Use of Co-milling to Improve Physical Stability of Amorphous Salbutamol Sulphate

In recent years, co-milling of active pharmaceutical ingredients (APIs) with excipients is being investigated as a promising technique to improve desired properties such as solubility and dissolution profiles[1], bioavailability[2], aerosolization[3] and physical stability[4]. Traditionally, excipients are simply blended into a drug formulation to improve the manufacturability or product quality, e.g. to improve the ease of tablet compaction, to increase solubility or bioavailability[5]. As milling is an energy intensive process, it tends to induce structural disorders leading to the formation of amorphous regions, which are located particularly at the surfaces of milled particles[6]. This amorphous phase possesses high molecular mobility and tends to revert back to the more stable crystalline state upon storage. Stabilization of this amorphous form is important because this solid-state change can be detrimental to the drug performance as it affects critical particle properties such as morphology, particle size distribution, specific surface area, chemical and physical reactivity[7] and dissolution rates[8].

In this study, salbutamol sulphate (SS) was selected as a model drug as it typically transforms from the crystalline to the amorphous form during milling. As the glass transition temperature (T_g) of SS is close to typical storage temperatures at elevated relative humidity conditions, milled SS particles are physically unstable during normal storage and tend to undergo agglomeration[9]. Pfeiffer and co-workers[9,10] suggested that the increase in particle size of micronized SS was caused by re-crystallization of the amorphous regions. It was also shown that storage of partially amorphous SS at accelerated stress test conditions of 40°C and 75% RH resulted in complete re-crystallization in 5 hrs[9]. In our previous work, a new co-milling method using crystalline excipients was devised to minimize the amorphization of SS below the detection limits of dynamic vapor sorption (DVS) and differential scanning calorimetry (DSC) [11,12]. However, although the amorphous form is unstable, it can sometimes be highly desired because of its higher reactivity and better dissolution properties. As polyvinyl pyrrolidone (PVP) was shown to inhibit the crystallization in amorphous solid dispersions and promote stabilization of the drug in metastable state[13], the present study aims to stabilize the amorphous form of SS by co-milling with PVP.

Different mass ratios (1:1, 1:2, 1:3, 1:5, 2:1, 3:1, 5:1) of SS and PVP were co-milled at 300 rpm in a planetary ball mill for 1 h. The co-milled (CM) mixtures along with their individual components and physically blended (PB) mixtures were subjected to storage conditions of 22°C/75%RH and 22°C/15%RH for 7 days. Powder X-Ray Diffraction (PXRD) and Scanning Electron Microscopy (SEM) analyses prior and after storage were carried out to evaluate changes in crystallinity and morphology. Before storage, PXRD patterns of all CM and PB mixtures showed an amorphous halo, which indicated that SS was present in the amorphous state. After storage at 22°C/75%RH (Figure 1), only CM mixture at SS:PVP (1:5) ratio was able to retain the fully X-ray amorphous character. All other mixtures including PB mixtures were found to be unstable and showed re-crystallization behavior upon storage at 22°C/75%RH, which was similarly observed in milled SS. The results showed that co-milling of SS with PVP at (1:5) ratio was effective in stabilizing the amorphous form of SS. As a control, all CM and PB mixtures remained

X-ray amorphous when stored at 22°C/15%RH as the humidity conditions were not sufficient to induce re-crystallization (Figure 2). The PXRD results were further supported by SEM analysis, as no agglomeration behavior was observed in CM mixtures having mass ratios higher than SS:PVP (1:2). This indicated that CM mixtures at ratios higher than SS:PVP (1:2) were able to minimize the agglomerative tendency of milled SS and improved the physical stability of amorphous SS. The thermal properties of these CM mixtures were also analyzed using Differential Scanning Calorimetry (DSC). Preliminary DSC studies indicated the absence of a recrystallization exotherm in the thermograms of CM mixtures, which was observed in the thermogram of milled SS. All PB mixtures were found to re-crystallize upon heating as indicated by the presence of a re-crystallization exotherm. This suggested that in CM, the amorphous SS has fused with PVP into a solid dispersion.

Figure 1

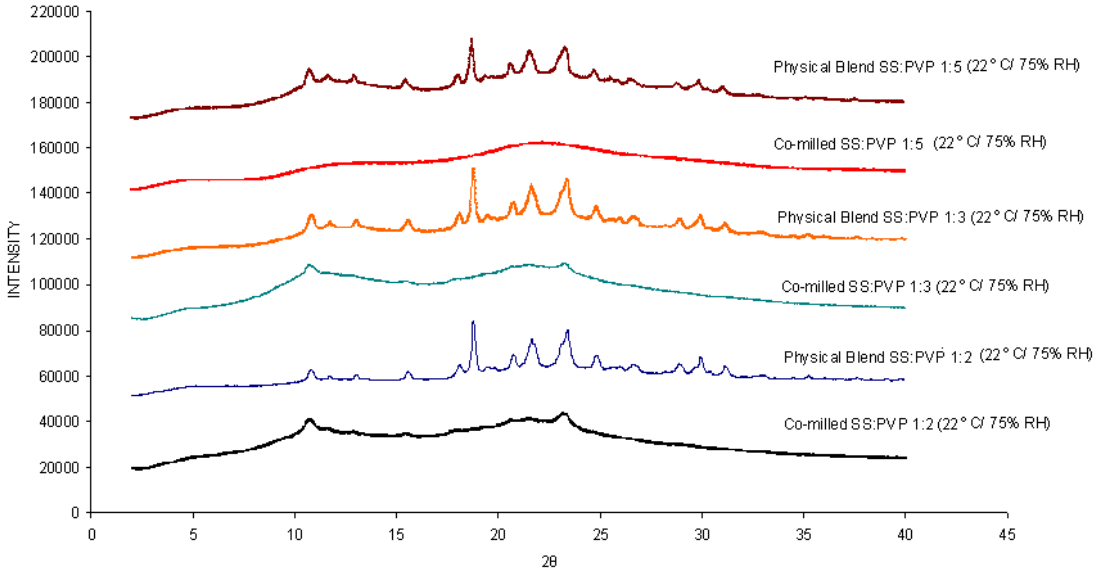
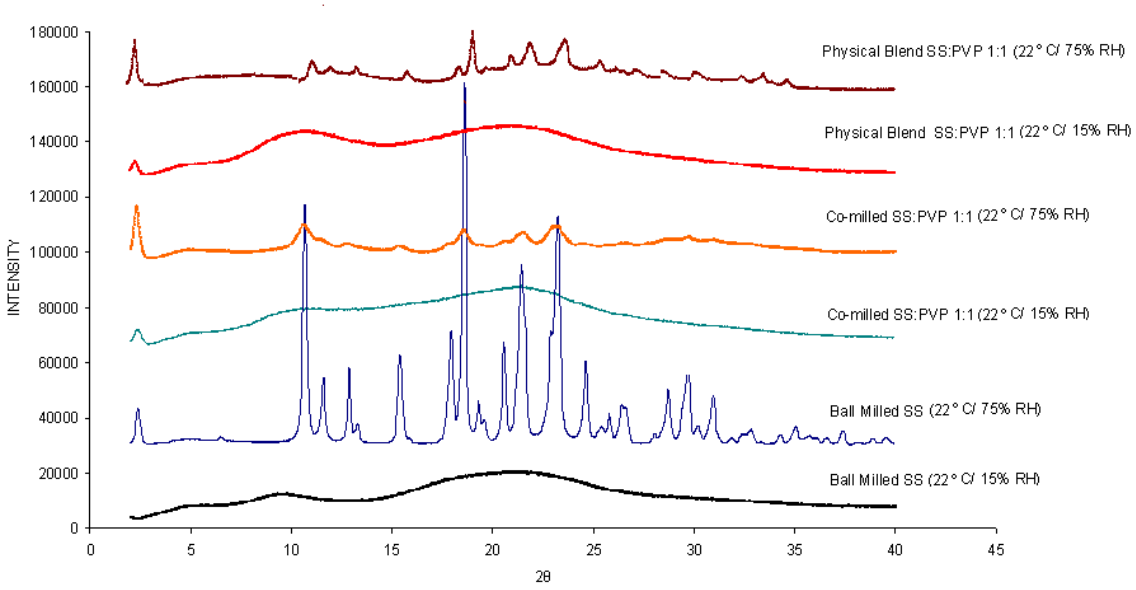


Figure 2



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