European Journal of Pharmaceutics and Biopharmaceutics 124 (2018) 147–157

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Physical stability of API/polymer-blend amorphous solid dispersions

Kristin Lehmkemper[a,b], Samuel O. Kyerematenga[a,*], Mareike Bartels[b,1], Matthias Degenhardt[a], Gabriele Sadowski[b,*]

[a] AbbVie Deutschland GmbH & Co. KG, Global Pharmaceutical R&D, Knollstraße, D-67061 Ludwigshafen am Rhein, Germany
[b] TU Dortmund, Department of Biochemical and Chemical Engineering, Laboratory of Thermodynamics, Emil-Figge-Str. 70, D-44227 Dortmund, Germany

ARTICLE INFO

Keywords:
Amorphous solid dispersion
Polymer blends
Thermodynamic model
PC-SAFT
Kwei equation
Phase behavior
Physical stability
Excipients

ABSTRACT

The preparation of amorphous solid dispersions (ASDs) is a well-established strategy for formulating active pharmaceutical ingredients by embedding them in excipients, usually amorphous polymers. Different polymers can be combined for designing ASDs with desired properties like an optimized dissolution behavior. One important criterion for the development of ASD compositions is the physical stability. In this work, the physical stability of API/polymer-blend ASDs was investigated by thermodynamic modeling and stability studies. Amorphous naproxen (NAP) and acetaminophen (APAP) were embedded in blends of hydroxypropyl methylcellulose acetate succinate (HPMCAS) and either poly(vinylpyrrolidone) (PVP) or poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA64). Parameters for modeling the API solubility in the blends and the glass-transition temperature curves of the water-free systems with Perturbed-Chain Statistical Associating Fluid Theory and Kwei equation, respectively, were correlated to experimental data. The phase behavior for standardized storage conditions (0%, 60% and 75% relative humidity (RH)) was predicted and compared to six months-long stability studies. According to modeling and experimental results, the physical stability was reduced with increasing HPMCAS content and increasing RH. This trend was observed for all investigated systems, with both APIs (NAP and APAP) and both polymer blends (PVP/HPMCAS and PVPVA64/HPMCAS). PC-SAFT and the Kwei equation turned out to be suitable tools for modeling and predicting the physical stability of the investigated API/polymer-blends ASDs.

1. Introduction

A huge number (up to 90%) of promising active pharmaceutical ingredients (APIs) in the development pipeline shows poor water solubility leading to low oral bioavailability [1,2]. The preparation of so-called amorphous solid dispersions (ASDs) is a well-established strategy to increase the bioavailability of such APIs by embedding its higher soluble but metastable amorphous form [3–8] in an excipient [9–14], usually in amorphous polymers [15]. Besides the inhibition of API crystallization during the storage, ASDs may have an improved dissolution behavior compared to the pure API comprising a favorable dissolution rate and the inhibition of API crystallization and therefore prolongation of the supersaturation in the gastrointestinal tract after its release [9–15]. Physical stability and dissolution behavior strongly deviate for different compositions and depend on the selection of the polymeric excipient.

Examples for polymers which can be found as ASD excipients in several products on the market are poly(vinylpyrrolidone) (PVP), poly

Abbreviations: a, Helmholtz energy (J); $\Delta c^{SL}_{p,0,API}$, difference in the solid and liquid heat capacities of the pure API (J/mol K); $\Delta h^{SL}_{0,API}$, enthalpy of fusion of the pure API (J/mol); k_B, Boltzmann constant; k_{ij}, PC-SAFT binary interaction parameter; K, Gordon-Taylor binary parameter; m^{seg}, segment number; M, molar mass (g/mol); N^{assoc}, number of association sites; p, pressure (Pa); q_{ij}, Kwei binary interaction parameter; R, universal gas constant (8.1345 J mol^{-1} K^{-1}); T, temperature (K); $T^{SL}_{0,API}$, melting temperature of the pure API (K); T_g, glass-transition temperature (K); u/k_B, dispersion-energy parameter; w, content (wt%); x, mole fraction; γ, activity coefficient; ε^{AiBi}/k_B, association-energy parameter; κ^{AiBi}, , association-volume parameter; ρ, density (g/cm^3); σ, segment diameter; 0, pure component; A_i, B_i, association sites A and B of molecule i; assoc, association; b, intercept; calcd, calculated; disp, dispersion; exptl, experimental; hc, hard chain; i, j, component indices (API, polymers, water); k, component index (polymers); L, liquid phase; LV, liquid-vapor; m, slope; res, residual; S, solid phase; seg, segment; SL, solid-liquid; V, vapor; APAP, acetaminophen; API, active pharmaceutical ingredient; ARD, average relative deviation; ASD, amorphous solid dispersion; DSC, differential scanning calorimetry; HPMC, hydroxypropyl methylcellulose; HPMCAS, hydroxypropyl methylcellulose acetate succinate 126G; NAP, naproxen; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; PC-SAFT, Perturbed-Chain Statistical Associating Fluid Theory; PVP, poly(vinylpyrrolidone) (Kollidon 25); PVPVA64, poly(vinylpyrrolidone-co-vinyl acetate) (VA64); PXRD, powder X-ray diffraction; RH, relative humidity; SLE, solid-liquid equilibrium; VLE, vapor-liquid equilibrium

* Corresponding authors.
E-mail addresses: samuel.kyeremateng@abbvie.com (S.O. Kyerematenga), gabriele.sadowski@tu-dortmund.de (G. Sadowski).
[1] GSK Vaccines GmbH, Emil-von-Behring-Straße 76, 35041 Marburg, Germany.

https://doi.org/10.1016/j.ejpb.2017.12.002
Received 24 October 2017; Received in revised form 8 December 2017; Accepted 11 December 2017
Available online 18 December 2017
0939-6411/

(vinylpyrrolidone-co-vinyl acetate) (PVPVA), hydroxypropyl methylcellulose (HPMC), and HPMC acetate succinate (HPMCAS) [10–12,15]. PVP and PVPVA are well-known for their high hydrophilicity which enhances wettability of the formulation leading to an increased dissolution rate compared to the pure crystalline or amorphous API [16,17]. As expected, those formulations absorb huge amounts of water when exposed to humid environment. The water softens the formulation and reduces form stability and physical stability [11,18–21]. High glass-transition temperatures and high API solubilizing abilities of PVP and PVPVA result in high physical stability of ASDs based on these polymers as long as the absorption of water is kept small. That was shown in literature for several APIs, e.g. naproxen (NAP) [19,20], acetaminophen (APAP) [20], nifedipine [22], and indomethacin [23]. Even small amounts of PVP or PVPVA stabilize amorphous APIs (e.g. felodipine [24,25], indomethacin [26], and APAP [27]) which can be derived from strong specific interactions between APIs and these polymers [24–27]. In contrast, HPMC and HPMCAS are less hydrophilic than PVP and PVPVA. Therefore, ASDs based on modified celluloses absorb less water when exposed to humid environment than PVP and PVPVA ASDs and maintain higher glass-transition temperatures leading to higher form stability [28,29]. However, the modified celluloses form weaker specific interactions with some APIs than PVP and PVPVA and therefore inhibit crystal growth from an amorphous API less effectively (e.g. felodipine [24,25], nifedipine [30], and APAP [27]). However, HPMCAS and HPMC have a higher stabilizing effect on dissolved APIs in supersaturated aqueous solutions so that they prevent API crystallization and prolong supersaturation after dissolution in the gastrointestinal tract for a longer period than PVP and PVPVA [28,31,32].

Obviously, different polymer types provide different advantages and disadvantages for the ASD formulations. One possibility to design desired ASD properties, like a certain dissolution behavior, is combining different polymers and thus using polymer blends as excipients [33,34]. Physical stability, the prevention of the API crystallization during storage, is one important criterion for the development of the API/polymer-blend composition.

The aim of this work is to assess the physical stability of API/polymer-blend ASDs by thermodynamic modeling and six months-long stability studies at different temperatures and relative humidities (RH). Dry storage (25 °C/0% RH) as well as humid storage at 25 °C/60% RH and 40 °C/75% RH, as proposed by the International Council of Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH), were investigated. NAP and APAP were used as model APIs, which are highly suitable for studying the physical stability of ASDs due to their high crystallization propensity. Pure NAP was found to recrystallize fast from its melt even at high cooling rates and APAP recrystallized in supersaturated ASDs on short-time scale (less than two weeks) when kinetic stability was low [20]. The polymers PVP, PVPVA64 (60/40 (wt%/wt%) ratio between vinylpyrrolidone and vinyl acetate), and HPMCAS as well as their blends were used as excipients. The chemical structures of all substances used in this work are shown in Fig. 1. Blends of vinylpyrrolidone-based polymers and modified celluloses have already been applied in literature for designing beneficial properties of pharmaceutical formulations in terms of API release and physical stability (e.g. PVP/HPMC [33,35,36] or PVP/HPMCAS [35,36]). However, the impact of the composition of such API/polymer-blend ASDs on the long-term physical stability was not yet investigated systematically.

The physical stability of ASDs is strongly dependent on two contributions: The API solubility in the excipient and the glass-transition temperature [20,37]. The formulation is thermodynamically stable when the API content is lower than the API solubility in the excipient. When a supersaturated amorphous sample is stored below its glass-transition temperature it is kinetically stabilized. In this work, the API solubility in the excipient was calculated using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). PC-SAFT is an equation of state developed by Sadowski and Gross which can be used for calculating activity coefficients in mixtures of all kinds of substances [38–40]. In recent works, it was applied for calculating the API solubility in single polymers as well as the influence of RH on these solubility curves [19,20,29,37]. It was also used to predict the API solubility in blends of PVPVA64 and low-molecular-weight excipients (LMWEs) [41]. Within this work, the knowledge regarding the influence of RH on the solubility curves in single-polymer ASDs is combined to the modeling of ternary API/excipient-blend formulations. The glass-transition temperature was calculated using the Kwei equation [42], which is an extension of the Gordon-Taylor equation [43]. In literature, the Kwei equation has been proven to be suitable for modeling the glass-transition temperatures of amorphous mixtures which deviate from Gordon-Taylor calculations due to strong specific interactions between the components [29,42,44–46]. Fig. 2 shows a schematic phase diagram depicting solubility and glass-transition temperature curves (adapted from [11,37]).

In the phase diagram, the solubility temperature and the glass-transition temperature are plotted against the API content in the formulation. At the very left (0 wt% API) the glass-transition temperature of the API-free excipient, which can either be a single polymer or a polymer blend, can be read. The melting and glass-transition temperatures of the pure API can be found on the very right (100 wt% API). For API/polymer-blend systems, the ratio between the two polymers is kept constant for all API contents.

Solubility and glass-transition temperature curves divide the diagram into four areas. If the API content is lower than the API solubility in the excipient (to the left of the solubility curve) the amorphous formulation is thermodynamically-stable and the API will never crystallize. This thermodynamically-stable formulation might be a melt above the glass-transition temperature curve (area I) and a glass below the glass-transition temperature curve (area II). Samples with API contents to the right of the solubility curve are supersaturated and thus thermodynamically-unstable. Thermodynamically-unstable samples above the glass-transition temperature curve (area IV) are also kinetically-unstable so that an early crystallization of the API is highly probable.

Thermodynamically-unstable samples below the glass-transition temperature (area III) are kinetically stabilized due to low molecular mobility. The time until crystals can be detected in area III samples mainly depends on two factors: the distance between the API content in the samples and the API solubility at the storage temperature ("a" in Fig. 2) which represents the thermodynamic driving force for crystallization [47]. The larger the "a" distances, the faster the crystallization. Furthermore, the molecular mobility of the system decreases with increasing distance between glass-transition and storage temperatures ("b" in Fig. 2) [48]. For this reason, crystallization occurs later for larger distances "b". Thermodynamically-unstable samples can even be kinetically stabilized to an extent that the sample does not crystallize within its shelf-life as long as the distance "b" is sufficiently large [48].

In addition, other effects like specific interactions between API and excipient and/or the general crystallization tendency of the pure amorphous API also influence the crystallization kinetics [24,27,49,50]. Besides crystallization, amorphous demixing can also lead to thermodynamic instability [51,52]. This is not in the focus of this work but has to be considered for the evaluation of the experimental results and should be investigated alongside with the crystallization propensity during the ASD development.

2. Modeling

2.1. Calculating the API solubility in excipients

2.1.1. Solubility equation

The API solubility is the maximum API content which can be dissolved in the polymeric excipient(s). In this work, all excipients are amorphous and therefore considered as liquids. The API solubility x_{API}^{L}