Amorphization of pharmaceutical compounds by co-precipitation using supercritical anti-solvent process

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INTRODUCTION

Recently, the increase in the number of newly discovered poorly water soluble drug candidates has heightened the interest in developing novel methods to improve aqueous-solubility. A new approach using supercritical fluids for particle design of pharmaceutical materials is being actively pursued due to its major advantages over conventional pharmaceutical processing such as high purity of products, ability to control particle size and narrow particle size distribution, single step process and free from residual solvent. Besides these advantages, one major challenge is to improve bioavailability and stability of poorly water soluble active pharmaceutical ingredient (API) using supercritical fluids particle design technology [1]. Therefore, the aim of this work is to investigate the feasibility of using supercritical co-precipitation technique to influence the crystallinity or amorphous character of a crystalline API. In cases where low solubility limits absorption, the amorphous form may have an advantage in improving dissolution properties. The dissolution rate of poorly water soluble drug can also be improved by dispersing it in a water-soluble biocompatible carrier such as poly(vinylpyrrolidone) (PVP), polyethylene glycol, hydroxyl propyl methylcellulose, etc., which inhibit the crystallisation of the drug [2]. The API-excipient composites were generated by varying process conditions such as API-excipient ratios, relative flow rates of supercritical carbon dioxide and API solution, pressure and types of solvent. In addition, stability stress test on SAS formulated powders were carried out at 75% RH and room temperature or 40^{o}C in order to evaluate their physical stability. The untreated and SAS powders (after and before storage) were characterized using scanning electron microscopy (SEM, morphology), powder X-ray diffractometry (PXRD, crystallinity), USP dissolution tester and thermogravimetric analysis (TGA).

MATERIALS AND METHODS

Indomethacin, IDMC (Fluka) and poly(vinylpyrrolidone), PVP MW 360,000 (Sigma) were used as received. Carbon dioxide 99.95% (SOXAL) purity was used as an anti-solvent for SAS process. Mixtures of IDMC and PVP at various weight ratios of 85:15, 50:50 and 20:80 were prepared by dissolving it into a mix-solvent containing reagent grade of acetone and dichloromethane. All SAS co-precipitations are conducted at 85 bar and 35^{o}C. Similar compositions of physically blended PB IDMC-PVPs were also prepared using Turbula T2F shaker-mixer at 49 rpm for 1 hour. Besides that, spray-dried IDMC (SD IDMC) was also prepared using BÜCHI Mini Spray Dryer.

PXRD diffractograms were collected for powdered sample using a Bruker XRD D8 Advance. Data were collected over the 2θ range 4-55^{o} with a step size of 0.05^{o} and step time of 1 s. The

morphology of SAS co-precipitated was characterized using scanning electron microscopy (JEOL JSM-6700F SEM-EDX) at 5kV accelerating voltage.

Thermal stability of powdered sample was determined using TGA-Q500 at a heating rate of 10^{o}C/min from room temperature to 900^{o}C and at 40mL/min of nitrogen flow. The dissolution rates of powdered samples were investigated using a Varian VK7010 8-spindle, 8-vessel USP dissolution apparatus with automated online UV-Vis measurement. The dissolution medium consisted of 900 mL of phosphate buffer pH 6.8, maintained at temperature of 37±0.5^{o}C and agitation rate was 100 rpm. An UV detection wavelength of 320 nm was used to determine the IDMC concentration.

Physical stability stress tests were conducted on powdered samples at controlled temperature and relative humidity (RH) based on procedures from International Conference on Harmonization (ICH) –ICH Q1A (R2). The powdered samples were stored at room temperature or 40^{o}C and 75% RH. The changes in crystallinity were analysed using PXRD.

RESULTS

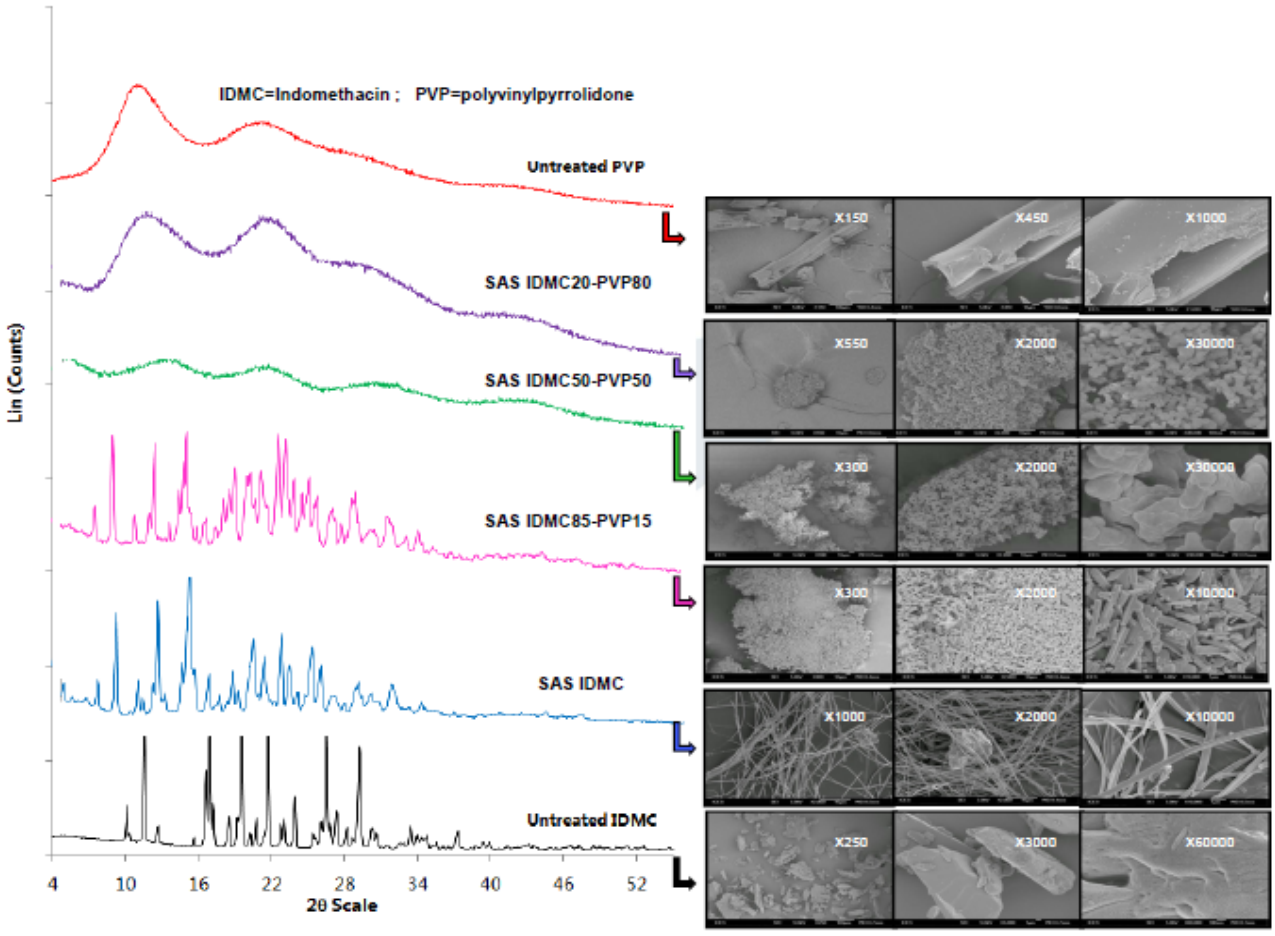

Figure 1: Effect of co-precipitation ratio on crystallinity using SAS process

Figure 1 shows that X-ray amorphous SAS IDMC-PVPs was formed at PVP contents above 50 wt.%. Gong et al., [3] also obtained X-ray amorphous IDMC-PVP using solvent-free supercritical fluid processing. However, the amorphous co-precipitate in Gong's work required high PVP content of 80 wt.% and above. Besides that, SEM images showed the morphologies of untreated IDMC were multi-faceted structures and PVPs were rod-like, whereas SAS IDMC and SAS PVP were predominantly thread-like and agglomerated rounded fines, respectively.

Figure 2 shows that the composition of SAS co-precipitates were close to the feed compositions, which indicated that the co-precipitation was well controlled. The thermograms of SAS co-precipitates also superimposed on their respective physical blends of PB IDMC-PVP thermograms (no shown). IDMC and PVP started to decompose at 220 and 380^{o}C respectively.

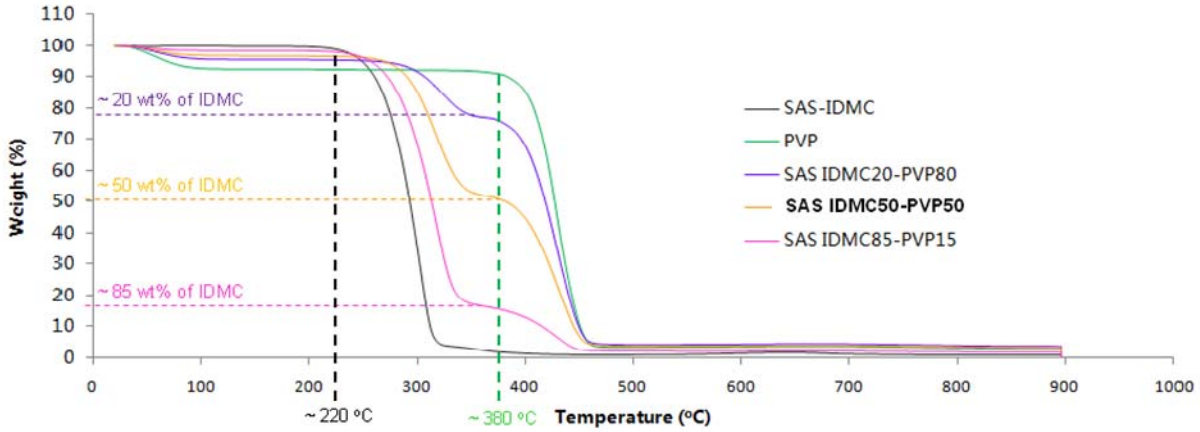

Figure 2: Thermograms of SAS IDMC-PVPs and untreated PVP

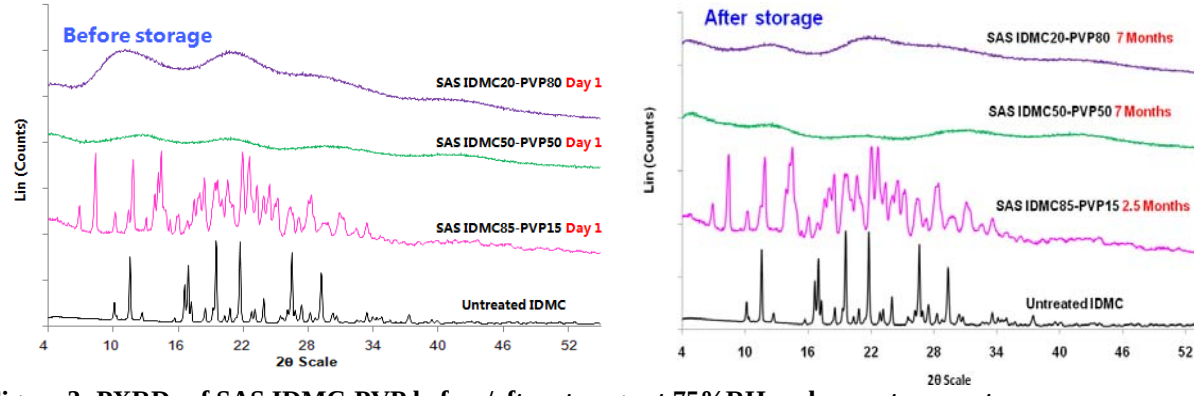

Figure 3: PXRDs of SAS IDMC-PVP before/after storage at 75%RH and room temperature

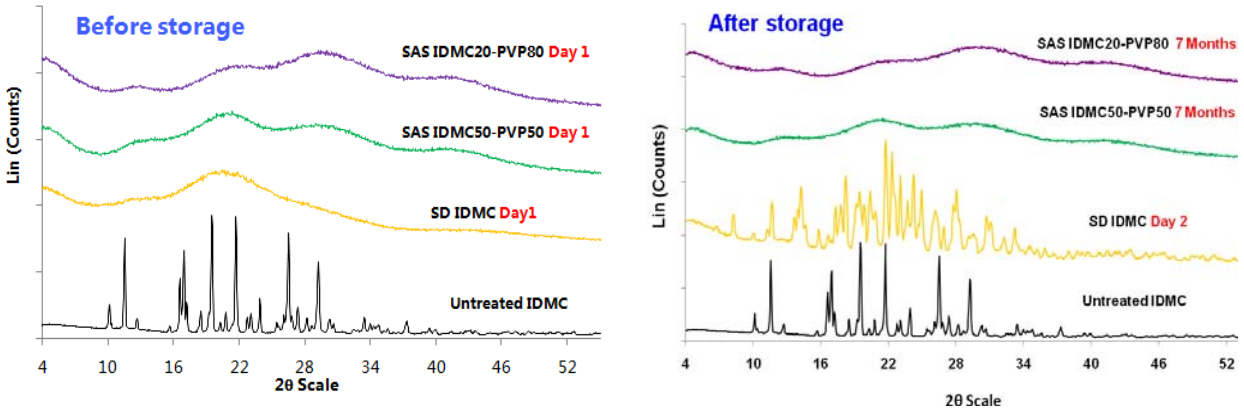

Figure 4: PXRDs of SAS IDMC-PVP and Spray-dried IDMC before/after storage at 75%RH and 40°C

Figure 3 shows the PXRD diffractograms of SAS co-precipitates that were subject to storage at 75%RH and room temperature. It can be seen that SAS co-precipitates with PVP content above 50 wt.% remained stable in X-ray amorphous form after 7 months. Figure 4 shows the generated SD IDMC was X-ray amorphous before storage. However, recrystallisation of SD IDMC was observed after storage of 1 day at 75%RH and 40°C (Figure 4). Interestingly, the SAS co-precipitate with PVP content above 50 wt.% remained X-ray amorphous under the same conditions. The presence of PVP could have inhibited the recrystallisation of IDMC by restricting the IDMC molecules mobility. Therefore, it is suggested that excipient PVP could be a suitable "amorphous inducing and stabilizing" agent for SAS process.

Figure 5 shows that the dissolution rate of SAS IDMC and SAS IDMC85-PVP15 (both crystalline forms) were improved as compared to the untreated IDMC. Besides that, further improvement of IDMC dissolution rates were obtained using amorphous SAS IDMC50-PVP50 and SAS IDMC20-PVP80. The higher dissolution rates of IDMC might be due to the amorphous nature of SAS co-precipitate, increased in surface areas or both. Figure 6 shows physical blends of PB IDMC-PVP did not have improved dissolution rates as compared with that untreated IDMC.

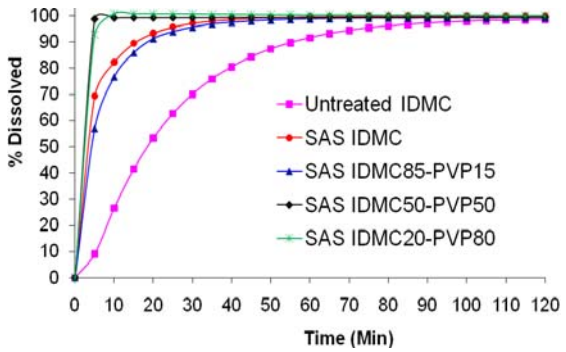

Figure 5: Effect of SAS co-precipitation ratios

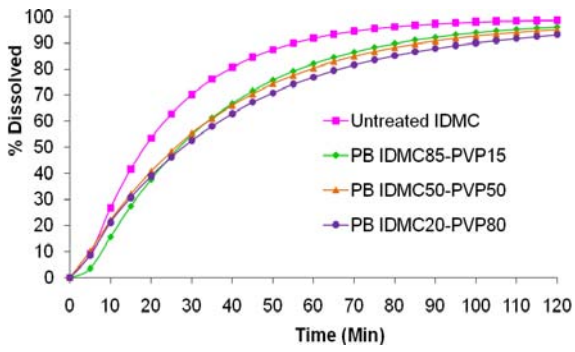

Figure 6: Effect of physical blends PB IDMC-PVP

CONCLUSION

Our results revealed that it was technically feasible to generate X-ray amorphous API by co-precipitation with selected excipients using SAS. Co-precipitation using SAS process can be used to obtain IDMC with different morphologies and crystallinity. The amorphous form remained stable after 7-months storage at 75% RH and room temperature or 40^{o}C. The amorphous content of the co-precipitated API was found to be influenced by the API-excipients ratios. By using different processing conditions and excipient ratios, the morphologies of an API-excipient composite can be varied. Amorphous form of IDMC produced by SAS has improved dissolution properties as compared to the crystalline form. This form is also stable under stress test conditions compared with spray-dried amorphous IDMC. It is suggested that excipient PVP could be a suitable "amorphous inducing and stabilizing" agent for SAS process.

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