The design and development of high drug loading amorphous solid dispersion for hot-melt extrusion platform

Tian, Y., Jacobs, E., Jones, D. S., McCoy, C. P., Wu, H., & Andrews, G. P. (2020). The design and development of high drug loading amorphous solid dispersion for hot-melt extrusion platform. *International Journal of Pharmaceutics*, 586, [119545].

Published in:
International Journal of Pharmaceutics

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

Copyright 2020 Elsevier B.V.
This manuscript is distributed under a Creative Commons Attribution-NonCommercial-NoDerivs License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits distribution and reproduction for non-commercial purposes, provided the author and source are cited

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

1 The design and development of high drug loading
2 amorphous solid dispersion for hot-melt
3 extrusion platform

4

5 Yiwei Tian^{1*}, Esther Jacobs¹, David S. Jones¹, Colin P McCoy¹, Han Wu^{2,3}, Gavin P.
6 Andrews,

7

8 1. School of Pharmacy, Queen's University Belfast, 97 Lisburn Road, Northern
9 Ireland, UK, BT9 7BL.

10 2. Department of Chemical Engineering, University College London, London,
11 UK, WC1E 7JE

12 3. Centre for Nature Inspired Engineering, University College London,
13 London, UK, WC1E 7JE.

14

15 * *Corresponding author: Dr. Yiwei Tian*

16 *Corresponding address: School of Pharmacy, Queen's University Belfast, 97 Lisburn*
17 *Road, Northern Ireland, United Kingdom, BT9 7BL*

18 *Email: y.tian@qub.ac.uk*

19 *Tel: +4428 9097 2689*

20

21 *KEY WORDS:* amorphous; amorphous solid dispersion; thermodynamic phase
22 diagram; Flory-Huggins; hot-melt extrusion, small angle x-ray scattering
23

24 **ABSTRACT**

25 Amorphous solid dispersion (ASD) is a formulation strategy extensively used to
26 enhance the bioavailability of poorly water soluble drugs. Despite this, they are
27 limited by various factors such as limited drug loading, poor stability, drug-
28 excipient miscibility and the choice of process platforms. In this work, we have
29 developed a strategy for the manufacture of high drug loaded ASD (HDASD) using
30 hot-melt extrusion (HME) based platform. Three drug-polymer combinations,
31 indomethacin-Eudragit®E, naproxen-Eudragit®E and ibuprofen-Eudragit®E,
32 were used as the model systems. The design spaces were predicted through Flory-
33 Huggins based theory, and the selected HDASDs at pre-defined conditions were
34 manufactured using HME and quench-cooled melt methods. These HDASD
35 systems were also extensively characterised via small angle/wide angle x-ray
36 scattering, differential scanning calorimetry, Infrared and Raman spectroscopy
37 and atomic force microscopy. It was verified that HDASDs were successfully
38 produced via HME platform at the pre-defined conditions, with maximum drug
39 loadings of 0.65, 0.70 and 0.60 w/w for drug indomethacin, ibuprofen and
40 naproxen respectively. Enhanced physical stability was further confirmed by high
41 humidity (95%RH) storage stability studies. Through this work, we have
42 demonstrated that by the implementation of predictive thermodynamic
43 modelling, HDASD formulation design can be integrated into the HME process
44 design to ensure the desired quality of the final dosage form.

45

1. INTRODUCTION

Poor aqueous solubility and subsequent limited bioavailability of many active pharmaceutical ingredients (APIs) is a significant issue in the current pharmaceutical industry with approximately, 90% of new chemical entities in the development pipeline characterised as poorly water-soluble compounds (Kalepu and Nekkanti, 2015). New, sophisticated formulation strategies have been implemented, of which, the amorphous form has proved to be a promising strategy (Repka et al., 2018). The amorphous form exists as a higher energy state, due to the lack of long range order, resulting in increased free energy level and molecular mobility compared to their crystalline counterparts, thus, provides a desirable route to increase solubility and dissolution performances (Hancock and Zografi, 1997). To capture these advantages, amorphous solid dispersion (ASD) has been widely utilised. The concept of solid dispersions was first proposed in 1960s where the drug molecule is homogenously distributed within a suitable carrier(s), typically a polymer-based material. to improve its physical stability. This approach has enabled a number of marketed products with significant bioavailability enhancement (Zhang et al., 2018). Noticeable progresses may also be highlighted for the development of fix-dose combination products, such as kalydeco®, ORKAMBI®, symdeco® and trikafta™, where the efficacy of the main compound ivacaftor was successfully enhanced by amorphous solid dispersion strategy (FDA, 2019a, 2019b, 2015, 2012).

Despite the successes achieved in exploration of ASD for enabling formulation development, majority of excipient selections are still based on trial-and-error methodologies with a handful of tried tested polymeric systems (Zhang et al.,

2018). We are still deficient in selecting of excipients for a given drug molecule to be formulated into a stable ASD, particularly with the integration of various manufacturing technologies, such as spray drying, hot-melt extrusion or cryo-milling. Several parameters are proposed to be influential for the stability of ASDs, such as; glass transition temperature, molecular mobility, hydrogen-bonding interactions, ionic interaction and other non-specific interactions (Anderson, 2018; Mistry et al., 2015; Quinteros et al., 2008; Song et al., 2015). However, it is still not certain what manufacturing technology is the most suited for a given drug-polymer combination at various process conditions. For example, high drug loading amorphous solid dispersion (HDASD, drug loading >50% w/w), may offer numerous advantages such as reduce the dose size, pill burden and increase the therapeutic compliance, in addition to the enhanced solubility of the amorphous system (Alshahrani et al., 2015; Dedroog et al., 2019). However, HDASD system has not been widely explored due to the potential stability issues. When the drug weight fraction increases, associated processability, inhomogeneity and potential phase separation will undoubtedly affect the quality and performances of the final product. Spray drying and cryo-milling, widely recognising as the preferred techniques for these HDASD systems, are possessed with various limitations (Caron et al., 2011; Tian et al., 2014).

Quality by Design (QbD) aiming to improve the integration of pharmaceutical formulation design and product realisation leads itself into the area of predictive science. The implementation of fundamental principles and data-driven digital frameworks using *in silico* methods, such as, thermodynamic modelling, molecular dynamic/metadyanmic simulation and machine learning, will unquestionably improve the productivity of quality-orientated research and development for the

amorphous solid dosage forms (Baird et al., 2010; Edueng et al., 2017; Graeser et al., 2009; Knopp et al., 2015; Luebbert et al., 2017; Mahlin and Bergström, 2013; Schammé et al., 2018; Tian et al., 2013). This field of cross-disciplinary research between advanced therapeutics, computational tools and manufacturing technologies under the umbrella of QbD based digital frameworks will ultimately transform the amorphous formulation design and process into a new field of predictive science. Subsequently, we believe that the specific knowledge and expertise will be combined to develop reliable amorphous formulation and process design tools for quality and rapid realisation of advanced therapies in the foreseeable future (Dadou et al., 2020). Therefore, the development of digital framework based on both thermodynamic and kinetic principles for drug-polymer combinations integrated with specific manufacturing techniques will be vital for this industry.

Here, we have investigated the interesting properties of one particular category of amorphous solid dispersion for the formation of HDASD via hot-melt extrusion platform, where strong intermolecular interaction between drug and polymer can provide the main mechanism for amorphisation during high temperature processing. This type of drug-polymer combination has been reported for amorphous systems such as drug lapatinib with HPMCP (Araujo et al., 2017) and drug naproxen with Eudragit® E (Ueda et al., 2015). A significant increase in the drug loading and amorphous stability is commonly reported for these systems. We suggest that the formation of strong intermolecular interaction, such as strong hydrogen-bonding or ionic interaction, should be considered as one of the key

principles for formulation design based on the HME platform. High drug loading capacity, improved processability and amorphous stability and reduced drug thermodegradation may be achieved through this principle. In this study, the thermodynamic aspects of formulation design integrated with HME platform were investigated, where the weak acidic drugs (indomethacin, ibuprofen and naproxen) with amorphous polymeric carrier Eudragit® E (EPO) were considered as the suitable combinations. The thermodynamic phase diagrams for three HDASD systems were constructed and utilised to guide the design of the hot-melt extrusion process. The processability and storage stability of HDASDs were further investigated using various conventional and advanced analytical techniques.

2. MATERIALS AND METHODS

2.1 Materials

Indomethacin (IND), naproxen (NPX) and ibuprofen (IBU) with a purity of 99% were purchased from Sigma Aldrich (Irvine, UK) and Kemprotec (Kent, UK). Polymer Eudragit® E (EPO) is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate with a ratio of 2:1:1, was generously donated by Evonik GmbH (Darmstadt, Germany). The chemical structures of the polymer and drugs are shown in Figure 1 and the physicochemical properties of these substances used in this study are summarised in Table 1.

2.2 Methods

2.2.1 Physical mixture preparations

Drug and polymer mixtures with different compositions were firstly mixed using a mortar and pestle followed by a ball mill mixer (Retsch, model MM200, Germany). In a typical procedure, drug and polymer powder sample totalling 500mg was milled inside the ball mill mixer with two stainless steel ball at 20 Hz, except for IBU where 15Hz was used. A high milling frequency would normally result a fully amorphous IBU samples up to 0.5 w/w. A pre-defined milling time of two minutes was chosen which was subsequently followed by a two-minute interval. This procedure was repeated to a maximum of up to ten mill-stop cycles (max 20-minutes mill time). The ball-milled samples were subjected to a range of thermal analyses for the construction of phase diagram.

2.2.2 Temperature dependent small angle/wide angle x-ray scattering

The solid-state properties of ball-milled samples and the dissolution/melting behaviours of crystalline drug into the polymeric matrix as a function of temperature were analysed using a small angle/wide angle x-ray scattering (SAXS/WAXS, Ganesha 300XL, Xenocs, France). Powerful microfocus x-ray was generated from a copper source with a motorised collimation system of 4-bladed single crystal slits. Movable solid-state photon-counting detector (PILATUS 300K, Dectris AG, Switzerland) was mounted on an uninhibited transverse rail along the beamline. A total 1.4-meter movement on the detector allows for instant interchange between SAXS and WAXS configurations. The temperature control of the sample was realised by a modified Linkam stage vertically installed inside the vacuum chamber. The SAXS/WAXS system was carefully calibrated using lanthanum hexaboride and validated again before each measurement. In a typical temperature-dependent SAXS/WAXS experiment, a ball milled sample (~ 20 milligrams) was packed in an envelope of aluminium foil, secured on the centre of the heating plate on Linkam stage, and was then subjected to a heat-cool-heat cycle similar to the differential scanning calorimetry experiment. The sample was heated from 25°C to 160°C at rate of 5 °C/min, then fast cooled to -40°C at rate of 40 °C/min. A second heating procedure was conducted from -40°C to 160°C at rate of 5 °C/min. The WAXS was collected every 60 seconds at exposure time of 30 seconds during the heat-cool-heat cycle. SAXS was also collected on selected samples with 600 seconds of exposure time at key temperature points.

2.2.3 Hot-melt extrusion

Hot-melt extrusion of drug-polymer physical mixtures were conducted using 10mm diameter co-rotating twin-screw extruder (Rondol microlab, France). Drug

and polymer premixes at defined ratios were firstly prepared using mortar and pestle, then fed into the extruder using a twin-screw powder feeder at a constant rate. The process conditions (screw speed and temperature) for extrusion were selected based on the phase diagrams (solubility curve) constructed within this study (Table 2).

2.2.4 Thermal analysis

Power compensation differential scanning calorimetry (DSC8000, Perkin Elmer, UK) was used throughout to study the physical properties of drug and polymer systems before and after HME process. Nitrogen was used as the purge gas for low speed scanning (1-50 °C/min); helium gas was used for high speed scanning (≥ 100 °C/min). A 5-10 mg powder sample was packed into an aluminium pan with a lid. A pinhole was made in the lid to allow moisture to escape. Before conducting the experiments, all ball-milled samples were dried in a vacuum oven for at least 24 hours. Melting depression experiments were conducted at heating rate of 1°C/min from -40 °C to 200 °C. The endpoint of the melting endothermic peak was calculated from the intercept point of the endothermic trace and the post-melting baseline. Given that the drug-polymer particle surface interaction is a critical requirement for melting point depression experiments, different milling cycles were tested to achieve the optimal depression results. The choice of optimal milling time for preparing the physical mixtures was reported in our previous work (Donnelly et al., 2014; Tian et al., 2013).

For identification of glass transition temperatures for HDASDs immediately after HME processing, freshly prepared samples were cut into small pieces and placed

directly into the DSC pan, a scan rate of 10 °C/min was used across a temperature range between -50 to 180°C.

To validate the phase separation in IBU-EPO HDASD, high scanning rate was also used (100 °C/min). The freshly prepared HDASD was first held at various conditions relevance to the theoretical spinodal boundary of the system for prolonged period, then subjected to a quench-cooling and fast scanning procedure. The temperature ranges were chosen between -50 to 100°C for IBU samples. It is noted that only IBU-EPO was suitable for this study, because the predicted spinodal boundary was above the melting temperature and below the thermal degradation temperature of IBU. For IND-EPO and NPX-EPO systems, the predicted spinodal boundaries were both above the thermal degradation temperature of the drugs.

Thermogravimetric analysis (TGA) was also employed to assess the thermal degradation temperature of the drugs and polymer EPO. In a typical procedure, small amount of sample was loaded to an open aluminium pan after initial taring step, subjecting to a heating process from room temperature to 250 °C at a rate of 10 °C/min. The onset temperatures of any significant weight loss (>10% w/w) for drugs and polymer EOP were recorded.

2.2.5 Attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR)

Analysis on the drug-polymer interactions of ASDs were conducted using ATR-FTIR spectroscopy (Spectrum 2, Perkin Elmer, UK). Extruded samples (outside and cross section) were directly placed on the ATR stage and spectrum range of 4000 – 650 cm⁻¹ was collected based on 4 cm⁻¹ resolutions, 64 runs.

2.2.6 Atomic force microscopy (AFM)

The NaioAFM (Nanosurf, Switzerland) instrument was used to obtain topographic and phase images, allowing calculation of the surface roughness of the solid dispersions. Samples of extrudate were softened immediately after HME between two flat glass slides and then cooled on metal block. The slides were then carefully removed, and the solid sample was placed on the sample holder. Both topographic and phase images were generated with the instrument operating in dynamic mode using a Tap 190Al-G cantilever (BudgetSensors, Bulgaria). Image sizes were 10x10 μm or 25x25 μm , taken at a speed of 0.8 seconds per line. Additional parameters were varied depending on each sample and optimum sensitivity. The setpoint of the cantilever was varied from 50% to 60% of the free vibrational amplitude, which was varied from 200-1000 mV. Nanosurf Naio software was used to control, obtain the data and Image J was used to further analyse the images.

2.2.7 microRaman Spectroscopy

The recrystallisation of the drug from HDASDs during high humidity storage study were studied using a RamanStation R3 (Avalon, Instruments, Belfast, UK) coupled with a RamanMicro 300 Raman microscope (PerkinElmer, Waltham, MA, USA) with objectives at various magnifications ($\sim 1.25 \mu\text{m}/\text{pixel}$). A laser source of 785 nm was used and the Raman scattering of the samples was collected between 3200-400 cm^{-1} using an acquisition time of 20 s at resolution of 2 cm^{-1} .

2.2.8 Statistical Analysis

The statistical analysis for the effects of temperature on F-H interaction parameters for all three drug-EPO combinations was carried out using Kruskal-Wallis one-way ANOVA followed by Tukey-Kramer post hoc tests; $p < 0.05$ was

considered as significant. For comparison of the spectra from microRaman chemical mapping and surface roughness of the freshly extruded samples (AFM), a two-tailed t test was performed $p < 0.05$.

3. RESULTS AND DISCUSSIONS:

3.1 In situ temperature dependent SAXS/WAXS analysis

Small angle/wide angle x-ray scattering has the capacity to provide the spatial distribution of the dynamic features of a particle (small molecules, peptides and proteins) at nano/micro-scale ranges. It has suggested that strong intermolecular interactions can drive the formation of amorphous system under gentle mixing and moderate heating (Dave et al., 2007). Thus, in this study, it would be of significant interests to directly observe the temperature dependences of x-ray scattering pattern for the crystalline drugs (IND, NPX and IBU) in the presence of polymeric carrier. In general, the dissolution of the crystalline drug into polymeric matrix can result in the decrease of scattering intensity in the WAXS graph and eventually, completely loss of the well-defined scattering pattern (Figure 2). Examples of 3D Bragg's peak for the physical mixtures (three drugs at 0.7 w/w) as a function of temperature are shown in Figure 2 with WAXS scattering graphs provided at four key temperature points. Due to the strong intermolecular interactions between drugs and the polymeric carrier EPO, a gradual decrease in the intensity of Bragg's peaks associated with crystalline component can be observed with increased temperatures.

For example, in IND-EPO physical mixtures, the temperature for complete dissolution of 0.7 w/w IND was recorded at 125 to 130 °C which is approximate 30°C lower than the melting temperature of pure IND (DSC, 160°C). Whilst, for

NPX-EPO and IBU-EPO systems containing 0.7 w/w drug loading, the solubilisation temperatures were also recorded at 120-125°C and 50-55 °C respectively (Figure 2 b and c). This information is particularly useful for the design of hot-melt extrusion process, where a fully amorphous solid dispersion can be generated at conditions that are i) significantly lower than the melting of the crystalline drug (e.g. 30°C lower in IND-EPO case); ii) at much high drug loadings (~0.7 w/w for IND-EPO system). The unwanted thermodegradation associated with melting of the drug may be completely avoided since the amorphisation of crystalline drug is driven by the dissolution rather than melting. The in situ temperature dependent SAXS/WAXS analysis (complementary to DSC) can also be used to provide a very direct observation at conditions that can be related to the hot-melt extrusion platform (Sylvie, Tencé-Girault et al., 2019).

3.2 The drug-polymer temperature-composition phase diagram

Flory-Huggins theory (F-H), first established to estimate the miscibility of solvent-polymer system, has now been expanded to many areas. There have been several published drug-polymer binary systems employed using the Flory-Huggins theory to investigate the level of drug-excipient interactions, from drug-solvent activity derived interaction to drug-small molecule interaction and full temperature-composition drug-polymer phase diagram (Huang et al., 2017; Keen et al., 2014; Lin and Huang, 2010; Pajula et al., 2010; Tian et al., 2018, 2015). The implementation of this classic theory in predicting the miscibility of small molecules within macromolecular matrices has provided an simple and important route for ASD design (DiNunzio et al., 2010). The integration of this classical theory into the formulation design and process development based upon selected

297 advanced process technologies would have undoubtedly offered great
298 advancement for the future of pharmaceutical manufacturing (Badman and Trout,
299 2014).

300 For an informative design of ASD based on hot-melt extrusion for all three model
301 drugs, small scale DSC based F-H approach to construct the temperature-
302 composition phase diagram was used. Through the ball milling process, a range of
303 uniform drug-polymer physical mixtures at various ratios were prepared.
304 Although, the selection of optimum ball-milling time has been previous discussed,
305 the resultant physical mixtures were deemed not suitable for the systems in this
306 study. Particularly for drugs with low glass transition temperature in its
307 amorphous state (IBU and NPX), a rubber mixture was usually obtained after a
308 very short period of milling. For example, for 0.5 w/w IBU-EPO system, the
309 physical mixture can be converted to full amorphous within only 10 minutes of
310 ball-milling at frequency of 15 Hz (confirmed by DSC and SAXS/WAXS, Figure 3).
311 Therefore, to achieve sufficient experimental points from the DSC measurement
312 for construction of thermodynamic phase diagram, the drug/polymer ratio was
313 selected from 0.95 – 0.7 w/w. An example of the DSC thermogram for the IND-EPO
314 system is shown in Figure 4. For all three EPO based systems, melting endpoint
315 was not observed at a drug-polymer ratio lower than 0.7 w/w. Nevertheless, a
316 quick estimation of the drug-EPO interaction parameters for all three drugs at
317 multiple compositions may be obtained with a minimum four experimental
318 points. A plot of interaction parameter, χ , versus temperature for these systems
319 were shown in Figure 5a. The fitting constants at selected temperature regions
320 were obtained for IND-EPO, NPX-EPO and IBU-EPO with goodness of fit ranging
321 from 0.93, 0.94 to 0.97 respectively. The obtained interaction parameter constants

for all three systems are summarised in Table 3. It should be highlighted that, from all the published phase diagrams for various drug-polymer combinations, an upper critical solution temperature (UCST) where a positive B and a negative A were obtained for the drug-polymer interaction parameters (Lin and Huang, 2010; Marsac et al., 2009, 2006; Tian et al., 2018, 2013; Zhao et al., 2010). Thus, it was very interesting to observe that a concave spinodal profile was obtained for all three HDASD systems ($B < 0$ and $A > 0$) indicating the lower critical solution temperature (LCST) behaviour (Table 3). Such behaviour has been observed for many temperature responsive polymer-water systems where a polymer solution to gel transition can be observed as the temperature increases (Jones, 2004; Mori et al., 2010). Similar behaviours were also reported in polymer-polymer mixtures (Kapnistos et al., 1996; Meredith and Amis, 2000). However, it is to our knowledge, a LCST behaviour for drug-polymer binary ASD was rarely reported in the literature so far apart from the combination of carbamazepine-AFFINISOL™ (Huang et al., 2016). All three systems IND, NPX and IBU with polymer EPO have exhibited LCST behaviour with $B < 0$ and $A > 0$ at the experimental temperature range. As the temperature decreases, the experimental values for the χ became more negative suggesting a stronger drug-polymer interaction and increased drug-polymer miscibility at lower temperature range.

Furthermore, it should also be highlighted that the values of F-H interaction parameter constants (B and A) of the three drug-EPO systems were very different from the previously published systems (Tian et al., 2014). In all our previously published drug-polymer systems such as felodipine-HPMCAS, felodipine-Soluplus and felodipine-PVP, weaker intermolecular interactions were proposed at high temperatures (close to the melting point of the drug) resulting a positive B and

negative A values. The value of B highly depends on the strength of drug-polymer interaction where stronger felodipine-polymer interaction normally results a smaller B value (felodipine-PVP). Therefore, the miscibility ranking between three polymers with neutral drug felodipine was suggested to be PVP > Soluplus > HPMCAS (Tian et al., 2014). The F-H interaction parameter χ is assumed to be consisted of enthalpic term (B) and entropic term (A) fitting constants (Rubinstein and Colby, 2003). In comparison to weak hydrogen-bonding based ASDs, strong intermolecular interactions between drugs IND, NPX and IBU and polymer EPO were suggested. Therefore, it is perhaps not surprised that the change from a positive B to a negative B value may be due to the negative enthalpic contributions to the system. The exact mechanisms of such strong drug-polymer interaction between a weakly acidic drug with weakly basic polymer or vice versa in a non-aqueous environment should be further investigated, particularly for the application of HME platform (Mistry et al., 2015; Ueda et al., 2015). Indeed, similar negative enthalpic contribution to the mixing of the system has been widely discussed and utilised for the formation of molten salts, ionic liquids or eutectic mixtures (Dave et al., 2007; Emel'yanenko et al., 2007).

With the interaction parameter constants for all three drug-EPO systems obtained at various temperatures, the maximum drug solubility in polymer EPO may be approximated. As expected, with a strong enthalpic contribution from the drug-EPO systems, large drug solubility values in polymer were predicted for all three drug-EPO systems (Figure 6). The solid-liquid curves represent the extrapolation of dissolution/melting endpoints for drug IND, NPX and IBU with polymer EPO based on the temperature-dependent interaction parameters. The experimental glass transition temperatures for all three HDASDs at various compositions are

summarised within the graphs. The theoretical glass transition temperatures were calculated using Gordon-Taylor model (Baird and Taylor, 2012). The theoretical spinodal curves for IND-EPO, NPX-EPO and IBU-EPO derived from the temperature-dependent interaction parameters (χ) are also plotted in the graphs (Figure 6).

Considering the previously published drug-polymer phase diagrams, we clearly observe a significant increase on the predicted solubility values of drug IND, NPX and IBU with the polymer EPO. Approximate 0.63 w/w for IND-EPO, 0.473 w/w for NPX-EPO and 0.55 w/w for IBU-EPO were predicted as the maximum drug solubility in polymer EPO at temperature 20°C. A gradually increase on the maximum drug solubility within EPO can also be observed for all three drugs with elevated temperatures, however such a change was not as dramatic since the inverse contributed of the entropic term (ΔS). The predicted solubility values for all three drugs within polymer EPO at several critical temperatures were summarised in Table 4. Similar high drug-polymer solubility has also been reported in literature when a strong interaction was proved to be the main cause. For example, Mistry et al. (2015) has discussed that the strong ionic interactions between weakly basic drug ketoconazole and polymer poly (acrylic acid) can be probed by both infrared and solid-state NMR (Mistry et al., 2015). The strong drug-polymer interaction has also resulted a very high drug solubility value (0.6 w/w). Ueda et al. (2015) have also reported a high solubility for weakly acidic drug NPX in cationic polymer EPO (Ueda et al., 2015). A crystallisation was observed for NPX only when the drug loading was increased to 0.7 w/w or more.

3.3 The importance of phase diagram for QbD of amorphous solid dispersion

To accommodate the needs of emerging pharmaceutical formulations, there is a continuous requirement for parallel innovation in process development and quality control/assurance of the final drug products. In response, the ICH and FDA released Quality by Design (QbD) frameworks to facilitate the implementation of digital innovation in the pharmaceutical industry. QbD allows quality to be built into the formulation/process design in a predictive manner. In order to successfully implement the QbD framework, the consideration of specific process platform must be integrated into the Design Space. It is critical to be aware that the crystalline drug solubility and amorphous drug miscibility with amorphous polymer are two separate definitions. Particularly, when the second component polymer is a long chain macromolecule where the dynamic aspect of phase separation can be extremely slow and highly temperature/environment dependent. In most scenarios, ASDs are produced at higher temperature or solvent-assisted environment using various process platforms. The amorphous drug is kinetically “trapped” in a non-equilibrium state attributing to both the drug-polymer interaction and other kinetic factors related to both polymeric carrier and preparation method (Paudel et al., 2012). Hence, most experimental results show significantly higher apparent drug miscibility with polymeric carrier than the predicted thermodynamic solubility. It is imperative that we can access the kinetic behaviours of the “trapped” non-equilibrium state and relate it to the physical stability of ASD systems through the identification of the miscibility curve. The thermodynamic miscibility curve for the system can be predicted by the phase diagram as the liquid-solid line, whilst, the binodal and spinodal curves are together defined as the metastability boundary between one phase

421 amorphous state and amorphous-amorphous phase separation (AAPS) (Luebbert
422 et al., 2017; Tian et al., 2019). The position of AAPS in relation to the
423 thermodynamic liquid-solid curve will certainly provide vital information on the
424 kinetic stability of the system (Tanaka and Nishi, 1989). An illustration of three
425 possible positions for spinodal curves in relation to the liquid-solid line is
426 postulated in Figure 7 for the LCST behaviours.

427 The position of spinodal curve to the liquid-solid curve can strongly affect the
428 kinetics of amorphous-amorphous phase separation (Tian et al., 2015). The
429 verification of these positions will provide significant advances to the
430 understandings of stability of ASD systems. Luebbert et al., (2018) recently
431 reported a phase diagram (constructed by Perturbed-Chain Statistical Associating
432 Fluid Theory) exemplified as UCST behaviour with AAPS inserted through the
433 solid-liquid curve (Luebbert et al., 2018). An AAPS was evidenced at high
434 temperatures that are well above the melting point of the drug. Purohit and Taylor
435 also reported a study using high spatial resolution atomic force microscopy
436 techniques to probe the AAPS in freshly prepared ASDs, nano-scale spherical
437 domains were obtained on the surface of ASD films representing a classical
438 binodal pattern within the phase diagram (Purohit and Taylor, 2015). In
439 comparison, we are reporting a LCST behaviour for all three HDASD systems, IND-
440 EPO, NPX-EPO and IBU-EPO, where the estimated positions for binodal, spinodal
441 and solid-liquid curves may be described by Figure 7. From the theoretical point
442 of view, a thermodynamic stable drug-EPO amorphous system without the
443 potential of AAPS (temperature dependent) is indeed possible at this LCST
444 scenario, particularly for drug loading below 0.5 w/w. For example, a red dot is
445 used to illustrate a condition for LCST behaviour. The position is sitting below the

spinodal curve meaning the system will remain one phase during HME process. In addition, the position is sitting outside of the liquid-solid line indicating a lower free energy level for the ASD in comparison to the crystalline system. Therefore, with suitable mechanical energy input to overcome the viscosity barrier, the crystalline drug-polymer physical mixture at this condition will be converted into a homogenous ASD without AAPS.

To validate the phase diagram and the position of spinodal demixing, the IBU-EPO system was chosen due to the reason that predicted spinodal demixing region was well below the temperatures of thermodegradation for both components. For IND-EPO and NPX-EPO systems, the predicted spinodal demixing regions were above their thermodegradation temperatures, thus, experimental validation was not conducted (Figure 6). A physical mixture of 0.5 w/w IBU to EPO was prepared as described in method section followed by quench-cooling to form a homogeneous ASD. The freshly prepared 0.5 w/w IBU-EPO ASD sample was then subjected to annealing experiments at two temperatures, 70 °C and 110 °C. These two temperatures ($T_{\text{annealing}} > T_m$ of IBU) were identified as one-phase amorphous region and AAPS region for system 0.5 w/w IBU-EPO respectively (Figure 6c). Through the characterisations of PLM and microRaman chemical mapping, an AAPS ASD was obtained after annealed at 110 °C for 24 hours, whilst the ASD stayed homogeneous after annealed at 70 °C for similar time-scale (Support Information Figure S1).

3.4 In situ formation of HDASDs via HME

With the guidance from thermodynamic phase diagram, it was possible to design the HME process for all three HDASDs. The exact process conditions and initial

crystalline drug loadings are presented in Table 2. The location of these HDASDs were also marked in the phase diagrams in Figure 6. In each drug-EPO combinations two drug loadings were selected to be in the one-phase amorphous region and one drug loading was selected to be near the crystalline region. The extrusion process temperatures were chosen to be below the melting points of the parent crystalline drug but above the glass transition of the polymer EPO as guided by the phase diagrams.

The freshly prepared extrudates were then characterised using DSC and ATR-FTIR and directly compared with the results collected from the physical mixtures (PM) and ASDs prepared by quench-cooled method (QCPM). A similar trend was obtained for the thermograms of all three drug-EPO systems, outlining the in situ formation of one-phased HDASDs by HME at pre-defined conditions predicted by phase diagrams (Figure 6). Previously, HME methods relied on higher temperatures amorphisation and mixing of the crystalline drug into the polymer were commonly documented. However, the presence of a single distinctive glass transition with the absence of melting endothermic event was observed for all drug-EPO systems prepared by HME at predicted conditions (Figure 6, EXT denoted for extruded samples). When comparing the thermograms of EXT samples to the PM and QCPM, several clear differences can be summarised: 1) the number of glass transitions, 2) the temperature of glass transitions and 3) the melting event from the residual crystalline drug (Tablet 5-7).

In the case of IBU-EPO system, a homogeneous ASD can be achieved by both ball milling and HME at drug loading below 0.6 w/w, whilst, HME can further facilitate the generation of one phase IBU ASD up to 0.65 w/w with EPO (Table 5). The high

amorphisation capability of HME may be attributed to the fact that processing temperature is very close to the melting point of IBU. Additional shearing induced temperature elevation during HME can contribute to further dissolution of IBU into EPO carrier (Censi et al., 2018; Liu et al., 2010). In addition, a higher T_g obtained from the EXT samples also indicates a more stable amorphous solid dispersion system in comparison to the QCPMs.

In the case of NPX-EPO system, given the predicted NPX solubility in EPO was 0.614 w/w at the processing temperature (120 °C, Table 4), it was anticipated that one-phase ASDs should be obtained for 0.45 and 0.60 w/w NPX-EPO system. This was first validated by the thermal analysis, where a single T_g with the absence of melting event from NPX was recorded for NPX-EPO EXT samples (Table 6). Again higher T_g s were recorded for all NPX-EPO EXT samples in comparison to the PM or QCPM samples, where the presence of two T_g s and/or melting event was recorded. It was apparent that the use of HME enhanced the level of mixing allowing for amorphisation of NPX-EPO at temperatures well below the melting of crystalline NPX. Furthermore, for the PM sample containing 0.65 w/w NPX, there was a broad melting endothermic peak observed before the crystalline NPX.

In the case of IND-EPO system, similar to the thermograms of NPX-EPO, both PM and HME have converted the crystalline IND to amorphous at drug loading < 0.6 w/w (Table 7). In addition, two T_g s were observed for PM IND-EPO at 0.6 w/w without the presence of melting events. It is clear that high drug loaded ASD can be created well below the melting of the drug, with the use of F-H interaction parameter as a guide, highlighting again the excellent miscibility of drug to

polymer in the selected HDASDs. Furthermore, the T_g s of all systems were also significantly higher than the values predicted by the Gordon Taylor equation.

The implementation of HDASD systems in the design of HME process has enabled the drug to dissolve in the polymeric carrier, reduced the viscosity of the system and further enhanced amorphisation. The strength of the drug-polymer interaction was further assessed using of the ATR-FTIR where the ASDs prepared by HME and quench-cooled methods were compared. The IR absorption peaks highlighting the carbonyl regions of the NSAIDs and amine regions of the EPO were summarised in Table 8.

Based on the standard IR spectra for all the individual components, the characteristic peak of the carbonyl group from EPO is normally observed at 1728cm^{-1} , whilst, the carbonyl group for amorphous and crystalline IBU was recorded at 1730 cm^{-1} and 1705 cm^{-1} respectively. These original IR absorption peaks of IBU and EPO were used as the reference points as shown in Table 8. The changes of these characteristic peaks after formation of ASD may indicate the level of interactions within the system. An additional broadened peak was recorded at 1576 cm^{-1} for extruded IBU-EPO samples at all drug loadings. This peak was recorded to 1566 cm^{-1} in QCPM at 0.4 w/w IBU-EPO, but absent from higher drug loadings. This peak was suggested to be the N-O stretching after the formation of strong hydrogen-bonding (Moustafine et al., 2006). The broadening of the spectrum is more prevalent in the extruded samples, highlighting the formation of a strong hydrogen-bonding interaction during the production (Abu Ali et al., 2016). Carbonyl peak shifts were observed at the positions of 1709 to 1719 cm^{-1} for IBU after extruded with EPO. These peak shifts represent the breaking of

541 carbonyl (C=O) dimer structure in the original crystalline IBU. Interestingly, a
542 strong absorption peak at this position was observed in all extruded IBU-EPO
543 sample in comparison to the ASDS prepared by quench-cooled method.
544 Additionally, peak at 1716 cm^{-1} in 0.7 w/w IBU-EPO QCPM samples also suggests
545 the presence of crystalline IBU.

546 Similar to the IBU-EPO case, a stronger drug-polymer interaction between IND
547 and EPO was also suggested in the extruded ASDs in comparison to the quench-
548 cooled method (Figure 9). Peaks of relevance for crystalline IND were the
549 carbonyl group at 1713 cm^{-1} and 1690 cm^{-1} , whilst, three peaks at 1735, 1710 and
550 1684 cm^{-1} were observed for amorphous IND. From the IR spectra, it can be
551 shown that the presence of the peak at 1682 cm^{-1} , corresponding to the
552 amorphous IND (benzoyl C=O) was evidenced in all ASD samples except in 0.7
553 w/w IND-EPO prepared by quench-cooled method.

554 The peak at 1690 cm^{-1} for 0.7 w/w quench-cooled IND-EPO indicated the presence
555 of crystalline IND. Additionally, the presence of the amorphous IND peak (1735 cm^{-1})
556 for both extruded samples and the 0.4 w/w quench-cooled IND-EPO ASD
557 suggests the amorphous nature of IND (Liu et al., 2012). The absence of the dimer
558 formation (1710 cm^{-1}) for carbonyl peak at 1710 cm^{-1} also suggests the formation
559 of stronger intermolecular interactions between IND and EPO in the extruded
560 HDASDs (Liu et al., 2012). Similar disruption of the dimer formation at the
561 carbonyl peak of the drug has also been discussed for hydrogen-bonding based
562 ASD systems (Taylor and Zografi, 1997).

563 The spectra of NPX with EPO (Figure 10) showed different characteristic peaks to
564 the other NSAID systems, with less focus on the carbonyl regions. In comparison

of all the ASDs with crystalline NPX, an additional band at 1682 cm^{-1} relating to the carboxylic acid dimer was only recorded for 0.65 w/w NPX-EPO system prepared by quench-cooled method. The appearance of this peak indicated the lack of drug-polymer interactions between EPO and NPX (Adibkia et al., 2013; Doreth et al., 2016). An additional peak was recorded between $1200\text{--}1230\text{ cm}^{-1}$ for all the rest samples suggesting the formation of strong drug-polymer interaction (Figure 10b). The effects of strong drug-EPO intermolecular interactions for all three system facilitated by HME were further examined by in vitro drug release studies. The rate and extend of drug release were significantly higher for EXT samples in comparison to the QCPM samples (support information Figure S3).

3.5 Verification of residual crystal in extrudates

Atomic force microscopy (AFM) was further used for to determine residual crystal after extrusion. Through the use of phase contrast mode, outlining the phase differences based on the adhesion and friction on the surface of the extrudates, nanoscale and microscale domains may be differentiated. Examples of AFM phase images ($10\times 10\text{ }\mu\text{m}$) of the NPX-EPO HDASD at three drug loadings (0.45, 0.6, 0.7 w/w) were presented in Figure 11 (d-f) with corresponding 3D map of the surface (a-c). The root mean square surface roughness of the extrudates were also calculated based on the average of randomly selected five different samples. When the initial drug loading was close to/exceeding the predicted liquid-solid curve (Figure 6), an increase on the surface roughness was observed for both NPX-EPO and IND-EPO HDASD systems. However, it was very difficult to characterise the IBU-EPO HDASD systems using AFM due to the stick and rubbery nature of these

samples at room temperature. Nevertheless, a smooth, homogenous surface (low surface roughness, Figure 11g) with the absence of structured particles were normally observed for NPX-EPO HDASD at drug loadings of 0.45 w/w (d) and 0.6 w/w (e). In comparison, when drug loading was increased to 0.65 w/w (predicted to be crystalline in NPX-EPO system), a sudden increase on surface roughness with the appearance of structured particles can be observed by the AFM (Figure 11 c, f and g). With the calculated root mean square surface roughness for each extruded systems, it was possible to direct visualise the transitions of the system from one-phase amorphous to extrudates with residual crystals (Lauer et al., 2018).

3.6 Storage of HDASDs at high humidity conditions

Due to the ingress of water in the system at high humidity, microRaman spectroscopic analysis was employed to monitor the appearance of crystalline drug during storage. This technique has also been widely recommended to offer the sensitivity of differentiating the crystalline and amorphous nature of the drug within ASDs without the influence of moisture (Esmonde-White et al., 2017). It was also suggested that the stability of these HDASDs system may be further enhanced by the potential moisture-induced ionic interactions between weak acidic drugs and polymer EPO (Sarode et al., 2013). In this work, the storage conditions (~95% RH) were achieved by preparing a saturated salt solution of potassium nitrate at 20°C. High humidity and high drug loading (0.6 w/w) were used to accelerate the potential phase separation and crystallisation of drug from the HDASDs (Figure 12). The correlation maps were constructed based on the relative spectra correlation calculation between the freshly prepared HDASDs and the spectra of crystalline drugs (white to black rainbow colour chart was used to

represent the correlation ratio of 0.999 – 0.599). In the case of NPX, as observed in the spectra shown in Figure 12a, the key peak of interest in the NPX spectrum is at 3070 cm⁻¹. This peak was observed in crystalline NPX but absent in the amorphous form attributing to the aromatic CH stretching. At 0.6 w/w NPX drug loading, the sample was shown to be amorphous both prior to and after three weeks of high humidity storage with potential aggregation and amorphous phase separation (T=3 weeks, chemical map). Similarly, IND also showed no recrystallisation after 3 weeks of storage at the same high humidity conditions (Figure 12b) indicating by the carbonyl peak at 1680 cm⁻¹ in comparison to the 1700 cm⁻¹ from crystalline IND. This characteristic peak of amorphous IND was recorded for 0.6 w/w IND-EPO HDASD prior to and after three weeks of storage. Finally, in the case of 0.6 w/w IBU-EPO system where the characteristic peak at 1608 cm⁻¹ in the crystalline IBU and 1613 cm⁻¹ in the HDASD was also clearly observed (Rossi et al., 2009). Again, there was no apparent recrystallisation of the drug after three weeks at high humidity storage (Figure 12c), however, a shift on the correlation between amorphous and crystalline IBU was recorded with potential drug aggregation after the storage.

4. Conclusion

Flory-Huggins based thermodynamic modelling is an informative framework for the establishment of a design space of amorphous solid dispersion. Through the constructed phase diagrams for all three HDASD systems, LCST behaviours were obtained indicating the possibility of forming stable amorphous systems at high drug loadings and low temperatures. Further characterisations on the extrudates confirmed that the amorphisation of NPX, IBU and IND at these pre-defined

conditions can be achieved by one-step continuous HME process. The establishment of predictive thermodynamic model allows the interpretation and evaluation of HME process in a well-defined space, in return, ensure the quality of amorphous solid dispersions. Further work will be focused on the investigations of kinetic impacts of the HME process based on the pre-defined thermodynamics of the HDASD systems.

References

- Abu Ali, H., Omar, S.N., Darawsheh, M.D., Fares, H., 2016. Synthesis, characterization and antimicrobial activity of zinc(II) ibuprofen complexes with nitrogen-based ligands. *J. Coord. Chem.* 69, 1110–1122. <https://doi.org/10.1080/00958972.2016.1149819>
- Adibkia, K., Barzegar-Jalali, M., Maheri-Esfanjani, H., Ghanbarzadeh, S., Shokri, J., Sabzevari, A., Javadzadeh, Y., 2013. Physicochemical characterization of naproxen solid dispersions prepared via spray drying technology. *Powder Technol.* 246, 448–455. <https://doi.org/10.1016/j.powtec.2013.05.044>
- Alshahrani, S.M., Lu, W., Park, J.B., Morott, J.T., Alsulays, B.B., Majumdar, S., Langley, N., Kolter, K., Gryczke, A., Repka, M.A., 2015. Stability-enhanced Hot-melt Extruded Amorphous Solid Dispersions via Combinations of Soluplus® and HPMCAS-HF. *AAPS PharmSciTech* 16, 824–834. <https://doi.org/10.1208/s12249-014-0269-6>
- Anderson, B.D., 2018. Predicting Solubility/Miscibility in Amorphous Dispersions: It Is Time to Move Beyond Regular Solution Theories. *J. Pharm. Sci.* <https://doi.org/10.1016/j.xphs.2017.09.030>

662 Araujo, G.L.B. De, Benmore, C.J., Byrn, S.R., 2017. Local Structure of Ion Pair
 663 Interaction in Lapatinib Amorphous Dispersions characterized by
 664 Synchrotron X-Ray diffraction and Pair Distribution Function Analysis. Nat.
 665 Publ. Gr. 1–10. <https://doi.org/10.1038/srep46367>
 666 Badman, C., Trout, B.L., 2014. Achieving Continuous Manufacturing. Int. Symp.
 667 Contin. Manuf. Pharm. 104, Intro White Paper.
 668 <https://doi.org/10.1002/jps.24246>
 669 Baird, J. a., Taylor, L.S., 2012. Evaluation of amorphous solid dispersion
 670 properties using thermal analysis techniques. Adv. Drug Deliv. Rev. 64, 396–
 671 421. <https://doi.org/10.1016/j.addr.2011.07.009>
 672 Baird, J.A., Van Eerdenbrugh, B., Taylor, L.S., 2010. A Classification System to
 673 Assess the Crystallization Tendency of Organic Molecules from Undercooled
 674 Melts. J. Pharm. Sci. 99, 3787–3806. <https://doi.org/10.1002/jps.22197>
 675 Caron, V., Tajber, L., Corrigan, O.I., Healy, A.M., 2011. A Comparison of Spray
 676 Drying and Milling in the Production of Amorphous Dispersions of
 677 Sulfathiazole/Polyvinylpyrrolidone and
 678 Sulfadimidine/Polyvinylpyrrolidone. Mol. Pharm. 8, 532–542.
 679 <https://doi.org/10.1021/mp1003674>
 680 Censi, R., Gigliobianco, M.R., Casadidio, C., Di Martino, P., 2018. Hot Melt
 681 Extrusion: Highlighting Physicochemical Factors to Be Investigated While
 682 Designing and Optimizing a Hot Melt Extrusion Process. Pharmaceutics 10.
 683 <https://doi.org/10.3390/pharmaceutics10030089>
 684 Dadou, S.M., Senta-Loys, Z., Almajaan, A., Li, S., Jones, D.S., Healy, A.M., Tian, Y.,
 685 Andrews, G.P., 2020. The development and validation of a quality by design

686 based process analytical tool for the inline quantification of Ramipril during
 687 hot-melt extrusion. *Int. J. Pharm.* 584.
 688 <https://doi.org/10.1016/j.ijpharm.2020.119382>
 689 Dave, H., Gao, F., Lee, J.H., Liberatore, M., Ho, C.C., Co, C.C., 2007. Self-assembly in
 690 sugar-oil complex glasses. *Nat. Mater.* 6, 287–290.
 691 <https://doi.org/10.1038/nmat1864>
 692 Dedroog, S., Huygens, C., Van den Mooter, G., 2019. Chemically identical but
 693 physically different: A comparison of spray drying, hot melt extrusion and
 694 cryo-milling for the formulation of high drug loaded amorphous solid
 695 dispersions of naproxen. *Eur. J. Pharm. Biopharm.* 135, 1–12.
 696 <https://doi.org/10.1016/j.ejpb.2018.12.002>
 697 DiNunzio, J.C., Hughey, J.R., Brough, C., Miller, D. a, Williams, R.O., McGinity, J.W.,
 698 2010. Production of advanced solid dispersions for enhanced bioavailability
 699 of itraconazole using KinetiSol Dispersing. *Drug Dev. Ind. Pharm.* 36, 1064–
 700 78. <https://doi.org/10.3109/03639041003652973>
 701 Donnelly, C., Tian, Y., Potter, C.C.C., Jones, D.S.D.S., Andrews, G.P.G.P., 2014.
 702 Probing the Effects of Experimental Conditions on the Character of Drug-
 703 Polymer Phase Diagrams Constructed Using Flory-Huggins Theory. *Pharm.*
 704 *Res.* 32, 167–179. <https://doi.org/10.1007/s11095-014-1453-9>
 705 Doreth, M., L?bmann, K., Grohgan, H., Holm, R., Lopez de Diego, H., Rades, T.,
 706 Priemel, P.A., 2016. Glass solution formation in water - In situ
 707 amorphization of naproxen and ibuprofen with Eudragit? E PO. *J. Drug Deliv.*
 708 *Sci. Technol.* 34, 32–40. <https://doi.org/10.1016/j.jddst.2016.02.003>
 709 Edueng, K., Mahlin, D., Bergström, C.A.S., 2017. The Need for Restructuring the

710 Disordered Science of Amorphous Drug Formulations. Pharm. Res.
 711 <https://doi.org/10.1007/s11095-017-2174-7>

712 Emel'yanenko, V.N., Verevkin, S.P., Heintz, A., 2007. The Gaseous Enthalpy of
 713 Formation of the Ionic Liquid 1-Butyl-3-methylimidazolium Dicyanamide
 714 from Combustion Calorimetry, Vapor Pressure Measurements, and Ab Initio
 715 Calculations. J. Am. Chem. Soc. 129, 3930–3937.
 716 <https://doi.org/10.1021/ja0679174>

717 Esmonde-White, K.A., Cuellar, M., Uerpmann, C., Lenain, B., Lewis, I.R., 2017.
 718 Raman spectroscopy as a process analytical technology for pharmaceutical
 719 manufacturing and bioprocessing. Anal. Bioanal. Chem. 409, 637–649.
 720 <https://doi.org/10.1007/s00216-016-9824-1>

721 FDA, 2019a. FDA expands approval of treatment for cystic fibrosis to include
 722 patients ages 6 and older [WWW Document]. URL
 723 [https://www.fda.gov/news-events/press-announcements/fda-expands-](https://www.fda.gov/news-events/press-announcements/fda-expands-approval-treatment-cystic-fibrosis-include-patients-ages-6-and-older)
 724 [approval-treatment-cystic-fibrosis-include-patients-ages-6-and-older](https://www.fda.gov/news-events/press-announcements/fda-expands-approval-treatment-cystic-fibrosis-include-patients-ages-6-and-older)

725 FDA, 2019b. FDA approves new breakthrough therapy for cystic fibrosis [WWW
 726 Document]. URL [https://www.fda.gov/news-events/press-](https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis)
 727 [announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis](https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis)

728 FDA, 2015. Orkambi Prescribing information 1–16.

729 FDA, 2012. Approval letter for Kalydeco. Approv. Lett. 1–5.
 730 <https://doi.org/10.13664/j.cnki.pcr.2011.05.029>

731 Graeser, K.A., Patterson, J.E., Zeitler, J.A., Gordon, K.C., Rades, T., 2009. Correlating
 732 thermodynamic and kinetic parameters with amorphous stability. Eur. J.

733 Pharm. Sci. 37, 492–498. <https://doi.org/10.1016/j.ejps.2009.04.005>

734 Hancock, B.C.C., Zografi, G., 1997. Characteristics and significance of the
 735 amorphous state in pharmaceutical systems. J. Pharm. Sci. 86, 1–12.
 736 <https://doi.org/10.1021/js9601896>

737 Huang, S., O'Donnell, K.P., Delpon de Vaux, S.M., O'Brien, J., Stutzman, J., Williams,
 738 R.O., 2017. Processing thermally labile drugs by hot-melt extrusion: The
 739 lesson with gliclazide. Eur. J. Pharm. Biopharm. 119, 56–67.
 740 <https://doi.org/10.1016/j.ejpb.2017.05.014>

741 Huang, S., O'Donnell, K.P., Keen, J.M., Rickard, M.A., McGinity, J.W., Williams, R.O.,
 742 2016. A New Extrudable Form of Hypromellose: AFFINISOL™ HPMC HME.
 743 AAPS PharmSciTech 17, 106–119. [https://doi.org/10.1208/s12249-015-](https://doi.org/10.1208/s12249-015-0395-9)
 744 0395-9

745 Jones, D., 2004. Pharmaceutical Applications of Polymers for Drug Delivery,
 746 Polysaccharides for Drug Delivery and Pharmaceutical Applications.

747 Kalepu, S., Nekkanti, V., 2015. Insoluble drug delivery strategies: Review of
 748 recent advances and business prospects. Acta Pharm. Sin. B.
 749 <https://doi.org/10.1016/j.apsb.2015.07.003>

750 Kapnistos, M., Hinrichs, A., Vlassopoulos, D., Anastasiadis, S.H., Stammer, A., Wolf,
 751 B.A., 1996. Rheology of a Lower Critical Solution Temperature Binary
 752 Polymer Blend in the Homogeneous, Phase-Separated, and Transitional
 753 Regimes. Macromolecules 29, 7155–7163.
 754 <https://doi.org/10.1021/ma960835n>

755 Keen, J.M., Martin, C., MacHado, A., Sandhu, H., McGinity, J.W., Dinunzio, J.C., 2014.

Investigation of process temperature and screw speed on properties of a pharmaceutical solid dispersion using corotating and counter-rotating twin-screw extruders. *J. Pharm. Pharmacol.* 66, 204–217.
<https://doi.org/10.1111/jphp.12106>

Knopp, M.M.M.M., Tajber, L., Tian, Y., Olesen, N.E., Jones, D.S.D.S., Kozyra, A., Löbmann, K., Paluch, K., Brennan, C.M.C.M., Holm, R., Healy, A.M.A.M., Andrews, G.P.G., Rades, T., Loebmann, K., Paluch, K., Brennan, C.M.C.M., Holm, R., Healy, A.M.A.M., Andrews, G.P.G., Rades, T., 2015. Comparative study of different methods for the prediction of drug-polymer solubility. *Mol. Pharm.* 12, 3408-3419.
<https://doi.org/10.1021/acs.molpharmaceut.5b00423>

Lauer, M.E., Maurer, R., Paepe, A.T. De, Stillhart, C., Jacob, L., James, R., Kojima, Y., Rietmann, R., Kissling, T., van den Ende, J.A., Schwarz, S., Grassmann, O., Page, S., 2018. A Miniaturized Extruder to Prototype Amorphous Solid Dispersions: Selection of Plasticizers for Hot Melt Extrusion. *Pharmaceutics* 10, 58. <https://doi.org/10.3390/pharmaceutics10020058>

Lin, D., Huang, Y., 2010. A thermal analysis method to predict the complete phase diagram of drug-polymer solid dispersions. *Int. J. Pharm.* 399, 109–115.
<https://doi.org/10.1016/j.ijpharm.2010.08.013>

Liu, H., Wang, P., Zhang, X., Shen, F., Gogos, C.G., 2010. Effects of extrusion process parameters on the dissolution behavior of indomethacin in Eudragit® E PO solid dispersions. *Int. J. Pharm.* 383, 161–169.
<https://doi.org/10.1016/j.ijpharm.2009.09.003>

Liu, H., Zhang, X., Suwardie, H., Wang, P., Gogos, C.G., 2012. Miscibility studies of

780 indomethacin and Eudragit® E PO by thermal, rheological, and
 781 spectroscopic analysis. *J. Pharm. Sci.* 101, 2204–2212.
 782 <https://doi.org/10.1002/jps.23075>
 783 Luebbert, C., Huxoll, F., Sadowski, G., Van Den Mooter, G., Grohgan, H., 2017.
 784 Amorphous-amorphous phase separation in API/polymer formulations.
 785 *Molecules* 22, 1–17. <https://doi.org/10.3390/molecules22020296>
 786 Luebbert, C., Klanke, C., Sadowski, G., 2018. Investigating phase separation in
 787 amorphous solid dispersions via Raman mapping. *Int. J. Pharm.* 535, 245–
 788 252. <https://doi.org/10.1016/j.ijpharm.2017.11.014>
 789 Mahlin, D., Bergström, C.A.S., 2013. Early drug development predictions of glass-
 790 forming ability and physical stability of drugs. *Eur. J. Pharm. Sci.* 49, 323–
 791 332. <https://doi.org/10.1016/j.ejps.2013.03.016>
 792 Marsac, P.J., Li, T., Taylor, L.S., 2009. Estimation of drug-polymer miscibility and
 793 solubility in amorphous solid dispersions using experimentally determined
 794 interaction parameters. *Pharm. Res.* 26, 139–151.
 795 <https://doi.org/10.1007/s11095-008-9721-1>
 796 Marsac, P.J., Shamblin, S.L., Taylor, L.S., 2006. Theoretical and practical
 797 approaches for prediction of drug-polymer miscibility and solubility. *Pharm.*
 798 *Res.* 23, 2417–2426. <https://doi.org/10.1007/s11095-006-9063-9>
 799 Meredith, J.C., Amis, E.J., 2000. LCST phase separation in biodegradable polymer
 800 blends: poly(D,L-lactide) and poly(epsilon-caprolactone). *Macromol. Chem.*
 801 *Phys.* 201, 733–739. [https://doi.org/10.1002/\(sici\)1521-](https://doi.org/10.1002/(sici)1521-3935(20000301)201:6<733::aid-macp733>3.3.co;2-x)
 802 [3935\(20000301\)201:6<733::aid-macp733>3.3.co;2-x](https://doi.org/10.1002/(sici)1521-3935(20000301)201:6<733::aid-macp733>3.3.co;2-x)

803 Mistry, P., Mohapatra, S., Gopinath, T., Vogt, F.G., Suryanarayanan, R., 2015. Role
804 of the Strength of Drug-Polymer Interactions on the Molecular Mobility and
805 Crystallization Inhibition in Ketoconazole Solid Dispersions. *Mol. Pharm.* 12,
806 3339–3350. <https://doi.org/10.1021/acs.molpharmaceut.5b00333>

807 Mori, T., Beppu, S., Berber, M.R., Mori, H., Makimura, T., Tsukamoto, A., Minagawa,
808 K., Hirano, Tomohiro, Tanaka, M., Niidome, T., Katayama, Y., Hirano, Tatsuya,
809 Maeda, Y., 2010. Design of temperature-responsive polymers with enhanced
810 hysteresis: α,α -disubstituted vinyl polymers. *Langmuir* 26, 9224–9232.
811 <https://doi.org/10.1021/la100020t>

812 Moustafine, R.I., Zaharov, I.M., Kemenova, V.A., 2006. Physicochemical
813 characterization and drug release properties of Eudragit® E PO/Eudragit®
814 L 100-55 interpolyelectrolyte complexes. *Eur. J. Pharm. Biopharm.* 63, 26–
815 36. <https://doi.org/10.1016/j.ejpb.2005.10.005>

816 Pajula, K., Taskinen, M., Lehto, V.-P.P., Ketolainen, J., Korhonen, O., 2010.
817 Predicting the Formation and Stability of Amorphous Small Molecule Binary
818 Mixtures from Computationally Determined Flory-Huggins Interaction
819 Parameter and Phase Diagram. *Mol. Pharm.* 7, 795–804.
820 <https://doi.org/10.1021/mp900304p>

821 Paudel, A., Nies, E., Van Den Mooter, G., 2012. Relating hydrogen-bonding
822 interactions with the phase behavior of naproxen/PVP K 25 solid
823 dispersions: Evaluation of solution-cast and quench-cooled films. *Mol.*
824 *Pharm.* 9, 3301–3317. <https://doi.org/10.1021/mp3003495>

825 Purohit, H.S., Taylor, L.S., 2015. Miscibility of Itraconazole-Hydroxypropyl
826 Methylcellulose Blends: Insights with High Resolution Analytical

827 Methodologies. *Mol. Pharm.* 12, 4542–4553.
828 <https://doi.org/10.1021/acs.molpharmaceut.5b00761>

829 Quinteros, D.A., Rigo, V.R., Kairuz, A.F.J., Olivera, M.E., Manzo, R.H., Allemandi,
830 D.A., 2008. Interaction between a cationic polymethacrylate (Eudragit E100)
831 and anionic drugs. *Eur. J. Pharm. Sci.* 33, 72–79.
832 <https://doi.org/10.1016/j.ejps.2007.10.002>

833 Repka, M.A., Bandari, S., Kallakunta, V.R., Vo, A.Q., McFall, H., Pimparade, M.B.,
834 Bhagurkar, A.M., 2018. Melt extrusion with poorly soluble drugs – An
835 integrated review. *Int. J. Pharm.* 535, 68–85.
836 <https://doi.org/10.1016/j.ijpharm.2017.10.056>

837 Rossi, B., Verrocchio, P., Viliani, G., Mancini, I., Guella, G., Rigo, E., Scarduelli, G.,
838 Mariotto, G., 2009. Vibrational properties of ibuprofen-cyclodextrin
839 inclusion complexes investigated by Raman scattering and numerical
840 simulation. *J. Raman Spectrosc.* 40, 453–458.
841 <https://doi.org/10.1002/jrs.2150>

842 Rubinstein, M., Colby, R.H., 2003. *Polymer physics*, Polymer International. Oxford
843 University Press. <https://doi.org/10.1002/pi.1472>

844 Sarode, A.L., Sandhu, H., Shah, N., Malick, W., Zia, H., 2013. Hot Melt Extrusion for
845 Amorphous Solid Dispersions : Temperature and Moisture Activated Drug –
846 Polymer Interactions for Enhanced Stability.

847 Schammé, B., Couvrat, N., Tognetti, V., Delbreilh, L., Dupray, V., Dargent, É.,
848 Coquerel, G., 2018. Investigation of Drug–Excipient Interactions in
849 Bicletymol Amorphous Solid Dispersions. *Mol. Pharm.*
850 [acs.molpharmaceut.7b00993](https://doi.org/10.1021/acs.molpharmaceut.7b00993).

851 <https://doi.org/10.1021/acs.molpharmaceut.7b00993>

852 Song, Y., Yang, X., Chen, X., Nie, H., Byrn, S., Lubach, J.W., 2015. Investigation of

853 Drug-Excipient Interactions in Lapatinib Amorphous Solid Dispersions

854 Using Solid-State NMR Spectroscopy. *Mol. Pharm.* 12, 857–866.

855 <https://doi.org/10.1021/mp500692a>

856 Sylvie, Tencé-Girault, Sylvie, L., Oana, B., Patrick, D., François, B., 2019. Crystals,

857 Vol. 9, Pages 271: Simultaneous SAXS-WAXS Experiments on Semi-

858 Crystalline Polymers: Example of PA11 and Its Brill Transition. *Crystals* 9,

859 271. <https://doi.org/10.3390/cryst9050271>

860 Tanaka, H., Nishi, T., 1989. Local phase separation at the growth front of a

861 polymer spherulite during crystallization and nonlinear spherulitic growth

862 in a polymer mixture with a phase diagram. *Phys. Rev. A* 39, 783–794.

863 <https://doi.org/10.1103/PhysRevA.39.783>

864 Taylor, L.S., Zografi, G., 1997. Spectroscopic characterization of interactions

865 between PVP and indomethacin in amorphous molecular dispersions.

866 *Pharm. Res.* <https://doi.org/10.1023/A:1012167410376>

867 Tian, Y., Booth, J., Meehan, E., Jones, D.S.D.S., Li, S., Andrews, G.P.G.P., 2013.

868 Construction of drug-polymer thermodynamic phase diagrams using flory-

869 huggins interaction theory: Identifying the relevance of temperature and

870 drug weight fraction to phase separation within solid dispersions. *Mol.*

871 *Pharm.* 10, 236–248. <https://doi.org/10.1021/mp300386v>

872 Tian, Y., Caron, V., Jones, D.S.D.S., Healy, A.-M.A.M., Andrews, G.P.G.P., 2014. Using

873 Flory-Huggins phase diagrams as a pre-formulation tool for the production

874 of amorphous solid dispersions: A comparison between hot-melt extrusion

875 and spray drying. J. Pharm. Pharmacol. 66, 256–274.

876 <https://doi.org/10.1111/jphp.12141>

877 Tian, Y., Jones, D.S.D.S., Andrews, G.P.G.P., 2015. An investigation into the role of

878 polymeric carriers on crystal growth within amorphous solid dispersion

879 systems. Mol. Pharm. 12, 150306122810000.

880 <https://doi.org/10.1021/mp500702s>

881 Tian, Y., Jones, D.S.D.S., Donnelly, C., Brannigan, T., Li, S., Andrews, G.P.G.P., 2018.

882 A New Method of Constructing a Drug-Polymer Temperature-Composition

883 Phase Diagram Using Hot-Melt Extrusion. Mol. Pharm. 15, 1379–1391.

884 <https://doi.org/10.1021/acs.molpharmaceut.7b00445>

885 Tian, Y., Qian, K., Jacobs, E., Amstad, E., Jones, D.S., Stella, L., Andrews, G.P., 2019.

886 The Investigation of Flory – Huggins Interaction Parameters for Amorphous

887 Solid Dispersion Across the Entire Temperature and Composition Range.

888 Pharmaceutics 11, 420.

889 Ueda, H., Wakabayashi, S., Kikuchi, J., Ida, Y., Kadota, K., Tozuka, Y., 2015.

890 Anomalous role change of tertiary amino and ester groups as hydrogen

891 acceptors in eudragit E based solid dispersion depending on the

892 concentration of naproxen. Mol. Pharm. 12, 1050–1061.

893 <https://doi.org/10.1021/mp5005417>

894 Zhang, J., Han, R., Chen, W., Zhang, W., Li, Y., Ji, Y., Chen, L., Pan, H., Yang, X., Pan,

895 W., Ouyang, D., 2018. Analysis of the Literature and Patents on Solid

896 Dispersions from 1980 to 2015. Molecules 23, 1–19.

897 <https://doi.org/10.3390/molecules23071697>

898 Zhao, Y., Inbar, P., Chokshi, P.H., Malick, A.W., Choi, D., 2010. Prediction of

thermal phase diagram of amorphous solid dispersions by Flory-Huggins

Theory. J. Pharm. Sci. 99, 4215–4227. <https://doi.org/10.1002/jps>

Table 1 Physicochemical properties for drugs and polymer used in this study (Cai et al., 2011; Kindermann et al., 2011; Li et al., 2016; Ng et al., 2013).

Substance	T _g (°C)	T _m (°C)	Molecular weight (g/mol)	Density (g/cm ³)
Eudragit® E (EPO)	48	—	47000.00	0.83
Naproxen	6	152	230.59	1.29
Ibuprofen	-44	76	206.29	1.03
Indomethacin	50	156	357.79	1.32

Table 2 HME process conditions and drug loadings for EPO with drug IND, NPX and IBU

Systems	Process condition, full convey (11mm, L/D 20:1)	Drug weight fractions (w/w)
indomethacin - EPO	120 °C, 60 RPM	0.4; 0.6; 0.7
naproxen - EPO	120 °C, 60 RPM	0.45; 0.6; 0.65
ibuprofen - EPO	65°C, 60 RPM	0.45; 0.6; 0.7

Table 3 Flory-Huggins interaction parameter constants for system IND+EPO, NPX+EPO and IBU+EPO

HDASDs	B	A	R ²
IND-EPO	-19601	42.39	0.93
NPX-EPO	-8072.5	17.28	0.94
IBU-EPO	-9083.2	24.86	0.97

914 Table 4 The predicted drug-EPO solubility as function of temperatures for IND,
915 NPX and IBU systems

Temperatures (°C)	IND solubility in EPO (w/w) [§]	NPX solubility in EPO (w/w)	IBU solubility in EPO (w/w)
20	0.631	0.473	0.541
30	0.634	0.480	0.557
50	0.641	0.495	0.611
70	0.651	0.516	0.766
90	0.664	0.544	1
120	0.699	0.614	Spinodal region

916 * data for drug solubility in polymer EPO was predicted through the constructed
917 temperature-composition phase diagrams

918 [§] denoted the values are not statistically significant at different temperatures
919 suggesting a less temperature dependent drug-polymer interaction parameters
920 (p>0.05)

921
922 Table 5 Thermal events recorded using DSC for IBU-EPO mixtures at selected drug
923 loadings

Sample	Glass Transition (°C)	Melting Event (°C)
0.45 IBU_PM	7.41 ± 0.32	-
0.45 IBU_EXT	3.62 ± 1.4	-
0.6 IBU_PM	- 15.97 ± 1.6	65.23-81.64
0.6 IBU_EXT	4.67 ± 1.1	-
0.65 IBU_PM	- 21.88 ± 0.91	58.78-84.57
0.65 IBU_EXT	-13.6 ± 0.81	-

924 * Glass transition temperatures were average value±standard deviation (n=3)

925 Table 6 Thermal events recorded using DSC for NPX-EPO mixtures at selected
926 drug loadings and production methods

Sample	Glass Transition (°C)	Melting Event(°C)
0.45 NPX_BM	36.57 ± 0.61	-
0.45 NPX_EXT	38.1 ± 0.69	-
0.6 NPX_BM	35.58 ± 0.93	-
0.6 NPX_EXT	38.23 ± 0.45	-
0.65 NPX_BM	28.34 ± 0.11	133.14 ± 1.50
0.65 NPX_EXT	36.42 ± 0.45	-

* Glass transition temperatures were average value $\pm$ standard deviation (n=3)

Table 7 Thermal events measured using DSC of IND_EPO mixes at different drug loading and production methods

Sample	Glass Transition ($^{\circ}\text{C}$)	Melting Event ($^{\circ}\text{C}$)
0.4 IND_BM	53.50 ± 0.36	-
0.4 IND_EXT	54.70 ± 0.46	-
0.6 IND PM	31.10 ± 1.4	81.35-120.45
0.6 IND EXT	59.49 ± 0.67	-
0.7 IND PM	19.24	82.2- 132.67
0.7 IND EXT	54.27 ± 0.77	126.21- 147.58

* Glass transition temperatures were average value $\pm$ standard deviation (n=3)

Table 8 The key IR absorption peaks for all drug-polymer ASDs prepared via different production methods

Tested samples	Key peaks presented by IR wavenumbers (cm^{-1})					
	IND_EPO		NPX_EPO		IBU_EPO	
	HME	QCPM	HME	QCPM	HME	QCPM
Higher drug loadings (0.65/ 0.7)	1682 1735	1690 -	- - -	1682 1176 1158	1576 1729	- 1716
Lower drug loadings (0.45/0.4)	1682 1735	1682 1735	- - -	- - -	1576 1729	1566 1719

Fig.1

939 Fig. 2

a_70%IND-EPO

940

b_70%NPX-EPO

941

Fig. 3

947 Fig. 4

948

949 Fig.5

950

951

952

953 Fig.6

954

955

956

957

Fig.7

962 Fig.8

963

964 Fig.9

965

966 Fig.10

967

968

969 Fig.11

970

971

973

974

975

976

977 *Figure 1 chemical structure of polymer Eudragit® EPO (a) and drug indomethacin*
 978 *(b) naproxen (c) ibuprofen (d), reported potential strong drug-polymer*
 979 *intermolecular interactions are highlighted in circles*

980

981 *Figure 2 Evolution of WAXS scattering profiles as a function of sample temperature*
 982 *for physical mixtures IND-EPO (a), NPX-EPO (b) and IBU-EPO (c) at drug loading*
 983 *of 0.7 w/w*

984

985 *Figure 3 The WAXS and SAXS scattering plots for 0.5 w/w IBU-EPO physical*
 986 *mixture processed via ball-milling at 15Hz for 10 minutes*

987

988 *Figure 4 Example of melting point depression thermograms for IND-EPO ball-milled*
 989 *physical mixtures, compositions from 1 to 0.75 w/w.*

990

991 *Figure 5 Plots of Flory-Huggins interaction parameters versus temperature for IND-*
 992 *EPO, NPX-EPO and IBU-EPO systems showing Lower Critical Solution Temperature*
 993 *behaviour with $B < 0$, $A > 0$ (LCST, at high temperature range)*

994

995 *Figure 6 the temperature-composition phase diagram for systems IND-EPO (a), NPX-*
 996 *EPO (b) and IBU-EPO (c) with associated errors; the calculated spinodal curves are*
 997 *shown in dash lines; the experimental and theoretical glass transition temperatures*
 998 *for these HDASDs are also included; EXT and (X) denoted the extrusion conditions*
 999

1000 *Figure 7 Schematic phase diagrams for various kinds of crystalline-amorphous*
1001 *polymer blends. The binodal and melting point are drawn by solid line (partially by*
1002 *dashed line) and spinodal curves are drawn by dotted lines; red dot illustrates the*
1003 *temperature and drug loading for a stable ASD from both thermodynamic and*
1004 *kinetic perspectives.*

1005
1006 *Figure 8 IR spectra of IBU-EPO mixtures prepared by HME (solid) and quench-*
1007 *cooled melt (QCPM, dashed) compared with pure crystalline drug and pure EPO*
1008 *polymer*

1009
1010 *Figure 9 IR spectra of IND-EPO mixtures prepared by HME (solid) and quench-cooled*
1011 *method (QCPM, dashed) in comparison to the crystalline IND*

1012
1013 *Figure 10 IR spectra of NPX and EPO mixtures prepared by HME (solid) and quench-*
1014 *cooled method (dashed) at the regions of carbonyl region (a) and C-N (b)*

1015 *Figure 11 Atomic force microscopic images of NPX-EPO extrudates containing 0.45,*
1016 *0.60 and 0.65 w/w drug loadings collected in both topography (a, b, c) and phase*
1017 *contrast modes (d, e, f); the root mean square surface roughness of the extrudates*
1018 *containing various drug loadings for systems NPX-EPO (g) and IND-EPO (h).*

1019
1020 *Figure 12 microRaman chemical maps and spectra (49x49 μm , pixel size 1.25*
1021 *μm /pixel) of HDASDs containing 0.6 w/w NPX (a) 0.6 w/w IND (b) and 0.6 w/w*
1022 *IBU (c) before and after three-week storage at 95%RH, the spectra for crystalline*
1023 *drugs are highlighted using the black arrows.*

1024
1025