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RESEARCH PAPER

Solution Behavior of PVP-VA and HPMC-AS-Based Amorphous Solid Dispersions and Their Bioavailability Implications

Feng Qian • Jennifer Wang • Ruiling Hartley • Jing Tao • Raja Haddadin • Neil Mathias • Munir Hussain

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ABSTRACT

Purpose To identify the mechanism behind the unexpected bio-performance of two amorphous solid dispersions: BMS-A/PVP-VA and BMS-A/HPMC-AS.

Methods Solubility of crystalline BMS-A in PVP-VA and HPMC-AS was measured by DSC. Drug-polymer interaction parameters were obtained by Flory-Huggins model fitting. Drug dissolution kinetics of spray-dried dispersions were studied under sink and non-sink conditions. BMS-A supersaturation was studied in the presence of pre-dissolved PVP-VA and HPMC-AS. Potency and crystallinity of undissolved solid dispersions were determined by HPLC and DSC. Polymer dissolution kinetics were obtained by mass balance calculation. Bioavailability of solid dispersions was assessed in dogs.

Results In solid state, both polymers are miscible with BMS-A, while PVP-VA solublizes the drug better. BMS-A dissolves similarly from both solid dispersions *in vitro* regardless of dissolution method, while the HPMC-AS dispersion performed much better in *vivo*. At the same concentration, HPMC-AS is more effective in prolonging BMS-A supersaturation; this effect was negated by the slow dissolution rate of HPMC-AS. Further study revealed that fast PVP-VA dissolution resulted in elevated drug loading in undissolved dispersions and facilitated drug recrystallization before complete release. In contrast, the hydrophobicity and slower HPMC-AS dissolution prevented BMS-A recrystallization within the HPMC-AS matrix for >24 h.

Conclusions The lower bioavailability of PVP-VA dispersion was attributed to BMS-A recrystallization within the undissolved dispersion, due to hydrophilicity and fast PVP-VA dissolution rate. Polymer selection for solid dispersion development has significant impact on *in vivo* performance besides physical stability.

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INTRODUCTION

Over the past decade, amorphous solid dispersions have gradually evolved into a platform technology to enhance the solubility and bioavailability of poorly water-soluble drugs in the pharmaceutical industry. Although rarely stable thermodynamically, the kinetically stable amorphous solid dispersion approach has been demonstrated to be a viable, versatile, and sometimes the single most practical strategy to materialize the clinical benefits of a drug with satisfactory drug product quality attributes, such as dissolution and bioavailability, chemical and physical stability, acceptable unit dosage size, and feasibility of forming fixed dose combination with another drug (1–7).

An amorphous solid dispersion is usually a matrix consisting of at least one drug and one polymer with all ingredients in amorphous state. Since most amorphous solid dispersions are inherently not stable thermodynamically, it is of primary concern that the system maintains physical stability without drug re-crystallization during the manufacturing process and storage. The physical stability of a homogenously mixed drug-polymer solid dispersion system is generally believed to be related to the thermodynamic nature of the drug molecule such as configurational entropy, fragility index, molecular mobility (8–11), and drug-polymer interaction (12–15). The process-induced amorphous inhomogeneity (16), as well as moisture-mediated de-mixing and recrystallization (17,18) in a solid dispersion system prepared by hot-melt extrusion or spray drying are additional risks to be evaluated and mitigated.

Although critically important, satisfactory physical stability of an amorphous solid dispersion over the shelf life is only the

first step towards the final goal of a successful solid dispersion based drug product. Ultimately, it must deliver the desirable *in vivo* pharmaceutical performance. To this end, the abilities of polymers to maintain drug supersaturation in aqueous solutions, and the abilities of polymers to inhibit amorphous drugs from crystallization in aqueous environment, were reported previously (19–23). Although such *in vitro* studies might help to predict the *in vivo* performance of different amorphous formulations, few studies were done systemically enough to provide a broader physical picture of amorphous solid dispersion dissolution process; or to demonstrate the correlation between the solution behavior and the actual *in vivo* performance. This current study attempted to compare the *in vitro* solution behavior and the *in vivo* performance of two amorphous drug-polymer solid dispersions, BMS-A/PVP-VA and BMS-A/HPMC-AS, and to identify the mechanism that caused their different *in vivo* pharmacokinetic (PK) performance.

BMS-A is a BCS Class II compound, i.e, poorly water soluble while highly permeable through gastrointestinal membrane. The molecular weight of BMS-A is about 500. BMS-A is non-ioniziable at physiologically relevant pH, its solubility in water is under 1 μg/mL at body temperature while its projected daily human dose is ~100 mg. BMS-A has a melting point of ~160°C and a glass transition temperature of ~45°C. At 25°C or 37°C, amorphous BMS-A has a high crystallization tendency in aqueous medium among the compounds we studied (i.e., "a fast crystallizer"), presumably due to its intrinsic molecular properties. The *in vivo* exposure of BMS-A can be achieved only by non-crystalline formulation approaches. Two drug-polymer amorphous solid dispersions, with poly (vinylpyrrolidone-*co*-vinylacetate) (PVP-VA) or hydroxypropylmethylcellulose acetate succinate (HPMC-AS) as the polymer matrix respectively, were prepared by spray drying. The interaction between the drug and the polymers in the dry state was characterized by thermal method, and the drug dissolution kinetics was studied under both sink and non-sink conditions. Surprisingly, none of these studies predicted the inferior *in vivo* bio-performance of the PVP-VA dispersion compared with the HPMC-AS system.

To identify the mechanism, studies were conducted to compare the two polymers' ability to maintain drug supersaturation in the dissolution medium. Other solution behavior of the solid dispersion, such as the dissolution kinetics of the polymers, the evolution of the undissolved solid dispersion during the dissolution study, etc, was also investigated. We concluded that, for a fast crystallizer like BMS-A, the selection of polymer for solid dispersion development might have significant impact on its *in vivo* performance besides its physical stability. The conventional USP II type of dissolution method under sink or non-sink condition, where only drug release kinetics is measured, may not be sufficient to predict the *in vivo* performance of the solid dispersions. Other solution behavior, such as the polymer's ability to maintain drug supersaturation, polymer dissolution kinetics, drug crystallization kinetics in the undissolved solid dispersion, etc, may all link to the potential risks of the bio-performance of amorphous formulation.

MATERIALS AND METHODS

Materials

BMS-A was synthesized by Bristol-Myers Squibb Company. PVP-VA was obtained from International Speciality Products (Wayne, NJ, USA) and HPMC-AS (MF grade) from Shin-Etsu Chemical Co., Ltd (Tokyo, Japan). The chemical structure and the water contact angles of HPMC-AS and PVP-VA were shown in Fig. 1 (refer to *"Determination of the contact angles of polymers and solid dispersions"* for contact angle measurement).

All buffer salts used for both dissolution medium, and methanol (HPLC grade) used for spray drying were obtained from Sigma-Aldrich Co. (Milwaukee, WI, USA).

Preparation of Spray-Dried Solid Dispersions

The BMS-A/polymer solid dispersions were made by spray drying (Büchi Mini Spray Dryer B-290, Büchi Labortechnik AG, Postfach, Switzerland). Two grams of BMS-A and 3 g of PVP-VA or HPMC-AS were dissolved in 50 mL of methanol, followed by a spray drying process under the following conditions: inlet air temperature 70°C, aspiration 65%, and outlet air temperature ~40°C. BMS-A/PVP-VA and BMS-A/HPMS-AS solid dispersions have the same drug loading of 40 wt.%. The solid dispersions were vacuum dried at least over night before further use. The solid dispersions were confirmed to be crystal free by powder x-ray diffraction (PXRD) and/or differential scanning calorimetry (DSC).

Solid dispersion tablets, containing less than 30% of PVP-VA or HPMC-AS solid dispersions, and common tablet excipients including filler/compression aid, disintegrant, glidant, and lubricant, were prepared by dry granulation process followed by tablet compression. The tablet weight is in the range of 500–1000 mg and the hardness is ~20 SCU. The solid dispersion tablets were used for the sink condition dissolution study and the dog PK evaluation.

Determination of the Contact Angles of Polymers and Solid Dispersions

Polymer or solid dispersion films were prepared on the surface of glass slides with a solvent casting method. Each polymer or solid dispersion was dissolved in acetone with a solid concentration of 10 wt.%. The acetone solution was

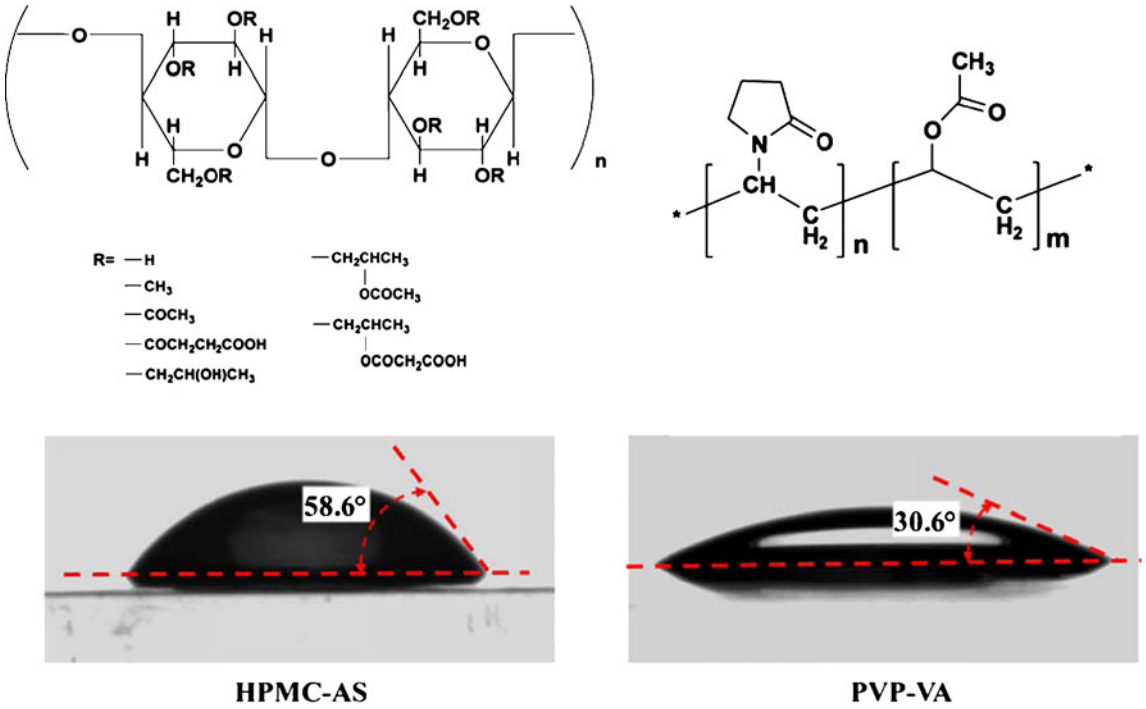

Fig. 1 Chemical structure and water contact angles of hydroxypropylmethylcellulose acetate succinate (HPMC-AS) and poly(vinylpyrrolidone-*co*-vinyl-acetate) (PVP-VA), two commonly used polymers for amorphous solid dispersion development.

then dropped on the surface of glass slides and air dried for 24 h, followed by vacuum drying at 40°C for another 24 h to remove any residual solvent. The contact angle of each polymer or solid dispersion film was measured using the sessile drop method with a contact angle measuring system (KRŮSS DSA10, Matthews, NC, USA). A drop of distilled water was gently dropped on the surface of the film using a fine needle (0.5 mm in diameter). Optical image of the water drop on the film surface was collected immediately (<5 s) once the water drops settled. The angle between the baseline of the drop and the tangent at the drop boundary is measured and reported as the contact angles (Fig. 1). Three contact angle measurements were performed at different locations for each type of films and average values were used.

Determination of the Drug-Polymer Interaction Parameters

Solubility of Crystalline BMS-A in Polymers

An intimate mixture of BMS-A and PVP-VA or HPMC-AS was first prepared by cryogenic milling with CertiPrep (Model 6800-115) at 10 Hz for 16 min. The mixture was then loaded into a hermetic DSC pan with a pin-hole on the lid. A DSC scanning method was used to determine the solubility of API in polymer (24). Briefly, this method involves heating up a drug/polymer mixture of known composition in DSC (TA DSC Q1000 Differential Scanning Calorimeter, New Castle, DE) at various scanning rates. When phase equilibrium is established during extremely slow heating, the dissolution endpoint is the solubility temperature of the given composition. In this work, the samples were first heated to 105°C, allowing water to escape, then scanned at 0.5, 1, and 2°C/min to observe the temperature endpoint of the dissolution endotherm (T_{end}) for the same composition samples. T_{end} obtained at different heating rates were then further extrapolated to zero heating rate to further approach equilibrium.

Drug-Polymer Interaction Parameter

The Flory-Huggins model was used to obtain the drug-polymer interaction parameters (25). The measured solubility data allowed us to calculate the activity of the drug in the polymer at solubility (i.e., data points in Fig. 2):

$$lna_1 = \frac{\Delta H_m}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \quad (1)$$

where T_m and ΔH_m are the melting temperature and molar heat of fusion of the pure drug, respectively; T is the

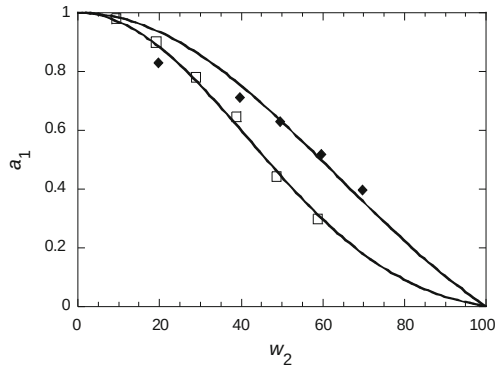

Fig. 2 Determine the interaction parameters of BMS-A/PVP-VA (□) and BMS-A/HPMC-AS (■) by Flory-Huggins fitting. In solid state, BMS-A has good miscibility with both PVP-VA and HPMC-AS, as demonstrated by their negative interaction parameters of and −2.5 for BMS-A/PVP-VA, and −1.1 for BMS-A/HPMC-AS.

solubility temperature of the given composition of a drug-polymer mixture.

Applying Flory-Huggins model (i.e., the fitting curves in Fig. 2), the activity of the drug in a drug-polymer mixture is given by:

$$lna_1 = lnw_1 + \left(1 - \frac{1}{x}\right)v_2 + \chi v_2^2 \quad (2)$$

where v_1 and v_2 are volume fractions of the drug and polymer of the total volume of the drug-polymer mixture, respectively; x is the molar volume ratio of the polymer and the drug, and χ is the drug-polymer interaction parameter. In this work, we assumed that the volume fraction is the same as the weight fraction, and the x is the ratio of the molecular weight of the polymer and the drug. The drug-polymer interaction parameter χ was obtained by fitting the activity-solubility relationship (i.e., data points in Fig. 2) using Eq. 2.

In Vitro Dissolution Study Under Sink Conditions

BMS-A/PVP-VA and BMS-A/HPMC-AS solid dispersion tablets were tested in a sink condition dissolution study (i.e., the dissolution medium can dissolve >3 times of the total drug dose in the dissolution study) using a USP II dissolution apparatus. The dissolution medium is pH 4.5 acetate buffer with 1.5% Brij 35 (Fisher Scientific, Pittsburgh, PA). The dissolution conditions are: sink dissolution medium: 1000 mL; paddle speed: 50 RPM, temperature: 37°C. Sampling time points: 10, 20, 30 45 and 60 min, and the BMS-A concentrations in the samples were analyzed by HPLC.

In Vitro Dissolution Study Under Non-Sink Conditions

BMS-A/PVP-VA and BMS-A/HPMC-AS solid dispersion powders were also tested in a non-sink condition dissolution study (dissolution medium cannot dissolve the total drug dose). The non-sink dissolution medium is a bio-relevant, simulated fasted duodenal solution (26), which consists of 20 mM sodium phosphate (Na_2HPO_4), 47 mM potsssium phosphate (KH_2PO_4), 87 mM sodium chloride (NaCl), and 0.2 mM potassium chloride (KCl), 7.3 mM sodium taurocholate (NaTC, USB Corporation, Cleveland, OH), and 1.4 mM 1-palmitoyl-2-oleyl-*sn*-glycero-3-phosphocholine (POPC, Avanti Polar Lipids Inc., Alabaster, AL, USA). The dissolution medium was adjusted to pH 6.5 with sodium hydroxide (NaOH).

For each solid dispersion, a total of 15 samples (~200 mg each sample, total 5 time points with 3 replicates) were prepared. Each sample was weighed accurately into a centrifuge tube followed by adding 10 mL of the non-sink dissolution medium. The tubes were vibrated for 30 s using a votexer (Vortex-Genie, Scientific Industries Inc., Bohemia, NY) prior to being vibrated at a frequency of 100 RPM using a shaker (Thermodyne AROS 160, Thermodyne Industries Inc., Denton, TX) for 0.25, 1, 2, 4 and 24 h. All samples were vortexed for 30 s and then placed backed onto the shaker at each time point. The dissolution test for each set of the samples was stopped at 0.25, 1, 2, 4, and 24.0 h time points, respectively, by centrifuging the sample at 2500 RPM for 3 min (Allegra X-22R Centrifuge, Beckman Coulter Inc., Brea, CA), followed by filtration using a 1.2 μm Vesapor® membrane filter (Acrodisc® 25 mm syringe filter, Pall Corporation, Port Washington, NY). The supernatant was then further diluted with methanol and analyzed for the concentration of the BMS-A using HPLC.

Determination of Drug Loading in Undissolved Dispersions and Polymer Release Kinetics During Non-Sink Dissolution Study

During the non-sink dissolution study, the solid dispersion suspension was centrifuged, and the precipitates were vacuum dried at room temperature for at least 48 h and then assayed for the BMS-A potency by HPLC to obtain the drug loading in the undissolved solid dispersion (P_{drug}).

The amount of polymer released at each time point was calculated by a mass balance approach. With the information of the initial sample weight (W_0), the initial drug loading of the solid dispersion (40 wt.%), the amount of drug released at each time point ($W_{\text{drug relased}}$), and the drug loading in the undissolved solid dispersion (P_{drug}), the amount of polymer released ($W_{\text{polymer released}}$) at each time point can be calculated using the following equation:

$$\frac{W_0 \cdot 40\% - W_{drug\ \ released}}{W_0 \cdot 60\% - W_{\text{polymer}\ \ \text{released}}} = \frac{P_{drug}}{1 - P_{drug}} \quad (3)$$

Effect of Polymers on the Supersaturation of BMS-A in Solution

In order to assess the ability of PVP-VA and HPMC-AS to maintain the supersaturation of BMS-A in the dissolution medium, PVP-VA or HPMC-AS was pre-dissolved in the non-sink condition dissolution medium at the concentration of 0.3 mg/mL and 3 mg/mL. BMS-A solution in acetone was prepared at 100 mg/mL. In each 10 mL of polymer containing dissolution medium, 0.1 mL of BMS-A acetone solution was added, and the solution was vibrated at a frequency of 100 RPM using a shaker. After 1, 2 and 4 h, the solution was centrifuged and the clear supernatant was analyzed for the concentration of BMS-A using HPLC.

Assessment of Drug Crystallization Tendency in Aqueous Environment

Approximately 20 mg of crystalline BMS-A was placed on a glass slide. The glass slide was heated up with a hot-stage (Linkam LTS 350, Linkam Scientific Instrument Ltd, Surrey KT20 5HT, UK) to a temperature ~5°C above the melting point of the drug and held for two minutes to ensure complete melting. The glass slide with molten drug was air cooled and observed under a polarized light microscope (Nikon Eclipse E600 POL, Nikon Corporation, Melville, NY) to ensure that there were no detectable drug crystals. The glass slide with the amorphous drug was then immersed into distilled water at room temperature. The sample was taken out periodically and observed immediately under the polarized microscope to qualitatively assess the crystallization kinetics of the amorphous drug in water.

DSC Analysis of the Solid Dispersion Powders Post-Dissolution Tests

The crystallinity of the undissolved solid dispersions at different time points, namely 15 min, 4 h and 24 h, during the non-sink dissolution study was monitored using a DSC method. About 5 mg of the vacuum dried precipitate at each time point (refer to previous Methods section) was loaded into a pin-holed hermetic pan for DSC analysis. The sample was first kept isothermal at 100°C for 5 min to remove any residual solvent and then scanned at 20°C/min from 0°C to 200°C to observe any endotherms.

Pharmacokinetic (PK) Study in Dogs

Male Beagle dogs (~10 kg) were fasted overnight with no intake of water 1 h before and after dosing. Studies were conducted with 4 dogs in a crossover design. Dose administration (75 mg) was followed immediately by gavage with 20 mL water. Blood samples (2 mL) were withdrawn from the cephalic vein at pre-dose, 1, 2, 3, 4, 6, 8, 24 and 48 h and placed in EDTA-containing vacutainer blood collection tubes. Samples were centrifuged at 400× g for 15 min at 4°C and the plasma isolated and stored at −80°C until HPLC-LC/MS analysis. Studies were performed in accordance with the standards recommended by the Guide for Care and Use for Laboratory Animals (Institute of Animal Laboratory Resources, 1995) and were approved by the institutional animal care use committee with full consideration to experimental refinement, reduction in animal use, and replacement with *in vitro* methods.

RESULTS AND DISCUSSION

Water Contact Angles

The water contact angle values on PVP-VA, HPMC-AS, BMS-A/PVP-VA, and BMS-A/HPMC-AS films are 30.6°, 58.6°, 60.6°, and 80.1°, respectively. The results indicate that PVP-VA is more hydrophilic than HPMC-AS, and BMS-A/PVP-VA solid dispersion is more hydrophilic than BMS-A/HPMC-AS solid dispersion.

Solid State Interaction Between Drug and Polymers

The solubility of crystalline BMS-A in PVP-VA and HPMC-AS was experimentally determined by a DSC method, which allowed the calculation of BMS-A activity in saturated polymer solutions, shown as the data points in Fig. 2 (refer to the Methods section for details). Comparing the two polymers, PVP-VA showed better dissolving power for BMS-A than HPMC-AS, due to the fact that same amount of PVP-VA reduced the activity of BMS-A more than HPMC-AS. By applying the Flory-Huggins model fitting (fitting lines in Fig. 2), the interaction parameters of BMS-A/PVP-VA and BMS-A/HPMC-AS were estimated to be −2.5 and −1.1, respectively. The negative interaction parameters between the drug and the two polymers indicate that the amorphous drug is completely miscible with both polymers, while the more negative interaction parameter between BMS-A and PVP-VA indicated a stronger drug-polymer interaction. Other characterizations, such as IR or solid state NMR, also proved the drug-polymer interaction in these systems (data not shown).

It is generally understood that the drug-polymer miscibility, solid dispersion uniformity, and a relatively high T_g are needed to ensure physical stability of the solid dispersions at normal storage conditions (15). Both PVP-VA and HPMC-AS dispersions used in this study were obtained by spray drying the drug-polymer solution in methanol, a volatile organic solvent. The very fast atomization and

evaporation process during this spray drying is unlikely to induce significant inhomogeneity in the BMS-A solid dispersions. In fact, although detailed data are not discussed in this paper, both PVP-VA and HPMC-AS dispersions showed single T_g of ~88 and ~67°C by DSC, respectively, and the solid dispersions were physically stable for at least 6 months under common stability conditions, such as 25°C/60% RH.

Drug Dissolution Kinetics Under Sink Condition

Figure 3a compared BMS-A dissolution kinetics from PVP-VA and HPMC-AS solid dispersion tablets. The two tablet formulations have identical composition, drug loading, and similar tablet hardness. Under this dissolution condition, the PVP-VA solid dispersion tablet appeared to dissolve faster than the HPMC-AS tablet in the first 20 min, where 65% and 50% BMS-A released from PVP-VA and HPMC-AS tablets, respectively, although similar amount of BMS-A (~75%) released after 60 min for both formulations. The incomplete drug release from the PVP-VA tablets is likely due to the slow paddle speed while that from the HPMC-AS tablets is more likely due to the pH dependent solubility of HPMC-AS (19,20). In another dissolution study where the paddle speed was increased from 50 RPM to 75 RPM (data not shown), 100% of BMS-A released from the PVP-VA tablets while the drug dissolution profile from the HPMC-AS tablet remained unchanged.

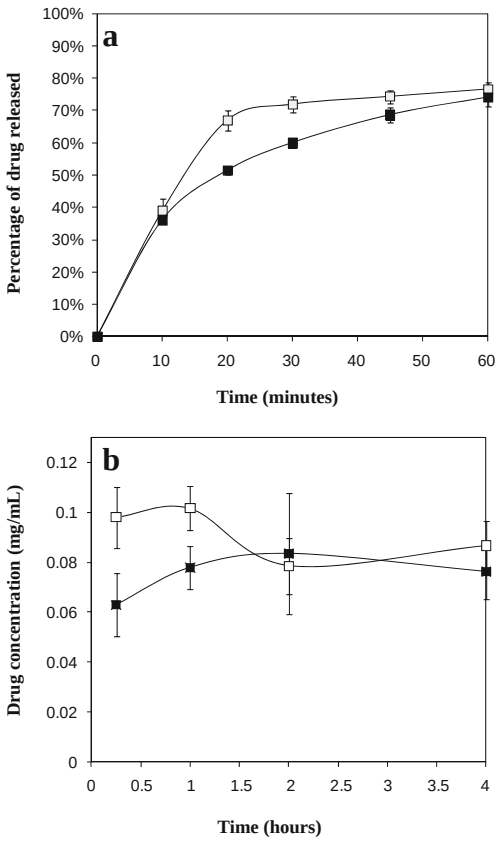

Fig. 3 *In vitro* release kinetics of BMS-A amorphous formulations. (**a**) USP II sink condition dissolution of PVP-VA (□) and HPMC-AS (■) solid dispersion tablets. Dissolution medium: 1000 mL of pH 4.5 acetate buffer with 1.5% Brij 35. Paddles speed 50 rpm. (**b**) Non-sink condition dissolution of PVP-VA (□) and HPMC-AS (■) solid dispersions. Dissolution medium: 50 mL model fasted duodenal (MFD) solution that consists pH 6.5 phosphate buffer, 7.3 mM sodium taurocholic acid (bile salt) and 1.4 mM POPC. Refer to the "Materials and Methods" section for the detailed dissolution method. (n=3 for all experiments).

It is worth noting that HPMC-AS (MF grade) is not soluble at pH<5.5. Thus, in the sink dissolution medium at pH 4.5, the drug release was presumably through a drug dissolution/diffusion process without polymer dissolved. This process simulates the dissolution process in the stomach environment (~0.5–2 h after administration of the formulation).

Drug Dissolution Kinetics Under Non-Sink Condition

Figures 3b compared the BMS-A release kinetics from PVP-VA and HPMC-AS solid dispersions under non-sink condition over 4 h. Between 15 min and 1 h, on average, more BMS-A was released from the PVP-VA dispersion than from the HPMC-AS dispersion, although the difference was not significant considering the standard deviation of the data. After 1 h, the amount of BMS-A release from both polymers was practically the same. The different hydrophobicity of the solid dispersions might have contributed to the faster initial drug release rate of the PVP-VA dispersion. The contact angles of BMS-A/PVP-VA and BMS-A/HPMC-AS dispersions are 60.6° and 80.1°, respectively, indicating the former system to be more hydrophilic and wettable.

In later time points after 1 h, drug concentration in both systems reached a plateau value of ~0.08 mg/mL, which could be the "amorphous solubility" of BMS-A where maximum concentration of BMS-A in the dissolution medium was reached. In fact, in another observation where the drug dose for dissolution study was decreased ~10 times (data not shown), similar drug release profiles from both PVP-VA and HPMC-AS dispersions were obtained, with the plateau concentration also at ~0.08 mg/mL, which supported the assessment that the "amorphous solubility" was reached.

Dog Pharmacokinetic Study of Solid Dispersions

A pharmacokinetic study was conducted in dogs where PVP-VA and HPMC-AS solid dispersion tablets with same drug loading and tablet composition were dosed (Fig. 4). To our surprise, the PVP-VA dispersion tablet showed a significantly lower bioavailability, with C_{max} and AUC of about 44% and 39%, respectively, of that of the HPMC-AS dispersion tablet.

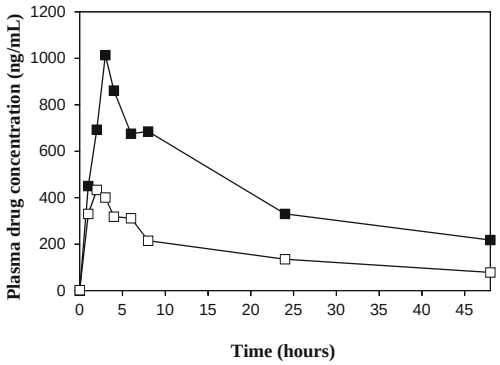

Fig. 4 *In vivo* pharmacokinetic (PK) performance of BMS-A amorphous solid dispersions. (A): BMS-A/PVP-VA solid dispersion (□) and BMS-A/HPMC-AS solid dispersion (■) in a dog PK study (n=4, 75 mg/dog). The difference in PK profiles is statistically significant.

Since none of the previous characterizations, either solid state interaction or drug dissolution kinetics studies predicted this *in vivo* difference between the two solid dispersions, further solution behavior investigation was warranted.

Supersaturation of BMS-A in Presence of PVP-VA and HPMC-AS

It is well known that different polymers could have different effects in maintaining the drug supersaturation in solution (20,21,23). In this study, we studied the kinetics of BMS-A supersaturation in presence of pre-dissolved PVP-VA (3 and 10 mg/mL) and HPMC-AS (0.3 and 3 mg/mL). The initial supersaturated BMS-A solution is 1 mg/mL, and the equilibrium solubility of crystalline BMS-A in the study medium was determined to be 0.0062 mg/mL.

As shown in Fig. 5, increasing the concentration of either polymer in the dissolution medium, the drug supersaturation was more prolonged. Comparing the two polymers at the same concentration of 3 mg/mL, HPMC-AS obviously

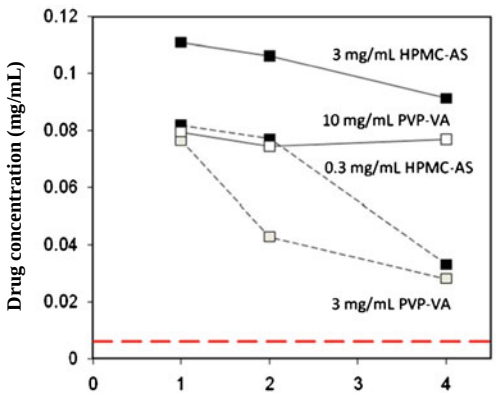

Fig. 5 Effect of polymers (PVP-VA: □ and HPMC-AS ■) on the supersaturation of BMS-A in the dissolution medium. The solubility of crystalline BMS-A in the dissolution medium without polymers is 0.0062 mg/mL as illustrated by the dotted line at the bottom.

maintained a higher supersaturation than PVP-VA: in dissolution medium pre-dissolved with 3 mg/mL of HPMC-AS or PVP-VA, BMS-A concentration decreased to ~0.09 mg/mL or ~0.03 mg/mL, respectively. In fact, 3 mg/mL pre-dissolved HPMC-AS maintained a higher BMS-A supersaturation than 10 mg/mL pre-dissolved PVP-VA.

It has been reported that HPMC-AS prolonged the supersaturation of some drugs better than other commonly used polymers (20,21,23), although no exact mechanism has been identified. This effect was also considered to be one of the potential advantages of HPMC-AS in the solid dispersion application. However, the above comparison between HPMC-AS and PVP-VA in this study and other literatures was conducted with pre-dissolved polymers in the dissolution medium at the same concentration. Practically, this information must be coupled with the polymer release kinetic to assess the effect of dissolved polymers in prolonging the drug supersaturation, since no pre-dissolved polymers exist in reality and the polymer release kinetics dictates the amount of polymer available to maintain drug supersaturation. Therefore, the polymer release kinetics is a critical component of the solution behaviors of amorphous solid dispersions.

Dissolution Kinetics of the Polymers

When comparing BMS-A release kinetics from the PVP-VA and HPMC-AS solid dispersions under the non-sink condition (Fig. 3b), the release kinetics of the two polymers were also obtained (Fig. 6a). It's interesting to note that HPMC-AS dissolves much slower than PVP-VA: the concentration of HPMC-AS in the dissolution medium slowly increased to ~0.3 mg/mL after 15 min and further increased to 1.5 mg/mL after 4 h; while the PVP-VA concentration rapidly reached 5.3 mg/mL after 15 min and 7.3 mg/mL after 4 h.

As discussed earlier (Fig. 5), HPMC-AS is more efficient in prolonging BMS-A supersaturation than PVP-VA when the same polymer concentration is used. However, as shown in Fig. 6a, PVP-VA dissolved much faster than HPMC-AS, thus more PVP-VA became available in solution to maintain BMS-A supersaturation. Considering the amount of PVP-VA and HPMC-AS released during the 4 h dissolution study, and their supersaturation power at different concentrations (Fig. 5), it becomes apparent to conclude that when used in the current BMS-A solid dispersions, PVP-VA and HPMC-AS have practically similar ability to prolong BMS-A supersatruation in solution.

The faster release rate of PVP-VA could be due to the its intrinsic hydrophilicity, as well as the better wettability of the BMS-A/PVP-VA solid dispersion. The water contact angles of PVP-VA and HPMC-AS are 30.6° and 58.6°, respectively. While the contact angles of BMS-A/PVP-VA

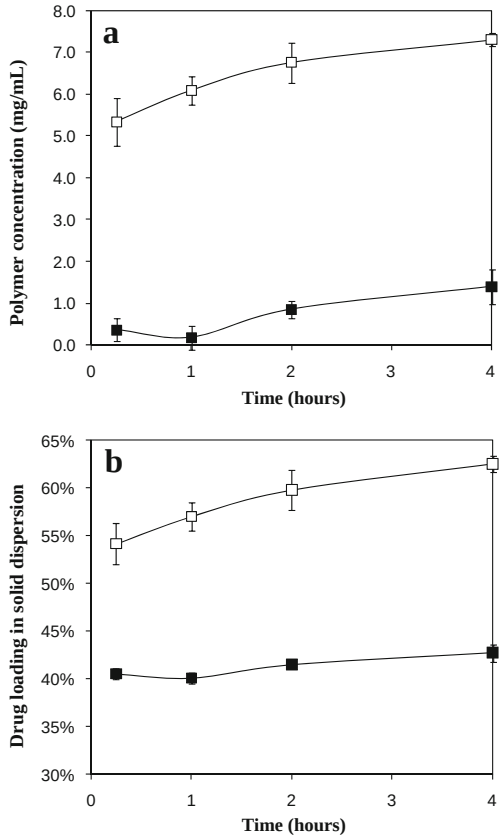

Fig. 6 (**a**) *In vitro* release kinetics of PVP-VA (□) and HPMC-AS (■) from BMS-A solid dispersions. (**b**) BMS-A drug loading in the undissolved PVP-VA (□) and HPMC-AS (■) solid dispersions during the dissolution study. Dissolution medium: 50 mL model fasted duodenal (MFD) solution that consists pH 6.5 phosphate buffer, 7.3 mM sodium taurocholate (bile salt) and 1.4 mM POPC. Refer to the "Materials and Methods" section for the detailed dissolution method. (n=3 for all experiments).

and BMS-A/HPMC-AS solid dispersions are 60.6° and 80.1°, respectively. All of these properties could contribute to the faster release kinetics of PVP-VA.

Change of Potency and Crystallinity in Undissolved Solid Dispersions

As discussed earlier, BMS-A dissolved similarly from PVP-VA and HPMC-AS solid dispersions (Fig. 3). Therefore, the different polymer dissolution rates caused the following changes in the undissolved solid dispersions:

First, the drug loading in the undissolved solid dispersions changed with the release of drug and polymer (Fig. 6b). In the PVP-VA dispersion, PVP-VA dissolved much faster than the drug, thus the drug loading in the undissolved dispersion increased from the initial 40% to 54% after 15 min. The drug loading kept increasing and reached 63% after 4 h. In contrast, HPMC-AS released slower from the HPMC-AS dispersion, at a rate similar to that of BMS-A, which resulted in an undissolved solid dispersions with practically constant drug loading (40%–43%) within the 4-hour dissolution study.

Second, the elevated drug loading in the undissolved PVP-VA solid dispersions exposed the drug to a higher crystallization risk. As shown in Fig. 7, in the absence of polymer inhibition, the pure amorphous BMS-A crystallizes rapidly in water. When amorphous BMS-A was exposed to water, drug crystallization occurred within a few minutes, and the crystallization of BMS-A on the amorphous sample surface completed within 15 min. The fast crystallization of amorphous BMS-A in water could be attributed to its intrinsic crystallization tendency, its T_g (45°C), and the plasticization of water. Water is a well known plasticizer due to its low T_g (−108–137°C, depending on methods) (27), therefore, T_g of wetted BMS-A would be much lower than 45°C.

The PVP-VA and HPMC-AS solid dispersions initially contained 40% BMS-A and their T_g's were 88°C and 67°C, respectively. During dissolution, the drug loading in the PVP-VA dispersions increased to 54% in 15 min and 63% in 4 h in the PVP-VA dispersion. The increase in drug loading, combined with water uptake, would significantly decrease the T_g of the undissolved PVP-VA dispersion and cause BMS-A, a fast crystallizer, to crystallize before release. In comparison, the drug loading in the HPMC-AS solid dispersion remained constant, and the HPMC-AS dispersion is also more hydrophobic, therefore the risk of BMS-A crystallization within the HPMC-AS dispersion was lower.

In fact, the higher drug crystallization risk in PVP-VA dispersion was confirmed by DSC analysis of the undissolved solid dispersions, shown as Fig. 8. Endothermic melting peak of crystalline BMS-A was detected in the undissolved PVP-VA dispersion 15 min after dissolution study started. Qualitatively, the heat of fusion (i.e., the size of the melting peaks) of the PVP-VA dispersions increased over time from 15 min to 24 h, indicating a gradual increasing of BMS-A crystallinity within the undissoved PVP-VA dispersion. Although details are not discussed in this paper, crystallization of BMS-A in the undissolved dispersion was also detected by Raman spectroscopy in real time during the dissolution study. However, quantitative measurement of drug crystallization kinetics within the undissolved dispersion in real time is challenging. Tools like DSC and IR require samples to be dried before measurement, other tools like PXRD also involves sample and instrument preparation, and extra data collection time on the instrument. Raman could potentially be used as an online Process Analytical Technology (PAT) to study undissolved dispersions in aqueous medium (21); however, the detection sensitivity is highly dependent on the drug property and the crystals amount. A highly sensitive analytical tool that allows real time detection of crystallization kinetics in the undissolved

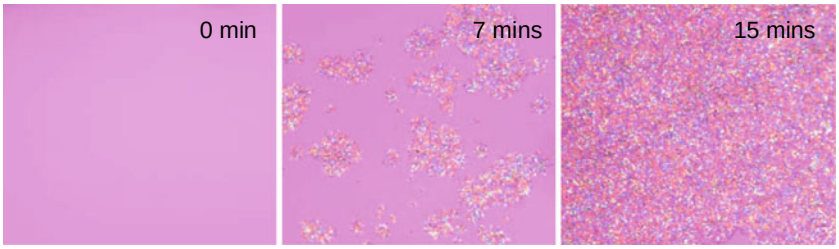

Fig. 7 Crystallization kinetics of amorphous BMS-A when submersed in water. The amorphous BMS-A was obtained by melting the crystalline API on glass slides. The slides were immersed in water and taken out for observation at different time points.

solid would be very beneficial to understand the solution behavior of amorphous solid dispersions.

Mechanism of the Different *In Vivo* Performance of BMS-A Solid Dispersions

Based on the findings discussed so far, we could hypothesize the main mechanism behind the different *in vivo* performance of the BMS-A solid dispersions: once dosed, PVP-VA is released from the solid dispersion much faster than BMS-A. The early depletion of PVP-VA caused a portion of BMS-A, a fast crystallizer, to crystallize before it had chance to release into the surrounding medium, thus the bioavailability of PVP-VA solid dispersion was lower than the HPMC-AS dispersion. Whereas in the case of HPMC-AS solid dispersion, HPMC-AS dissolved at the similar rate as BMS-A, and maintained BMS-A as amorphous in the undissolved solid dispersion. The difference between the supersaturation effect of HPMC-AS and PVP-VA on BMS-A at the same concentration was not the main contributor to the different *in vivo* performance of the two solid dispersion systems. This is because, the superior supersaturation effect of HPMC-AS was essentially negated by its slower release rate. Considering their release rates, PVP-VA and HPMC-AS have practically similar effects in prolonging the supersaturation of BMS-A.

Also, it's worth noting that the current study did not fully analyze the potential impact of the tablet disintegration on the bio-performance. While both PVP-VA and HPMC-AS tablets showed similar dissolution profiles in the sink condition study, the HPMC-AS dispersion tablets disintegrated faster (with 1 min) than the PVP-VA tablets (~5 min), combined with the main mechanism identified in this work, the slower disintegration could synergistically decrease the bioavailability of the PVP-VA formulation. The quantitative analysis will be a follow up research topic after the current report.

Certainly, the conclusion we reached above for the two BMS-A solid dispersion systems is highly dependent on the drug property (crystallization tendency, hydrophobicity, T_g, solubility, etc) and the drug-polymer ratio within the solid dispersions. Systematic investigation of more systems is needed to make any general conclusion. One speculation that worth further investigation is, should hydrophilic polymers like PVP-VA be considered less preferable for fast crystallizers, compared with more hydrophobic polymers like HPMC-AS? Hydrophilic polymers could be sufficiently effective in inhibiting supersaturated solution from recrystallization; however, they could be poor crystallization inhibitors for amorphous drugs within the undissolved solid dispersion matrix. As shown in the current study, for certain drug and certain drug-polymer ratio, these polymers might dissolve too fast and leave the amorphous drug prematurely without providing sufficient protection.

For drugs that crystallize much slower in aqueous medium at body temperature, the impact of polymer selection on the bioavailability of amorphous solid dispersions could be less. In another dog study where we evaluated the bioperformance of two solid dispersions of a slow crystallizer, it was observed that the bioavailability of a HPMC-AS based solid dispersion was essentially the same as a PVP based solid dispersion. The detailed data of this work will be published in the future.

Limitation of the Current *In Vitro* Dissolution Studies

Obviously, we need to reflect why our *in vitro* dissolution study, utilizing either sink or non-sink condition, did not differentiate the two BMS-A solid dispersions. Under the sink condition where the medium could completely dissolve the total drug dose, it is understandable that this study could be insensitive to physical changes occurring *in vivo*, such as the precipitation of dissolved drug and the crystallization of amorphous drug within the solid dispersion. A dissolution medium with sufficient solubility even for the crystalline drug essentially lost its ability to differentiate amorphous and crystalline drugs, which is the key to amorphous formulation evaluation.

Under the non-sink condition, BMS-A presumably reached the "amorphous solubility" in both PVP-VA and HPMC-AS dispersions. Despite the fact that BMS-A crystallized quickly in the undissolved PVP-VA dispersion (Fig. 8), and the tendency of the dissolved BMS-A to crystallize and precipitate, this plateau concentration remained constant over 4 h. This could be due to several reasons: first,

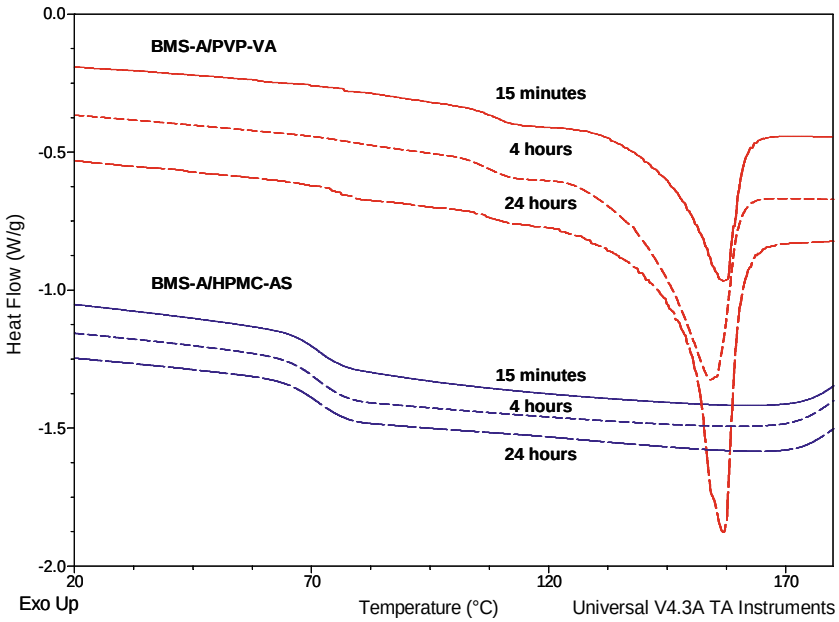

Fig. 8 DSC analysis of the BMS-A/PVP-VA and BMS-A/HPMC-AS undissolved solid dispersions after 15 min, 4 h, and 24 h in the dissolution medium. At each time points, the undissolved dispersions were centrifuged and vacuum dried before DSC study.

both PVP-VA and HPMC-AS, could maintain certain level of supersaturation over 4 h (Fig. 5) at their dissolved concentration (Fig. 6a); second, although BMS-A crystallized in the undissolved PVP-VA dispersion, as long as the amorphous BMS-A was not depleted over the 4 h dissolution time, the "amorphous solubility" could be maintained. In fact, the non-sink condition used in this study remained as non-sink even for amorphous BMS-A. During the dissolution study over 4 h, the amount of BMS-A dissolved was only several percentage of the total dose while the majority of BMS-A remained in the undissolved dispersion. As discussed above, within the 4 h time of our dissolution study, the crystallization of BMS-A within the undissolved dispersion was not directly reflected in the concentration of dissolved BMS-A. However, different crystallization kinetics of BMS-A within undissolved PVP-VA and HPMC-AS dispersions will certainly lead to different bioavailability in the *in vivo* study.

SUMMARY

Solution behavior and *in vivo* performance of amorphous solid dispersions are complex subjects to be studied, and obviously they are highly dependent on each individual drug and solid dispersion. In general, the complete picture of a solid dispersion dissolution process includes the drug dissolution kinetics, polymer dissolution kinetics, and the kinetics of physical form change of the undissolved solid. Understanding all the above would help to avoid potential performance risks of the amorphous formulation.

By analyzing two solid dispersion systems based on PVP-VA and HPMC-AS in this study, it could be concluded that conventional USP II type dissolution methods under sink or non-sink condition, where drug release kinetics is measured in a closed dissolution apparatus, might not predict all the performance risks of the amorphous formulations. Further efforts, such as understanding the crystallization tendency of the drug, the polymer dissolution kinetics, the evolution of the solid dispersion once exposed to aqueous medium, performing dissolution studies at different non-sink conditions by using multiple dose levels, different dissolution media, or different experimental setups, utilizing predictive modeling (28–31), could make the dissolution studies more "bio-relevant" thus enabling an early warning towards risky formulations before going to costly animal or human studies.

This study also reminds us that, understanding of the solid state drug-polymer interaction alone is not enough to guide amorphous formulation selection. Critical solution behavior should be assessed in parallel, so that an optimal amorphous formulation with both satisfactory physical stability and desired bio-performance could be selected for further development.

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