

An investigation into the factors governing the degree of dissolution enhancement of solid dispersion for poorly soluble drugs

Ahmed Bassam Farhan, Joan Quah, Elizabeth Pei Lin Lee, Siok-Yee Chan*

School of Pharmaceutical Sciences,

Universiti Sains Malaysia

Penang, Malaysia

*Corresponding Author

E-mail: sychan@usm.my

Abstract—Solid dispersion (SD) formulation has attracted much attention due to its potential in enhancing dissolution performances of poorly soluble active pharmaceutical ingredients (API). Recently, a review on dissolution performances of SDs classifies the improvement into 3 categories, where 82 % of the studies showed improved bioavailability, 8 % showed reduced bioavailability and 10 % revealed similar bioavailability as compared to pure APIs. This indicates the inconsistent degrees of dissolution improvement of poorly soluble APIs in SD. Although a few factors related to the choice of carriers have been suggested to contribute to the dissolution improvement, however, the underlying factor determining the discrepancy in the degree of dissolution improvement remains in vague. It is hypothesized that the API contributes to the degree of dissolution improvement of SD. Hence, the factor of amorphous solubility advantage of API which leads to the different degrees of dissolution enhancement of SD is investigated in this research. Polyvinylpyrrolidone vinyl acetate (PVPVA)-based SD is prepared with three poorly soluble APIs. Physicochemical properties of SD were characterized using infrared spectroscopy, differential scanning calorimetry (DSC) and X-ray powder diffraction. The dissolution efficiency of each SD was calculated and compared to physical mixture and pure API. Theoretical amorphous solubility advantage for each API was calculated using the thermal properties obtained from DSC. The calculated values were found to be correlating well with the dissolution enhancement of the respective SDs. Hence, this theoretical approach can be utilized as an initial screening tool of API candidates in SD formulation during early pharmaceutical development.

Keywords-Solid dispersion, Amorphous, PVPVA, Ketoprofen, Flurbiprofen, Piroxicam

I. INTRODUCTION

According to the literature, SD has shown to be a promising strategy in improving dissolution behaviour of poorly soluble drug. This in turns leads to growing interest of formulation of poorly soluble drug into amorphous form to increase its bioavailability. Theoretically, the increased dissolution rate is mainly ascribed to the amorphicity of the prepared drug that do not involve molecular bond breaking upon dissolution. The advantages of SD may further expedite with the use of hydrophilic polymer which increase wettability of a poorly

soluble drug. Even though many studies have shown the dissolution enhancement of SD, however, it is noticed that the degree of the enhancement is not straight forward. Recently, a thorough review on dissolution performances of solid dispersion by Newman et al. stated that among the published results, 82% of the studies (from the total of 40 investigated studies) shows dissolution rate enhancement after product being formulated into solid dispersion. Out of the 40 cases, 8% of the study revealed deterioration of dissolution performance and 10% of the studies declared similar bioavailabilities of the SD products [1]. Furthermore, due to the success -led in the publication process, one should not exclude the possibility of the existence of under reported cases for the deterioration of dissolution performance of SD systems. More recently the limited dissolution enhancement of ketoprofen and naproxen despite its formulation as fully amorphous SD in PVP homopolymer was reported [2, 3]. Similarly, other researchers have also reported limited increment of dissolution performance of SD system [4-8]. The inconsistent dissolution performances lead to the poor *in-vitro/ in-vivo* correlation of this type of formulation [9]. Consequently, only limited SD products are available commercially. The underlying factor of the inconsistent dissolution behaviours of the SD remains poorly understood. Therefore, assessment of the degree of solubility improvement of an amorphous drug is useful where it allows formulators to determine whether the solubility of amorphous form is high enough to justify the effort and investment in the manufacturing of SD at large scale [10].

To fill in the knowledge gaps on issue of dissolution performances of SD, PVPVA-based SD is formulated with 3 poorly soluble APIs namely, ketoprofen, flurbiprofen and piroxicam by spray drying method. PVP-VA is chosen as the carrier in this study as it encompasses the characteristics of an ideal carrier which include high T_g, able to interact with the API, less hygroscopic, and being able to stabilize the amorphous form of API in solid state as well as during the dissolution [11-15]. Flurbiprofen and ketoprofen are arylpropionic acids while piroxicam is an enolic acid, classified as non-steroidal anti-inflammatory drugs which possess anti-inflammatory, analgesic, and antipyretic effects.

They are used primarily to treat inflammation, mild-to-moderate pain, and fever. The resultant spray dried solid dispersions of flurbiprofen, ketoprofen and piroxicam with PVPVA as its drug carrier were characterized and correlated to their dissolution performances correspondingly to investigate the use of PVPVA 6:4 copolymer in different API system and the difference among the dissolution performances of solid dispersions of 3 different poorly soluble APIs in relation to their amorphous solubility advantages.

II. MATERIAL AND METHODS

A. Materials

The polyvinylpyrrolidone-vinyl acetate copolymer, Kollidon® VA 64 (PVPVA) was a generous gift from BASF distributed via ELITE ORGANIC SDN.BHD. Three model active pharmaceutical ingredients (APIs) namely Ketoprofen (KTP), Flurbiprofen (FBP) and Piroxicam (PIX) were purchased from AFINE Chemical LTD.

B. Solubility determination

Calibration curve for each API was constructed for known concentration of KTP, FBP and PIX based on the λ_{max} at 259nm, 247nm and 360nm respectively by using Beer Lambert plots. The API content in each sample was then measured using a Perkin-Elmer Lambda XLS UV/VIS spectrophotometer (USA). λ_{max} of KTP, FBP and PIX devoid of any interference from the carrier at 259nm, 247nm and 360nm respectively were used.

Experimental solubility of crystalline forms of the model APIs were measured in distilled water at room temperature. A saturated solution was prepared for respective API, by dissolving excess API powder into approximately 100mL of distilled water. The solution was stirred at 100 rate per minute for at least 24 hours at room temperature. Saturated solution of the drug is then filtered with mixed cellulose ester microfilter of 0.45 μ m pore size (MFS membrane filter, Lot no. 41CLCA). The filtrate was analysed for the corresponding λ_{max} of the APIs.

C. Estimation of amorphous solubility advantage

It has been demonstrated that amorphous drugs can provide higher solubility and faster dissolution rates than their crystalline counterparts [16]. However, solubility of amorphous drug is not easily measurable because of the tendency of rapid crystallization of amorphous solute upon contact with dissolution media [17, 18]. Thus, Hancock and Parks introduced a method for the estimation of the theoretical maximum solubility advantage of amorphous drugs, which directly reflects the driving force for their initial dissolution. This approach is based on calculation involving measured thermal properties of amorphous and crystalline forms of drugs from differential scanning calorimetry (DSC), including melting temperature, heat of fusion of the crystalline form and free energy difference between crystal and amorphous forms. From these properties, the amorphous solubility advantage

was predicted as a function of temperature using a simple thermodynamic calculation [19]. The solubility advantage of amorphous pharmaceuticals is reflected by solubility ratio of the amorphous to crystalline form, which is calculated by (1),

$$\frac{\sigma^{amorph}}{\sigma^{crystal}} = e^{\Delta G/RT} \quad (1)$$

where $\sigma^{amorph}/\sigma^{crystal}$ is the ratio of the solubility of the amorphous form to the solubility of crystalline form of API, which could be obtained from the experimental value in section II, B. ΔG is the free energy difference between the amorphous and crystalline form, R is the universal gas constant and T is the temperature in Kelvin [16]. The free energy difference between amorphous and crystalline counterparts, ΔG is obtained from the (2), i.e. Hoffman equation,

$$\Delta G = \frac{\Delta H_f \Delta T}{T_m} \quad (2)$$

where T is the operating temperature, ΔH_f is the enthalpy of fusion, T_m is the melting temperature, respectively which could be obtained by scanning the pure API using DSC and ΔT is T_m minus T. The trend of amorphous solubility advantage calculated in this section will then be compared to the dissolution performances of the prepared ASD system with the intention to unfold the underlying factor that lead to the different degrees of dissolution enhancement of SD in comparison to their PM systems, as observed among the literature.

D. Preparation of physical mixture and solid dispersion

Physical mixture (PM) of APIs (KTP, FBP, PIX) and PVPVA were prepared by gentle mixing of total 1g of weighed powders (30%w/w API in PVPVA) using a mortar and pestle for approximately 2 minutes.

Meanwhile, spray drying method is used for the production of SD in this study. A total of 5.0g of API and PVPVA mixtures in 30% API loading were prepared using 50% v/v ethanol in water. The spray-dried SD products were prepared using a Buchi mini-spray dryer B-290, with operating parameters set 60°C; for the corresponding systems shown in Table I. The yield obtained was approximately 25-30%.

TABLE I. PARAMETERS USED IN THE PREPARATION OF PVPVA-BASED SD SYSTEMS

Systems	Spray dry processing parameters		
	inlet	outlet	Feeding rate
SD 30% KTP PVPVA	80	60	5
SD 30% FBP PVPVA	80	60	5
SD 30% PIX PVPVA	90	75	5

E. Physical characterization of spray dried solid dispersion

a. Solid state characterization

Solid state characterization of the prepared solid dispersions and PM of API/PVPVA were carried out by scanning in differential scanning calorimetry (DSC), attenuated total reflectance- fourier transform infrared (ATR-FTIR) spectroscopy and X-ray powder diffraction (XRPD).

DSC measurements were performed with PerkinElmer Pyris 6 DSC. Approximately 2-4mg of samples was packed in crimped aluminium pan and heated under dry nitrogen purge. KTP and FBP samples were heated from -20°C to 200°C at 10°C/min, whereas PIX samples were heated from 0°C to 300°C. The results were analyzed using Pyris Data Analysis.

Attenuate Total Reflectance – Fourier Transform Infrared (ATR-FTIR) spectra of the raw, PM and SD samples were recorded over a wavenumber range of 500 cm⁻¹ to 4000 cm⁻¹ with a resolution of 4cm⁻¹ and 32 scans using Thermo Nicolet FTIR Nexus spectrometer coupled with ATR accessory. The spectra were analysed using OMNIC software.

XRPD analysis of raw materials, PMs and SDs were performed with an XRPD, Bruker D8 Advance equipped with a copper X-ray Tube (1.54060 Å). Samples were pressed into a sample holder to generate a flat and smooth plane surface. The samples were then exposed to an X-ray beam with voltage of 40 kV and a current 40 mA. All measurements were performed from 3θ to 50° (2θ) coupled with scanning speed of 0.02° / step and 1 second for every scan step to cover the characteristic peaks of the crystalline API.

b. Dissolution studies

Dissolution tests for PM and SD of API-PVPVA were performed using paddle method in a calibrated Varian VK7000 Dissolution Apparatus. 900mL of distilled water was used as a dissolution medium. The dissolution medium was set at 37.0 ± 0.5°C and the paddle speed of 50 rpm was used. Pure APIs, PVPVA, PM and SD products which were sieved to a controlled particle size range of 100-106 µm were added to the dissolution medium at the beginning of dissolution experiment. 10ml of the samples was withdrawn at 2, 5, 10, 15, 20, 30, 40, 50, 60 and 120 minutes. The volume of dissolution medium withdrawn was immediately replaced by introducing the same volume of fresh medium into the dissolution vessel. The samples were then filtered with mixed cellulose ester

microfilter of 0.45µm pore size (MFS membrane filter, Lot no. 41CLCA) and analyzed for content of APIs using UV-vis spectroscopy at their respective λmax. Dissolution performances of all the prepared SD were compared using dissolution efficiency (DE). DE is expressed as the area under the dissolution curve between time points t1 and t2 divided by the area under the curve at 100% dissolution, y100, over the same time period. DE was measured using the trapezoidal method, where the area under the curve is the sum of all the trapeziums defined by (3),

$$AUC = \sum_{i=1}^{j=n} \frac{(t_1-t_{i-1})(y_{i-1}+y_i)}{2} \tag{3}$$

where t_i is the ith time point, y_i is the percentage of dissolved product at time t_i [20]. Subsequently, percentage of DE (%) was calculated using (4) as below,

$$DE(\%) = \frac{\int_0^t yX dt}{y_{100} X t} \times 100\% \tag{4}$$

where y is the percentage of drug release (Khalid, 2015).

III. RESULT AND DISCUSSION

A. Theoretical estimation of amorphous solubility advantage ratio of the tested drug

Amorphous solubility advantage is reflected by the free energy difference between the amorphous API and crystalline counterparts, which was calculated according to (1) and (2) as described in section II, C [16], based on the thermal properties of API measured by DSC in section II, B. Table II illustrates the melting temperature, melting enthalpy, free energy difference between the amorphous form and crystalline form, experimental solubility and calculated solubility ratio of crystalline form amorphous forms and theoretical amorphous solubility of different APIs.

As shown in column 4 of Table II, PIX has the highest free energy difference between its amorphous and crystalline state. This is followed by FBP and KTP. This trend is in parallel to the predicted solubility ratio of amorphous API to crystalline API of the APIs as shown in column 6 of Table II.

TABLE II. MELTING TEMPERATURE OF THE CRYSTALLINE APIs, MELTING ENTHALPY OF THE CRYSTALLINE APIs, FREE ENERGY DIFFERENCE BETWEEN THE CRYSTALLINE APIs AND THEIR AMORPHOUS FORM, EXPERIMENTAL SOLUBILITY OF THE CRYSTALLINE APIs, SOLUBILITY RATIO AND THEORETICAL SOLUBILITY OF AMORPHOUS APIs

Drug-PVPVA	Melting Temperature (K)	Melting enthalpy ΔH (KJ/mole)	Free energy difference, ΔG, (KJ/mole)	Experimental Solubility (mg/mL)	Solubility ratio	Theoretical amorphous solubility (mg/L)
KTP	366.32	32.46	4.21	0.148	5.13	0.7575
FBP	386.03	30.47	4.81	0.027	6.46	0.1744
PIX	470.95	38.18	8.59	0.040	27.93	1.1193

B. Solid state characterization

Figure 1 presents DSC thermograms of the freshly prepared SD 30% APIs-PVPVA systems.

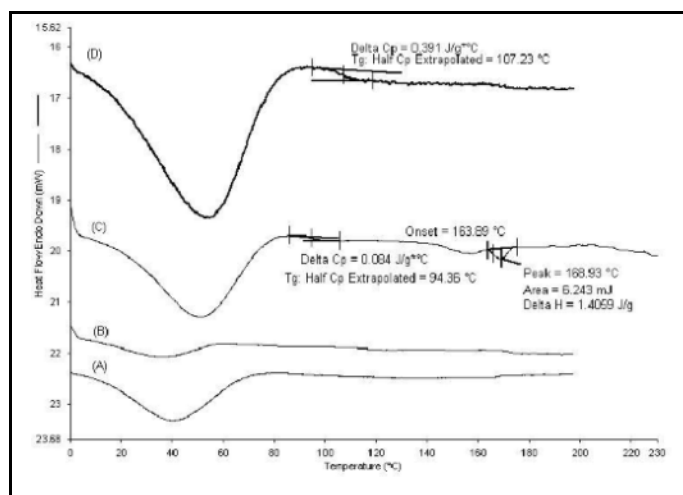


Figure 1. DSC thermograms of first heating cycle of (A) SD 30%w/w KTP PVPVA (B) SD 30%w/w FBP PVPVA (C) SD 30%w/w PIX PVPVA and (D) PVPVA.

The absence of any melting endothermic peak indicates the amorphous nature of SD products of KTP and FBP (Figure 1 (A) and Figure 1 (B)). Besides a T_g detected at circa 94.36°C , SD 30 PIX-PVPVA also shows a melting endotherm at circa 168.93°C due to its partly crystalline property (Figure 1 (C)). This suggests the combination of amorphous and crystalline components present in SD PIX PVPVA system. Generally, the presence of crystalline traces of PIX in the SD PIX PVPVA is predicted to interfere the dissolution. Amorphicity of the spray dried samples could be further confirmed via scanning in X-ray powder diffraction. Figure 2 shows the XRPD diffractograms of all the pure APIs and their corresponding physical mixture and spray dried samples.

All the tested drugs in this study show certain degree of drug polymer interaction through hydrogen bonding (data not shown). This may contribute to the better physical stabilization of the solid dispersion upon storage. The extent of hydrogen bond interaction between the APIs and PVPVA6:4 is reflected by the extent of C=O downshift. This is because weakening of vibration energy of C=O stretching after bonding to the hydrogen acceptor from API, causing the redshift to the lower wavenumber [2, 21]. Examining extend of C=O shift from PVPVA, estimation of the drug-polymer interaction is in the following trend i.e. $\text{KTP-PVP} > \text{PIX-PVPVA} > \text{FBP-PVPVA}$. However, due to the interference of several peaks in the region of C=O for the FBP system in this study, the suggested trend may only be treated as gross estimation.

The diffractograms showed the characteristic diffracted peak of all APIs (KTP, FBP, PIX) in the region of 3° to 30° (Figure 2 (A) to (C)). These peaks were also noted in all the physical mixtures which indicate the presence of crystalline APIs in those samples (Figure 2 (D) to (F)). However, halo

patterns were shown in the diffractograms of SD 30% KTP and FBP in PVPVA, respectively (Figure 2 (G) and (H) respectively). These results are in agreement to the deduction obtained from DSC (absence of any melting endothermic peak) which concludes that the SD 30%w/w KTP and FBP in PVPVA are amorphous in nature.

In contrast, characteristic peaks of the PIX in the region of 8° to 30° are detected in SD 30% PIX in PVPVA in lower diffracting intensities (Figure 2 (I)). This ascertains the presence of crystalline traces of PIX in the SD PIX PVPVA sample. Area under the diffracted peaks was calculated using ORIGIN 8.0 software. The obtained area revealed that the percentage of PIX crystallinity was less than 10%. Besides, doublet diffraction peaks were seen in the region of 8° which suggests the presence of different polymorph forms of PIX, i.e. Form II. Once again, this result is in agreement to the result deduced from ATR-FTIR finding (presence of Form II crystal as indicated by OH absorption peak at 3392cm^{-1}) and DSC finding (presence of melting endothermic peak).

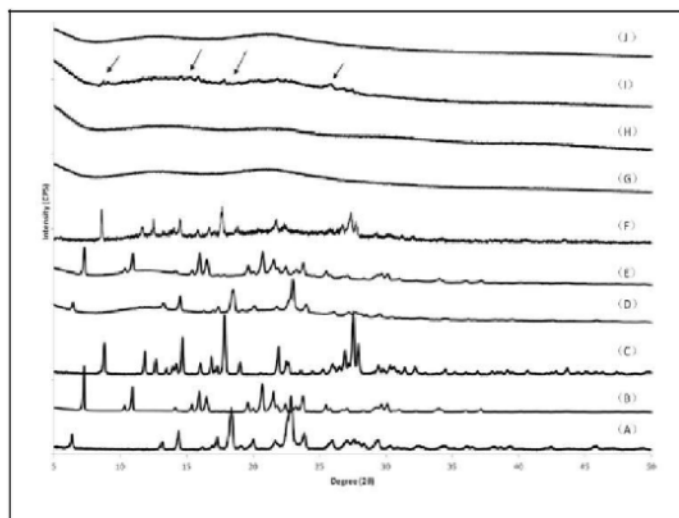


Figure 2. X-ray diffractograms of the investigated samples, (A) KTP, (B) FBP, (C) PIX, (D) PM 30%w/w KTP PVPVA, (E) PM 30%w/w FBP PVPVA, (F) PM 30%w/w PIX PVPVA, (G) SD 30%w/w KTP PVPVA, (H) SD 30%w/w FBP PVPVA, (I) SD 30%w/w PIX PVPVA and (J) PVPVA

C. Dissolution performances of solid dispersion and physical mixture

The ability of amorphous SD in producing formulations with enhanced dissolution rate and bioavailability was widely reported [2, 22-25]. This is due to the ability of amorphous system in exhibiting high level of supersaturation and thus higher apparent solubility than its crystalline counterpart [1]. After the basic characterization of the prepared SD APIs-PVPVA system, the dissolution performances of SD systems were compared to their corresponding pure API and PM systems in order to assess the advantages in dissolution performance of SD system. Figure 3 displays the dissolution profiles of the 3 different APIs in their pure powder form, PMs and SD systems.

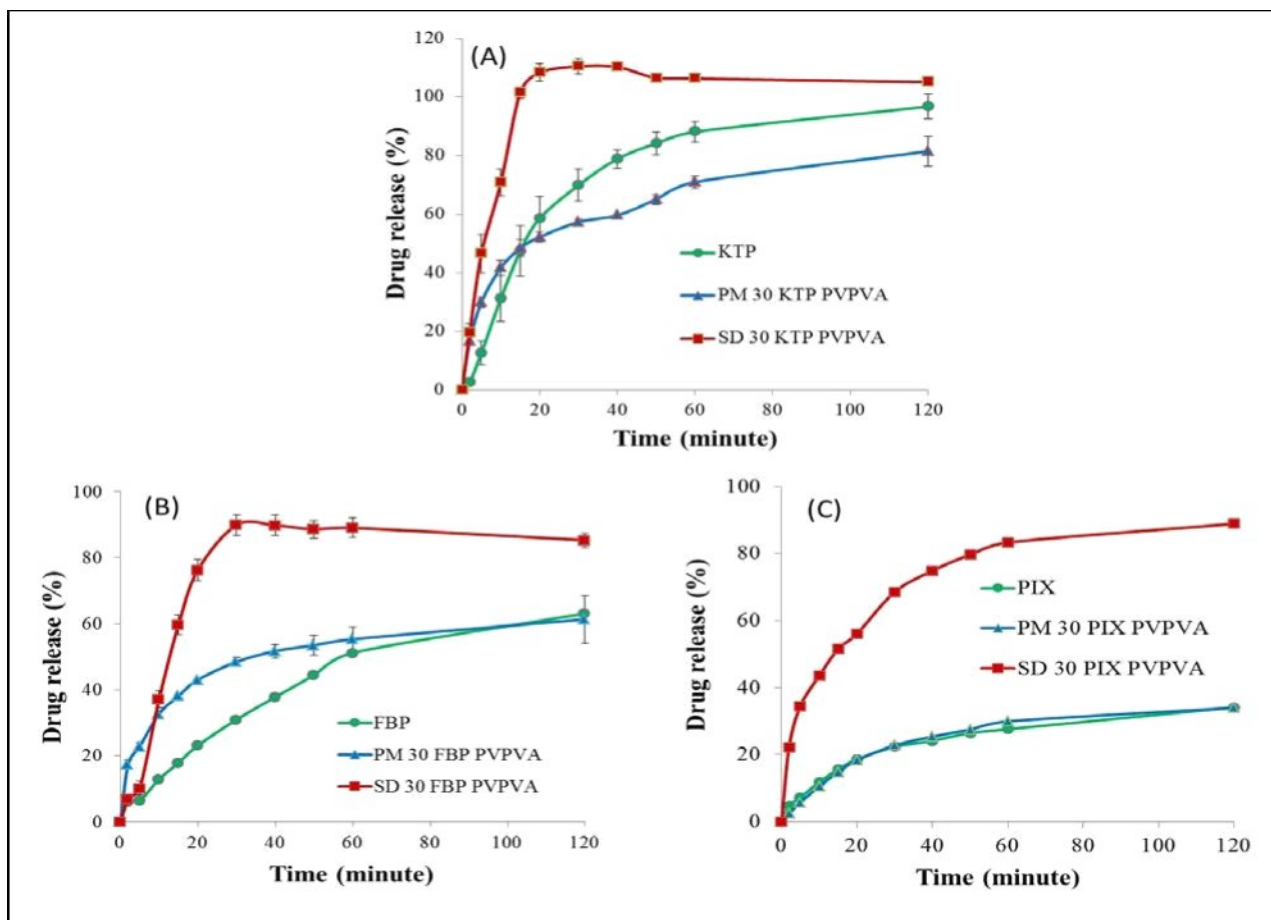


Figure 3. Comparison of dissolution profile among SD systems (A) KTP PVPVA system, (B) FBP PVPVA system and (C) PIX PVPVA system

Figure 3 demonstrated the dissolution rate of amorphous PM API-PVPVA systems (symbol “Δ”), which show a higher initial release rate than their corresponding API systems (symbol “o”) consistently, except PIX. The increase the dissolution rate of the PM in comparison to the API may be due to the wetting effect of the hydrophilic carrier [25, 26]. Besides, Figure 3 also demonstrated the dissolution rate of amorphous SD API-PVPVA systems (symbol “□”), which show a higher overall release rate than their corresponding PM API-PVPVA systems consistently.

SD KTP PVPVA system showed an equal dissolution rate as its PM system initially, followed by a slightly higher dissolution rate than its PM system (Figure 3 (A)). In FBP system (Figure 3 (B)), the initial dissolution rate of SD system is lower than the PM system, subsequently, the percentage of drug release of SD system was significantly higher than its PM system. Due to inconsistent degree of increment in drug release rate of SD system as compared to its PM system over the time period of dissolution, the dissolution profile is quantitatively analysed by using dissolution efficiency that has been described in section II, E, b. Table III displays the percentage of dissolution efficiency of the APIs, PMs, SDs systems and the degree of dissolution rate improvement in the dissolution performance of SD system as compared to the corresponding PM system. From the observation of Figure 3 and Table III, the rank order of the increased percentage of drug release of API in

SD system in comparison to their PM system, i.e. PIX > FBP > KTP was found to follow the exact trend seen in solubility advantage ratio of APIs as calculated in section III, A, Table II.

TABLE III. PERCENTAGE OF DISSOLUTION EFFICIENCY OF PURE API, PM API PVPVA AND SD API PVPVA

Systems	Dissolution efficiency (DE%)		
	KTP	FBP	PIX
Drug alone	76.72	43.20	29.20
PM	67.58	51.03	29.02
SD	99.51	78.95	79.31
Dissolution efficiency improvement of SD (%)	32.08	35.36	63.41

In the current study, dissolution efficiency results demonstrated that amorphous solid dispersion (ASD) can provide higher solution concentration than the crystalline PM system, which is in concordance with the expectation stated in Hancock and Parks [19] whereby amorphous state of an API contributes to the dissolution enhancement of poorly soluble system. However, different APIs used in this study exhibited different degree of dissolution rate increment despite similar drug loading, same carrier and method of preparation used. For instance, even though fully amorphous system of the SD KTP

PVPVA system was obtained, the degree of dissolution enhancement was limited as compared to the partially amorphous system as shown by the SD PIX PVPVA system which reveals dramatic dissolution rate increment in comparison to its PM system. This result has suggested that the presence of crystalline trace in a SD system may not be the main reason for the deterioration of dissolution performance of a crystalline SD system, as suggested in most of the published papers [22, 27].

Drug-polymer interaction has been suggested to be important in physical stabilization upon storage as well as dissolution [28, 29]. Likewise, some studies suggested that drug polymer interaction plays a significant role in precipitation inhibition and amorphous stabilization during dissolution process [1, 30]. However, in this study, dissolution performance of the ASD was the highest in PIX-PVPVA, i.e. approximately 2 folds increase in dissolution efficiency as compared to KTP and FBP SD systems. These results were not following the gross estimation trend of drug-polymer interaction. Therefore, in the current study, there is no clear relationship between the drug-polymer interactions to the degree of dissolution enhancement of SD system.

During dissolution, dissolution rate of solid is proportional to the surface area of solid and the difference between the concentration of the saturated solution surrounding the solid and the concentration in the bulk of solvent, as described by the Noyes and Whitney equation [31]. Upon achieving a constant release rate at the dissolving front, the solution at the saturated dissolving front would be equivalent to the solubility of the API. Thus, the higher solubility advantage of an amorphous API could drive its dissolution process, assuming other parameters that affect the dissolution process, i.e. surface area of API are kept constant [2]. Thus, the expected solubility improvement of amorphous form would be the highest in PIX, followed by FBP > KTP.

The solubility advantage of amorphous to crystalline state of the 3 APIs was found to correlate well to the extent of dissolution efficiency enhancement of the SD systems as compared to its PM systems of APIs, i.e. SD PIX -PVPVA > SD FBP-PVPVA > SD KTP-PVPVA, as presented by Table 2 and Table 3. This suggests that the dissolution performance of a SD API-PVPVA system is API-specific where the free energy difference between the amorphous and crystalline form largely dictate the overall dissolution performance of a spray-dried ASD system. However it is worth emphasizing that there were visible white particles in the midst of the dissolution vessel during the dissolution processes which settled down at the bottom of the vessel. Similar observations have been reported in other researches during dissolution process [32, 33]. Therefore, it is believed that the degree of dissolution enhancement of the ASD has been compromised due to the dramatic decrease of surface area as a result of extensive agglomeration. API with a higher amorphous solubility advantage may afford the phenomenon of agglomeration which sustains its amorphous advantages in the SD formulation during the dissolution process.

Hence, coupling the knowledge of amorphous solubility advantage in the preparation of SD formulation, one may

estimate if a candidate of API is suitable to be formulated as SD system by taking the compromising factor of agglomeration into consideration. With that, API with a high ratio of amorphous solubility advantage is preferred to be formulated as an ASD.

IV. CONCLUSION

Fully amorphous PVPVA-based SD systems have been successfully produced for the prepared SD FBP and KTP systems. On contrary, SD PIX PVPVA shows partially amorphous system with crystalline trace. Instead of viewing the presence of crystalline trace as undesirable characteristic, sample with crystalline traces in SD PIX PVPVA system have been found to have the highest dissolution efficiency among the tested systems.

Although it has been postulated that drug-polymer interaction contributes to dissolution improvement of SD, however, to the best of our knowledge, no research has successfully established a relationship between drug-polymer interactions with the degree of dissolution improvement. Similarly in this study, all the system shows certain degree of drug-polymer interaction, but no clear relationship could be concluded for the observed different degree of dissolution rate increment. With that, more studies should be focused on investigating the relationship between strength of drug-polymer interaction and the degree of dissolution improvement in SD formulation.

Theoretical approach suggested in this research for the use of future screening of API has shown to be correlated well to the degree of dissolution enhancement of SD. Even though there are only three systems tested in the current study, the use of this approach is worth for further investigation of other API-polymer systems. The benefit of this approach is laid in its simplicity where only the simple thermal property of the drug is required. This approach will enable early screening on the suitability of a newly identified compound to be formulated as an amorphous solid dispersion.

ACKNOWLEDGMENT

Financial support from the Fundamental Research Grant Scheme of Malaysia is greatly appreciated.

REFERENCES

- [1] Newman A, Knipp G, Zografi G. Assessing the performance of amorphous solid dispersions. *Journal of Pharmaceutical Sciences*. 2012, vol. 101, pp. 1355-77.
- [2] Chan SY. *The Development of PVP-based Solid Dispersions using Hot Melt Extrusion for the Preparation of Immediate Release Formulations*: University of East Anglia; 2013.
- [3] Chan SY, Quah J, Tan YL, Chung YY, Cheah XZ. The characterization and dissolution performances of spray dried solid dispersion of Ketoprofen in hydrophilic carriers. *Asian J Pharm Sci*. 2015, vol. 10, pp. 372-85.
- [4] Verheyen S, Blaton N, Kinget R, Van den Mooter G. Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions. *International Journal of Pharmaceutics*. 2002, vol. 249, pp. 45-58.
- [5] Tajarobi F, Abrahmsén-Alami S, Larsson A. Dissolution rate enhancement of parabens in PEG solid dispersions and its

- influence on the release from hydrophilic matrix tablets. *J Pharm Sci.* 2011a, vol. 100, pp. 275-83.
- [6] Moneghini M, Carcano A, Zingone G, Perissutti B. Studies in dissolution enhancement of atenolol. Part I. *International Journal of Pharmaceutics.* 1998, vol. 175, pp. 177-83.
- [7] van Drooge DJ, Hinrichs WLJ, Frijlink HW. Anomalous dissolution behaviour of tablets prepared from sugar glass-based solid dispersions. *Journal of Controlled Release.* 2004, vol. 97, pp. 441-52.
- [8] Saers ES, Craig DQM. An investigation into the mechanisms of dissolution of alkyl p-aminobenzoates from polyethylene glycol solid dispersions. *International Journal of Pharmaceutics.* 1992, vol. 83, pp. 211-9.
- [9] Greco K, Bogner R. Solution-mediated phase transformation: Significance during dissolution and implications for bioavailability. *Journal of Pharmaceutical Sciences.* 2012, vol. 101, pp. 2996-3018.
- [10] Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: I. A thermodynamic analysis. *Journal of pharmaceutical sciences.* 2010, vol. 99, pp. 1254-64.
- [11] Patterson JE, James MB, Forster AH, Rades T. Melt Extrusion and Spray Drying of Carbamazepine and Dipyridamole with Polyvinylpyrrolidone/Vinyl Acetate Copolymers. *Drug Development and Industrial Pharmacy.* 2008, vol. 34, pp. 95-106.
- [12] Hong SW, Lee BS, Park SJ, Jeon HR, Moon KY, Kang MH, et al. Solid dispersion formulations of megestrol acetate with copovidone for enhanced dissolution and oral bioavailability. *Archives of pharmacol research.* 2011, vol. 34, pp. 127-35.
- [13] Janssens S, Van Humbeeck J, Van den Mooter G. Evaluation of the formulation of solid dispersions by co-spray drying itraconazole with Inutec SP1, a polymeric surfactant, in combination with PVPVA 64. *Eu J Pharm Biopharm.* 2008, vol. 70, pp. 500-5.
- [14] Song Y, Wang L, Yang P, Wenslow RM, Tan B, Zhang H, et al. Physicochemical characterization of felodipine-kollidon VA64 amorphous solid dispersions prepared by hot melt extrusion. *Journal of pharmaceutical sciences.* 2013, vol. 102, pp. 1915-23.
- [15] Jung J-Y, Yoo SD, Lee S-H, Kim K-H, Yoon D-S, Lee K-H. Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique. *Int J Pharm* 1999, vol. 187, pp. 209-18.
- [16] Alonzo D, Zhang G, Zhou D, Gao Y, Taylor L. Understanding the Behavior of Amorphous Pharmaceutical Systems during Dissolution. *Pharmaceutical Research.* 2010, vol. 27, pp. 608-18.
- [17] Khalid SH. Investigation of inclusion complexation, chemical modification and microemulsion formulation of curcumin for enhanced antibacterial property: Universiti Sains Malaysia; 2015.
- [18] Kuentz M, Imanidis G. In silico prediction of the solubility advantage for amorphous drugs—Are there property-based rules for drug discovery and early pharmaceutical development? *European Journal of Pharmaceutical Sciences.* 2013, vol. 48, pp. 554-62.
- [19] Hancock BC, Parks M. What is the True Solubility Advantage for Amorphous Pharmaceuticals? *Pharmaceutical Research.* 2000, vol. 17, pp. 397-404.
- [20] Anderson N, Bauer M, Boussac N, Khan-Malek R, Munden P, Sardaro M. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. *Journal of pharmaceutical and biomedical analysis.* 1998, vol. 17, pp. 811-22.
- [21] Van Eerdenbrugh B, Taylor LS. Molecular weight effects on the miscibility behavior of dextran and maltodextrin with poly(vinylpyrrolidone). *Pharmaceutical research.* 2012, vol. 29, pp. 2754-65.
- [22] Patel JR, Carlton RA, Yuniatine F, Needham TE, Wu L, Vogt FG. Preparation- and structural characterization of amorphous spray dried dispersions of tenoxicam with enhanced dissolution. *Journal of pharmaceutical sciences.* 2012, vol. 101, pp. 641-63.
- [23] Yan Y-D, Sung JH, Kim KK, Kim DW, Kim JO, Lee B-J, et al. Novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes. *Int J Pharm.* 2012, vol. 422, pp. 202-10.
- [24] Chawla G, Bansal A. Improved dissolution of a poorly water soluble drug in solid dispersions with polymeric and non-polymeric hydrophilic additives. *Acta Pharmaceutica* 2008, vol. 58, pp. 257-74.
- [25] Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics.* 2002, vol. 231, pp. 131-44.
- [26] Biswal S, Sahoo J, Murthy P. Physicochemical properties of solid dispersions of gliclazide in polyvinylpyrrolidone K90. *AAPS Pharm Sci Tech.* 2009, vol. 10, pp. 329-34.
- [27] Langham ZA, Booth J, Hughes LP, Reynolds GK, Wren SAC. Mechanistic insights into the dissolution of spray-dried amorphous solid dispersions. *Journal of Pharmaceutical Sciences.* 2012, vol. 101, pp. 2798-810.
- [28] Thakral S, Thakral NK. Prediction of drug-polymer miscibility through the use of solubility parameter based flory-huggins interaction parameter and the experimental validation: PEG as model polymer. *Journal of Pharmaceutical Sciences.* 2013, vol. 102, pp. 2254-63.
- [29] Li Y, Pang H, Guo Z, Lin L, Dong Y, Li G, et al. Interactions between drugs and polymers influencing hot melt extrusion. *Journal of Pharmacy and Pharmacology.* 2014, vol. 66, pp. 148-66.
- [30] Chauhan H, Hui-Gu C, Atef E. Correlating the behavior of polymers in solution as precipitation inhibitor to its amorphous stabilization ability in solid dispersions. *Journal of Pharmaceutical Sciences.* 2013, vol. 102, pp. 1924-35.
- [31] Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. *Journal of the American Chemical Society.* 1897, vol. 19, pp. 930-4.
- [32] Alonzo DE, Gao Y, Zhou D, Mo H, Zhang GGZ, Taylor LS. Dissolution and precipitation behavior of amorphous solid dispersions. *Journal of Pharmaceutical Sciences.* 2011, vol. 100, pp. 3316-31.
- [33] Kanaujia P, Lau G, Ng WK, Widjaja E, Hanefeld A, Fischbach M, et al. Nanoparticle formation and growth during in vitro dissolution of ketoconazole solid dispersion. *Journal of Pharmaceutical Sciences.* 2011, vol. 100, pp. 2876-85.