45%, 60%, 75% and 90% relative saturation (RS) (RS = p / pS) was adjusted by mass-flow controllers mixing a stream of saturated vapor with dry nitrogen in the desired ratios. Prior to analysis, all samples were dried with dry nitrogen to remove residuals from the sample. The sorption isotherms were determined at 1 K/min, 2 K/min and 5 K/min heating rates from the first heating ramps, which is considered as the temperature at which the crystalline solubility of an API in HPC is calculated with Eq. (1) (Prausnitz et al., 1999).

\[
x_{API} = \frac{1}{T_{API}} \exp \left[ -\frac{\Delta h^S_{API}}{RT_{API}} \left( 1 - \frac{T}{T_{API}} \right) - \frac{\Delta c_{API} \cdot T_{API}}{R} \left( \frac{T_{API}}{T} - \frac{T}{T_{API}} + 1 \right) \right]
\]

Here, \(x_{API}\) is the mole-fraction solubility of the API in the liquid phase. The activity coefficient of the API \(\gamma_{API}\) accounts for all intermolecular interactions between the API and HPC and was obtained in this work from PC-SAFT. The melting properties of the solute are the melting temperature \(T_{m,API}\), the melting enthalpy \(\Delta h^S_{m,API}\), and the difference of the heat capacities of the solid and liquid API \(\Delta c_{API}\). R is the ideal gas constant \((8.3145 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1})\).

Amorphous phase separation (separation of a mixture into two liquid phases L1 and L2) is calculated by Eq. 2.

\[
x_i^{L1} \cdot n_i^{L1} = x_i^{L2} \cdot n_i^{L2}
\]

This equation was solved simultaneously for each component i in the mixture (e.g. for API as well as for HPC).

The activity coefficients required for phase diagram modelling were obtained in this work using PC-SAFT. PC-SAFT is a thermodynamic model which treats molecules as chains of spherical segments. Each molecule has a defined number of segments (segment number \(m^{seg}\)) with segment diameter \(\sigma\) and a dispersion energy parameter \(\alpha/\kappa_D\) describing the segment-segment interaction. PC-SAFT calculates the residual Helmholtz energy \(\alpha^{res}\) by summing up different contributions caused by repulsion (hard chain \(\alpha^{rep}\), attraction (dispersion \(\alpha^{disp}\) and association \(\alpha^{assoc}\)) of the molecules (Eq. 3). The detailed expressions of the contributions can be found in literature (Gross and Sadowski, 2002; Tumakaka et al., 2002; Gross and Sadowski, 2001).

\[
\alpha^{res} = \alpha^i + \alpha^{disp} + \alpha^{assoc}
\]

ASDs with 5 wt%, 15 wt% and 30 wt% API content were manufactured by spray drying (Büchi B290, Flawil, Switzerland). Inlet temperature, feed rate of the peristaltic pump and nitrogen stream were the same parameters as described in Section 2.2. In total, 1 g of solid (API and HPC) were weighted with an accuracy of ±0.1 mg in the desired API/HPC ratio, dissolved in 100 ml ethanol and spray dried.

All spray-dried ASDs were subjected to long-term stability studies for twelve weeks at 25 °C and 0% relative humidity (in vacuum chambers). Each ASD was weekly analyzed for the occurrence of crystals via powder X-ray diffraction (PXRD) and DSC. The minimum XRD detection limit of fenofibrate crystals was 0.4 wt%.

DSC and XRD are regarded as complementary when detecting the crystallinity in ASDs and only a combination of both methods yields a robust information on the actual degree of crystallinity. XRD has a high detection limit of crystals (e.g. Greco et al. reports a detection limit of 3% crystals (Greco et al., 2012)), and lower amounts of crystals can hardly be detected by that measurement technique. On the other hand, DSC can detect smallest traces of crystallinity but destroys the sample during heating it up (thermal degradation or recrystallization upon heating). We therefore decided to utilize both methods complementary. Crystallinity in the ASDs was additionally quantified via DSC by a linear heating ramp of 10 K/min from room temperature to 20 K above the melting temperature of the respective API. The measured melting enthalpy \(\Delta h^S_{API}\) divided by the product of pure-APIs melting enthalpy \(\Delta h^S_{API}\) and API mass fraction in the ASD \(w_{API}\) yielded the crystallinity in the ASD (crystallinity = \(\Delta h^S_{API}\/\Delta h^S_{API} \cdot w_{API}\)).

The PXRD measurements were carried out with approximately 5 mg of each ASD poured on a silicon sample holder in a Rigaku MiniFlex 600 PXRD (Tokyo, Japan). Samples were scanned in a range of 5° < 2θ < 30°.

2.5. Phase diagram modelling with PC-SAFT

The crystalline solubility of an API in HPC is calculated with Eq. (1) (Prausnitz et al., 1999).

\[
x_{API} = \frac{1}{T_{API}} \exp \left[ -\frac{\Delta h^S_{API}}{RT_{API}} \left( 1 - \frac{T}{T_{API}} \right) - \frac{\Delta c_{API} \cdot T_{API}}{R} \left( \frac{T_{API}}{T} - \frac{T}{T_{API}} + 1 \right) \right]
\]

The activity coefficients required for phase diagram modelling were obtained in this work using PC-SAFT. The melting properties of the solute are the melting temperature \(T_{m,API}\), the melting enthalpy \(\Delta h^S_{m,API}\), and the difference of the heat capacities of the solid and liquid API \(\Delta c_{API}\). R is the ideal gas constant \((8.3145 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1})\).

Amorphous phase separation (separation of a mixture into two liquid phases L1 and L2) is calculated by Eq. 2.

\[
x_i^{L1} \cdot n_i^{L1} = x_i^{L2} \cdot n_i^{L2}
\]

This equation was solved simultaneously for each component i in the mixture (e.g. for API as well as for HPC).

The activity coefficients required for phase diagram modelling were obtained in this work using PC-SAFT. PC-SAFT is a thermodynamic model which treats molecules as chains of spherical segments. Each molecule has a defined number of segments (segment number \(m^{seg}\)) with segment diameter \(\sigma\) and a dispersion energy parameter \(\alpha/\kappa_D\) describing the segment-segment interaction. PC-SAFT calculates the residual Helmholtz energy \(\alpha^{res}\) by summing up different contributions caused by repulsion (hard chain \(\alpha^{rep}\), attraction (dispersion \(\alpha^{disp}\) and association \(\alpha^{assoc}\)) of the molecules (Eq. 3). The detailed expressions of the contributions can be found in literature (Gross and Sadowski, 2002; Tumakaka et al., 2002; Gross and Sadowski, 2001).

\[
\alpha^{res} = \alpha^i + \alpha^{disp} + \alpha^{assoc}
\]

Contributions from interactions between unlike molecule species i and j in a mixture are calculated via the Berthelot-Lorentz mixing rules given in Eqs. 4 and 5.

\[
\sigma_{ij} = \frac{1}{2} (\sigma_i + \sigma_j)
\]

\[
\alpha_{ij} = (1 - k_j) \sqrt{\alpha_i \alpha_j}
\]
The dispersion energy $u_{ij}$ is corrected via the interaction parameter $k_{ij}$ which is fitted to experimental binary data. $k_{ij}$ might be a constant value or linearly depends on temperature as expressed in Eq. 6.

$$k_{ij} = k_{ij,0} + k_{ij, 	ext{lin}} \cdot T \ [K]$$

(6)

Hydrogen bonds formed between molecules like water or APIs are considered via a defined number of donor/acceptor sites $N^{\text{assoc}}$. Accounting for hydrogen-bond formation between these sites requires two more model parameters, namely the association energy $\varepsilon^{AB}$ and the association volume $\kappa^{AB}$. Cross association in mixtures of associating components was considered by applying mixing rules presented in Eqs. 7 and 8.

$$\varepsilon^{AB} = \frac{1}{2} \left( \varepsilon^{AA} + \varepsilon^{BB} \right)$$

(7)

$$\kappa^{AB} = \sqrt{\kappa^{AA} \kappa^{BB}} \left( \frac{2\sigma_i \sigma_j}{\sigma_i + \sigma_j} \right)^3$$

(8)

PVPVA64 does not self-associate with molecules of the own kind but nevertheless act as proton donor and acceptor when mixed with a self-associating component. For the molecule fenofibrate, $\varepsilon^{AB}$ was set to zero and $\kappa^{AB}$ was set to the value 0.02 (Brinkmann et al., 2019).

The $T_g$ of the ASDs as function of API mass fraction $w_{\text{API}}$ was modelled using the Gordon-Taylor Equation (Eq. 9) (Gordon and Taylor, 1952):

$$T_g = \frac{w_{\text{API}} \cdot T_g, \text{API} + K_{GT} \cdot w_{\text{PVPVA64}} \cdot T_g, \text{HPC}}{w_{\text{API}} + K_{GT} \cdot w_{\text{PVPVA64}}}$$

(9)

$T_g$ follows the Gordon-Taylor equation only in miscible mixtures, thus $T_g$ is only modelled in those regions. For the PVPVA64/HPC-blends, the API in Eq. 9 is replaced by PVPVA64. The binary Gordon-Taylor parameter $K_{GT}$ was either fitted to the obtained DSC data (in case of the PVPVA64/HPC blends) or (in case of the ASDs) predicted using the correlation $K_{GT} = \rho^{\text{HPC}} T_g, \text{API} / \rho^{\text{HPC}} T_g, \text{HPC}$ ($\rho$ is the density of the amorphous substances).

3. Results

3.1. Glass-transition temperatures of pure HPC grades

As mentioned in the introduction, the $T_g$ of pure HPC is hardly detectable since the step height of the heat capacity at the glass transition is nearly zero (a typical DSC thermogram of a HPC-UL sample is discussed in the supplement in Fig. S1).

The glass-transition temperatures of spray-dried HPC/PVPVA64 blends with 10 wt%, 25 wt%, 50 wt%, 75 wt% and 90 wt% HPC were investigated in this work (blends were prepared for all HPC grades). The measured DSC thermograms of the HPC/PVPVA64 blends are summarized in Fig. 1 (second heating ramp of a heat-cool heat procedure, compare Section 2.2). The measured glass-transition temperatures decrease from 109.7 °C in pure PVPVA64 upon addition of HPC-L to 84.41 °C in pure HPC-L (a broad glass-transition was detected by the software TA Universal Analysis, though it is not observable with the eye). The step heights at the $T_g$ decrease with increasing HPC content. The $T_g$ of pure HPC-L and the sample with 90 wt% HPC-L is not detectable anymore with the eye, whereas the $T_g$‘s in blends with up to 75% HPC-L can be well detected visually.

The glass-transition temperature obtained from those measurements is shown in Fig. 2 for all HPC/PVPVA64 blends as function of composition.

By fitting the Gordon-Taylor parameter and extrapolating to the unknown $T_g$ of the pure HPC grades, we were able to estimate the $T_g$‘s of all four investigated HPC grades, they are shown in Table 1. The HPC $T_g$‘s increase slightly with increasing HPC molecular weight (except for HPC-L). The extrapolated $T_g$‘s still are slightly error-prone due to the limitations of the Gordon-Taylor-approach in correctly describing the concentration-dependency of the $T_g$ in a polymer blend. However, also modelling approaches like that of Brosnok et al. did not improve the overall modelling accuracy (Brosnok et al., 2008).

The $T_g$ values reported in literature (19 °C (Rials and Glasser, 1988) – 124 °C (Dave et al., 1995)) strongly differ from our extrapolated values. Nyamweya and Hoang (Nyamweya and Hoag, 2000) in detail discussed possible reasons for the discrepancies among the literature values (e.g. different experimental techniques such as dynamic-mechanical analysis, torsional braid analysis or DSC, different polymer suppliers, different molecular weights, enthalpy relaxation, sample preparation etc.). The same authors tried to assess the $T_g$ of HPC via an extrapolation with blends of HPMC E5 and HPC. Unfortunately, they were not successful as they could not observe any change of $T_g$ upon addition of HPC. They assumed that the chosen polymer HPMC E5 is unexpectedly immiscible with HPC and thus not appropriate for an extrapolation. Karari et al. also did not succeed with a dynamic-mechanical determination of the $T_g$ of HPC (Karari et al., 1990). Selecting PVPVA64 as blend component in this work, we were now able to estimate $T_g$‘s of the HPC grades.

3.2. PC-SAFT pure-component parameter determination of HPC grades

The PC-SAFT pure-component parameters of HPC-UL were fitted simultaneously to sorption data in organic solvents with different polarity and to densities of ethanol/HPC-UL mixtures.

![Fig. 1. DSC thermograms (reversing heat flow) of HPC-L/PVPVA64-blends.](image1)

![Fig. 2. Measured $T_g$ as function of HPC content (symbols) and glass-transition modelled via Gordon-Taylor equation (lines). Squares indicate blends with HPC-UL, circles indicate blends with HPC-SSL, diamonds indicate blends with HPC-SL and triangles indicate blends with HPC-L.](image2)
Table 1
Glass-transition temperatures of HPC grades determined via extrapolating the glass transition of spray dried HPC/PVPPA64 blends.

| HPC grade | \(M_m/g\text{mol}\) | \(T_g/{}^\circ\text{C}\) |
|-----------|-----------------|------------------|
| UL        | 20,000          | 81.6             |
| SSL       | 40,000          | 81.8             |
| SL        | 100,000         | 86.2             |
| L         | 140,000         | 84.2             |

3.2.1. Sorption of organic solvents in HPC-UL
The equilibrium vapor sorption of the solvents as function of RS is summarized in Fig. 3.

3.2.2. Density of HPC-UL/water mixtures
Density values of the pure compound are essential for estimating the geometric parameters of the PC-SAFT modelling. Since the melt densities of the pure polymers are often not available, PC-SAFT parameters were alternatively fitted to the density of HPC-UL/solvent mixtures. The results are summarized in Table 2.

3.2.3. PC-SAFT parameters
The PC-SAFT pure-component parameters of HPC-UL were fitted to vapor sorption data (Fig. 3) and densities of HPC-UL/water mixtures (Fig. 4) and are shown in Table 3. Parameters of the APIs fenofibrate and itraconazole were obtained from literature.

PC-SAFT binary interaction parameters \(k_{ij}\) were obtained by altering the number of segments in the polymer chain. HPC-UL (20,000 g/mol) e.g. has a segment number \(m_{seg}^{\text{HPC-UL}} = 4467.38\), HPC-SSL (100,000 g/mol) has a segment number \(m_{seg}^{\text{HPC-SSL}} = 4467.38\) and HPC-L (140,000 g/mol) has a segment number \(m_{seg}^{\text{HPC-L}} = 6254.33\). All other PC-SAFT parameters remain constant and do not change with changing molecular weight. The via PC-SAFT calculated density of pure HPC-UL at 25 °C is 1.216 g/cm³, this lies in a reasonable range for a polymer and thus further validates the fitted parameters.

The values for the PC-SAFT binary interaction parameters \(k_{ij}\) are summarized in Table 4. These values are also valid for all HPC grades.

3.3. Phase behavior of HPC-containing ASDs
The phase diagram of the fenofibrate/HPC-UL ASD was modelled with PC-SAFT using the PC-SAFT parameters summarized in Table 3 and the APIs melting properties presented in Table 5.

The PC-SAFT calculation and all DSC measurements are summarized in the phase diagram shown in Fig. 5.

As can be seen, the measured solubility temperatures did not change for different fenofibrate loads in the ASDs compared to the melting temperature of pure fenofibrate (80.78 °C). The reason for this is an amorphous phase separation region (right of the PC-SAFT predicted black line in Fig. 3) - all ASDs within this temperature/composition range will undergo amorphous phase separation. Indeed, the experimentally-determined glass transitions of ASDs with fenofibrate mass fractions above 0.4 showed the same value as that for pure fenofibrate. This is a hint that those ASDs undergo amorphous phase separation and almost pure fenofibrate precipitates amorphously from the mixture with HPC-UL. Thus, the phase-diagram prediction (\(k_{ij} = 0\)) very well agrees with the observed phase behavior. Tg only follows Gordon-Taylor behavior in miscible blends, thus it was only calculated outside the region of amorphous phase separation.

As can be seen, the phase diagram can be predicted very well without...
fitting a binary interaction parameter ($k_{ij} = 0$). The predicted phase diagram reveals that the crystalline fenofibrate equilibrium solubility in HPC-UL at room temperature is 0.8 wt% and that thus all ASDs with higher fenofibrate loads are expected to crystallize during storage. Additionally, fenofibrate ASDs with fenofibrate loads above 5.8 wt% will undergo amorphous phase separation. This phenomenon was also visually observed in the DSC samples, where low-viscous fenofibrate covered the bottom of the sample pans and optically segregated from the polymer matrix. The glass transition temperature of the ASDs was predicted for the composition/temperature range in which no phase separation occurs (left side of the diagram). A comparable phase behavior is known from ASDs of ibuprofen and PLGA (Luebbert et al., 2017).

The PC-SAFT calculation and the DSC measurements of itraconazole/HPC-UL ASDs are summarized in the phase diagram shown in Fig. 6. The binary interaction parameter $k_{ij}$ for this system was fitted to −0.037. The solubility temperatures of the ASDs slightly decrease relative to the melting temperature of pure itraconazole (168.75 °C).

### Table 3

PC-SAFT pure-component parameters of HPC-UL, fenofibrate, and itraconazole.

| Substance  | $m_{\text{L}}^\text{L}/M_{\text{B}}$mol g$^{-1}$ | $n_\text{H}$/Å | $u_i/k_B$ | $\varepsilon_{\text{API}}/k_B$ | $\varepsilon_{\text{HPC}}$ | $N_{\text{assoc}}$ (donors/acceptors) | Parameter Ref. |
|------------|-----------------------------------------------|----------------|----------|------------------------------|----------------|--------------------------------------|----------------|
| HPC-UL     | 0.0446738                                     | 2.974          | 205.0    | 1600.0                       | 0.02           | 286/286                              | This work      |
| fenofibrate| 0.0106957                                     | 4.767          | 244.8    | 0                            | 0.02           | 0/2                                  | (Brinkmann et al., 2019) |
| itraconazole| 0.037                                         | 2.166          | 252.346  | 1204.88                     | 0.02           | 2/2                                  | (Paus et al., 2015) |

### Table 4

Binary PC-SAFT interaction parameters ($k_{ij}$) between HPC and the other investigated components.

|             | Water   | Cyclohexane | Acetone | Ethanol | Fenofibrate | Itraconazole |
|-------------|---------|-------------|---------|---------|-------------|--------------|
| $k_{ij}$    | −0.0623 | 0.0680      | −0.0050 | 0       | 0           | −0.037       |

### Table 5

Melting properties and $T_g$’s of the APIs fenofibrate and itraconazole obtained from literature.

| API       | $\Delta H^\text{D}_{\text{N}}$ /J/g | $T_g$ /°C | $T_{\text{cr}}$ /°C | $\Delta C_p$ API/°C (mol K)$^{-1}$ |
|-----------|-----------------------------------|----------|---------------------|--------------------------------------|
| Fenofibrate| 92.93 (Watterson et al., 2014)    | 80.78 (Brinkmann et al., 2019) | −18.44 (this work) | 124.3 (Watterson et al., 2014)         |
| Itraconazole| 98.78 (Paus et al., 2015)        | 168.75 (Paus et al., 2015)     | 58.16 (Paus et al., 2015)            | 177.8 (Paus et al., 2015)               |

According to the PC-SAFT calculation, the extrapolated solubility of itraconazole in HPC-UL at 25 °C is only 0.001669 wt%.

All investigated ASDs revealed a glass-transition temperature close to that of pure itraconazole. This is no direct evidence for amorphous phase separation as for example Raman Imaging (Luebbert et al., 2018b), but a strong indirect hint that also itraconazole is not fully miscible with HPC-UL and at least some of the here-investigated ASDs underwent amorphous phase separation (Nyangweya and Hoag, 2000; Brostow et al., 2008; Kim et al., 2003).

Using the $k_{ij}$ value fitted to the solubility data in Fig. 6, an amorphous phase separation was predicted. The predicted amorphous-phase-separation region agrees very well with the behavior observed in the DSC: In agreement with the DSC measurements, the PC-SAFT modelling predicts almost no melting point depression for all itraconazole concentrations in the ASD. The low solubility of itraconazole in HPC-UL ($w_{\text{itraconazole}} = 0.001669$ wt%) reveals that ASDs with higher itraconazole loads might crystallize during storage (at least after infinite time). Additionally, PC-SAFT predicts that ASDs with itraconazole loads above 2.0 wt% will undergo amorphous phase separation. According to the PC-SAFT predictions, the itraconazole-rich phase contains almost pure itraconazole. As the itraconazole-rich phase does contain almost no polymer that could prevent spontaneous nucleation, it can be expected that this phase crystallizes as quickly as pure amorphous itraconazole.

### 3.4. Influence of HPC molecular weight on the amorphous and crystalline API solubility

The influence of HPC molecular weight on the crystalline and amorphous solubility of fenofibrate and itraconazole in HPC was predicted using PC-SAFT in a range from 1000 g/mol to 1000,000 g/mol. The amorphous solubility is the concentration of API in the polymer above which amorphous phase separation occurs. It is predicted with Eq. 2 using the same PC-SAFT parameters as for calculations of crystalline solubility. Fig. 7 shows the result of this calculation at a temperature of 25 °C.
According to the prediction, the solubility of crystalline fenofibrate increases sigmoidally on a log($M_w$)-scale from 0.07 wt% at a molecular weight of 1,000 g/mol to 1.68 wt% at 1000,000 g/mol. At the same time, the solubility of the amorphous API (i.e. the API concentration in the HPC-rich phase of a demixed ASD; compare Fig. 5) decreases. The investigated HPC grades of 20,000 g/mol – 140,000 g/mol are found in the middle of the calculated $M_w$ range. Thus, amorphous phase separation will not occur in HPC grades with low molecular weight and the tendency of the ASD to undergo amorphous phase separation increases with increasing molecular weight of HPC.

According to the PC-SAFT predictions, the molecular-weight influence on the solubilities of crystalline and amorphous itraconazole and fenofibrate is quite different: The predicted crystalline itraconazole solubility remains constantly low at $w_{itraconazole} = 0.001669$ wt% and is not affected by HPC molecular weights in the range from 1,000 g/mol to 1000,000 g/mol. The same holds true for the solubility of amorphous itraconazole which is not affected by HPC molecular weight and remains about 2 wt%.

3.5. Long-term stability of fenofibrate/HPC and itraconazole/HPC ASDs

ASDs with API loads of 5 wt%, 15 wt%, and 30 wt% were prepared for each API/HPC combination. The spray-dried ASDs were stored at 25°C/0% RH and weekly analyzed via DSC and XRD for crystallinity. According to the PC-SAFT predictions (Fig. 5 and Fig. 6), all prepared ASDs were supersaturated and thus were expected to crystallize during storage.

The evaluation of a DSC heat-flow signal of an HPC-UL/fenofibrate 15% ASD after 12 weeks of storage is shown as an example in Fig. 8. The melting enthalpy determined from this measurement was 1.492 J/g, which corresponds to a crystallinity of $1.492 / (92.93 \times 0.15) = 10.7\%$.

The melting enthalpies of itraconazole/HPC-ASDs were often hard to quantify since recrystallization occurred during heating. In those cases, the recrystallization enthalpy was subtracted from the melting enthalpy (Fig. 8b). In this example, the crystallinity was $(7.761 - 5.732) / (98.78 \times 0.30) = 19.3\%$ according to the DSC measurement while the corresponding PXRD measurement did not reveal any crystals. The recrystallization occurring during heating made a reliable interpretation of the DSC baseline impossible and lead to error-prone crystallinity values for several itraconazole/HPC-ASDs (bold values in Table 6).

Three example PXRD diffractograms of HPC-UL/fenofibrate ASDs obtained after 12 weeks of storage are shown in Fig. 9 illustrating the influence of the fenofibrate load on the degree of final crystallinity.

The crystallinities of all ASDs determined via DSC function of time are shown in Table 6. The fenofibrate/HPC-UL ASDs with 5 wt% fenofibrate remained completely X-ray amorphous, the fenofibrate/HPC-UL ASD with 15 wt% fenofibrate was slightly crystalline and the fenofibrate/HPC-UL ASD with 30 wt% fenofibrate clearly crystallized.

The crystallinities of all ASDs determined via DSC function of time are shown in Table 6. The fenofibrate/HPC-UL ASDs with 30 wt% fenofibrate load were already highly crystalline after the first week. This might be explained by the occurrence of amorphous phase separation (compare Fig. 5): The evolving fenofibrate-rich phase is almost pure according to the prediction, thus has a high molecular mobility ($T_{g, fenofibrate} = -18\degree C$) and after demixing crystallizes as fast as the pure amorphous fenofibrate.

For the 5 wt% fenofibrate-loaded ASDs, only the polymers HPC-UL and HPC-SL successfully prevented the fenofibrate crystallization, whereas the other ASDs crystallized during storage.

Fig. 10 shows the fenofibrate crystallinity in the e/HPC ASDs with 15 wt% fenofibrate (data from Table 6). HPC-UL ASDs with 15 wt% fenofibrate content crystallized significantly slower than the other ASDs.
(see Fig. 10). The crystallization velocity of fenofibrate in HPC-UL is much slower than in the other three HPC grades. Thus, HPC-UL seems to stabilize fenofibrate ASDs best. The kinetics of crystallization we observed in ASDs with HPC-SSL, HPC-SL and HPC-L does not follow a sigmoidal increase with time as known from other works (Luebbert and Sadowski, 2018; Yang et al., 2010), but jumps abruptly to values of 40% crystallinity within the first week of storage (Fig. 10) and then stays more or less constant over time. Only in the HPC-UL samples, the crystallinity only very slowly increases to maximal 10.7%. Due to a certain solubility of fenofibrate in the polymers, not all fenofibrate molecules will crystallize. That is why the maximum crystallinity is limited to values below 100% (predicted equilibrium crystallinities can be found in Table 6).

The sometimes-higher crystallinities observed in the DSC measurements compared to the X-ray measurements are attributed to recrystallization during heating, making an accurate quantification of crystals impossible (compare Fig. 8b).

Even the highest crystallinities observed in this work remained significantly below the predicted equilibrium crystallinities. This supports the hypothesis that HPC cannot suppress crystal nucleation but

| Polymer | API     | w_{API} | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | Equilibrium |
|---------|---------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------------|
| HPC-UL  | fenofibrate | 5       | 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 83.2%       |
| HPC-UL  | fenofibrate | 15      | 0.0%| 0.7%| 1.3%| 2.0%| 2.7%| 2.0%| 5.3%| 10.7%| 7.3%| 8.7%| 13.3%| 10.7%| 94.4%       |
| HPC-UL  | fenofibrate | 30      | 48.7%| 49.3%| 50.7%| 52.7%| 50.7%| 50.7%| 54.0%| 55.0%| 63.3%| 60.0%| 61.3%| 64.3%| 97.2%       |
| HPC-SSL | fenofibrate | 5       | 4.0%| 16.0%| 14.0%| 22.0%| 18.0%| 16.0%| 18.0%| 16.0%| 22.0%| 24.0%| 30.0%| 50.0%| 76.1%       |
| HPC-SSL | fenofibrate | 15      | 36.7%| 52.7%| 51.3%| 52.7%| 44.7%| 48.0%| 51.3%| 56.0%| 60.7%| 56.7%| 63.3%| 62.0%| 92.0%       |
| HPC-SSL | fenofibrate | 30      | 42.7%| 50.0%| 48.7%| 47.3%| 48.7%| 53.0%| 50.3%| 53.3%| 59.7%| 58.7%| 60.7%| 63.0%| 96.0%       |
| HPC-SL  | fenofibrate | 5       | 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 2.0%| 0.0%| 69.7%       |
| HPC-SL  | fenofibrate | 15      | 21.3%| 51.3%| 45.3%| 43.3%| 46.7%| 45.3%| 44.0%| 42.0%| 48.7%| 48.0%| 55.3%| 52.0%| 89.9%       |
| HPC-SL  | fenofibrate | 30      | 53.0%| 56.3%| 50.7%| 53.7%| 58.3%| 52.7%| 56.0%| 57.7%| 58.0%| 56.0%| 62.3%| 58.7%| 95.0%       |
| HPC-L   | fenofibrate | 5       | 2.0%| 6.0%| 6.0%| 12.0%| 8.0%| 38.0%| 14.0%| 14.0%| 20.0%| 14.0%| 22.0%| 24.0%| 68.8%       |
| HPC-L   | fenofibrate | 15      | 42.7%| 52.0%| 49.3%| 51.3%| 57.3%| 47.3%| 48.7%| 59.3%| 56.7%| 62.0%| 56.7%| 62.0%| 89.6%       |
| HPC-L   | fenofibrate | 30      | 37.0%| 59.3%| 60.0%| 61.7%| 65.7%| 60.3%| 61.3%| 63.7%| 65.7%| 65.0%| 62.3%| 67.7%| 94.8%       |
| HPC-UL  | itraconazole | 5       | 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 100.0%       |
| HPC-UL  | itraconazole | 15      | 0.0%| 0.0%| 2.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 2.7%| 0.0%| 2.7%| 0.0%| 100.0%       |
| HPC-UL  | itraconazole | 30      | 0.0%| 0.0%| 1.7%| 1.0%| 1.7%| 1.0%| 1.0%| 0.0%| 1.0%| 0.3%| 0.7%| 1.0%| 0.7%| 100.0%       |
| HPC-SSL | itraconazole | 5       | 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 100.0%       |
| HPC-SSL | itraconazole | 15      | 0.0%| 0.0%| 0.0%| 0.0%| 0.7%| 0.0%| 0.0%| 0.0%| 0.0%| 3.3%| 0.7%| 0.0%| 0.7%| 100.0%       |
| HPC-SSL | itraconazole | 30      | 0.7%| 4.7%| 1.3%| 1.3%| 1.7%| 1.3%| 1.3%| 0.3%| 1.0%| 3.0%| 2.0%| 2.0%| 2.0%| 100.0%       |
| HPC-SL  | itraconazole | 5       | 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 6.0%| 0.0%| 100.0%       |
| HPC-SL  | itraconazole | 15      | 2.7%| 3.3%| 2.7%| 2.7%| 2.7%| 3.3%| 1.3%| 2.0%| 2.7%| 1.3%| 4.7%| 2.7%| 100.0%    |
| HPC-SL  | itraconazole | 30      | 2.3%| 5.7%| 3.0%| 6.7%| 3.0%| 2.3%| 5.3%| 2.0%| 3.7%| 8.7%| 11.7%| 4.0%| 100.0%    |
| HPC-L   | itraconazole | 5       | 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 0.0%| 2.0%| 0.0%| 0.0%| 100.0%       |
| HPC-L   | itraconazole | 15      | 0.0%| 6.7%| 6.0%| 3.3%| 5.3%| 4.7%| 6.0%| 4.0%| 6.0%| 8.0%| 6.7%| 6.0%| 100.0%       |
| HPC-L   | itraconazole | 30      | 7.3%| 2.7%| 7.7%| 5.0%| 5.7%| 9.7%| 2.3%| 1.7%| 1.0%| 7.3%| 6.0%| 4.3%| 100.0%       |
stabilizes an amorphous API very well against crystal growth even in the presence of seed crystals. Very similar observations were also made during dissolution tests by Sarode et al. (Sarode et al., 2014b).

A reason for this might lie in the HPC-molecular-weight dependence of the amorphous solubility of fenofibrate (Fig. 7): Amorphous phase separation occurs for HPC grades with higher molecular weight, thus those ASDs are more likely to crystallize fast. In the low-Mₙ grades HPC-UL, smaller polymer chains might increase the amorphous solubility and thus prevent amorphous phase separation.

Table 6 shows that also itraconazole ASDs are best stabilized by HPC grades of lower-molecular weight: itraconazole ASDs with HPC-UL showed an enhanced stability compared to the one with the other HPC grades and is thus considered to be best suitable for generating ASD formulations with HPC grades. However, due to the overall low crystalline API solubilities, HPC appears more suitable as co-exipient to amorphous solid dispersions with e.g. PVPVA64 or HPMCAS.

Despite the long-term storage stability, further considerations on the in-vitro dissolution behavior (e.g. in biorelevant media) are required to ultimately evaluate the potential of HPC as excipient in ASD development.

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.

Acknowledgement

This work was funded by Nisso Chemical Europe GmbH, Düsseldorf, Germany.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.xipj.2020.100070.

References

Anderson, B.D., 2018. Predicting Solubility/Miscibility in Amorphous Dispersions: it is Time to move beyond regular solution theories. J. Pharm. Sci. 107, 24–33. https://doi.org/10.1016/j.xphs.2017.09.030.

Baird, J.A., van Eerdenbrugh, B., Taylor, L.S., 2010. A classification system to assess the crystallization tendency of organic molecules from undercooled melts. J. Pharm. Sci. 99, 3787–3806. https://doi.org/10.1002/jps.22197.

Brinkmann, J., Hixoll, F., Luebbert, C., Sadowski, G., 2019. Solubility of pharmaceutical ingredients in triglycerides. Eur. J. Pharm. Biopharm. 145, 113–120. https://doi.org/10.1016/j.ejpb.2019.10.012.
nifedipine in PVP, PVP/VA, and PVAc. J. Pharm. Sci. 99, 4023–4031. https://doi.org/10.1002/jps.22251.

Tao, J., Sun, Y., Zhang, G.G.Z., Yu, L., 2009. Solubility of small-molecule crystals in polymers: D-mannitol in PVP, indomethacin in PVP/VA, and nifedipine in PVP/VA. Pharm. Res. 26, 855–864. https://doi.org/10.1007/s11095-008-9784-z.

Theil, F., Milsmann, J., Kyeremateng, S.O., Anantharaman, S., Rosenberg, J., van Lishaut, H., 2017. Extraordinary Long-Term-Stability in Kinetically Stabilized Amorphous Solid Dispersions of Fenofibrate. Mol. Pharm. 14, 4636–4647. https://doi.org/10.1021/acs.molpharmaceut.7b00735.

Tian, Y., Booth, J., Meehan, E., Jones, D.K., Li, S., Andrews, G.P., 2013. Construction of drug-polymer thermodynamic phase diagrams using Flory-Huggins interaction theory: identifying the relevance of temperature and drug weight fraction to phase separation within solid dispersions. Mol. Pharm. 10, 236–248. https://doi.org/10.1021/mp300386v.

Tian, B., Tang, X., Taylor, L.S., 2016. Investigating the correlation between miscibility and physical stability of amorphous solid dispersions using fluorescence-based techniques. Mol. Pharm. 13, 3988–4000. https://doi.org/10.1021/acs.molpharmaceut.6b00803.

Tumakaka, F., Groos, J., Sadowski, G., 2002. Modeling of polymer phase equilibria using Perturbed-Chain SAFT. Fluid Phase Equilib. 194-197, 541–551. https://doi.org/10.1016/S0378-3812(01)00785-3.

Vasconcelos, T., Sarmento, B., Costa, P., 2007. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov. Today 12, 1068–1075. https://doi.org/10.1016/j.drudis.2007.09.005.

Watterson, S., Hudson, S., Svard, M., Rasmuson, Å.C., 2014. Thermodynamics of fenofibrate and solubility in pure organic solvents. Fluid Phase Equilib. 367, 143–150. https://doi.org/10.1016/j.fluid.2014.01.029.

Yang, J., Grey, K., Doney, J., 2010. An improved kinetics approach to describe the physical stability of amorphous solid dispersions. Int. J. Pharm. 384, 24–31. https://doi.org/10.1016/j.ijpharm.2009.09.035.

Yang, Z., Nollenberger, K., Albers, J., Craig, D., Qi, S., 2013. Microstructure of an immiscible polymer blend and its stabilization effect on amorphous solid dispersions. Mol. Pharm. 10, 2767–2780. https://doi.org/10.1021/mp400209w.