کارکاه های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی

کارکاه آنلاین کاربرد نرم افزار SPSS در پژوهش

کارکاه آنلاین اصول تنظیم قراردادها

کارکاه آنلاین پروپوزال نویسی
Improvement of Physico-mechanical Properties of Partially Amorphous Acetaminophen Developed from Hydroalcoholic Solution Using Spray Drying Technique

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ABSTRACT

Objective(s): This study was performed aiming to investigate the effect of particle engineering via spray drying of hydroalcoholic solution on solid states and physico-mechanical properties of acetaminophen.

Materials and Methods: Spray drying of hydroalcoholic solution (25% v/v ethanol/water) of acetaminophen (5% w/v) in the presence of small amounts of polyvinylpyrrolidone K30 (PVP) (0, 1.25, 2.5 and 5% w/w based on acetaminophen weight) was carried out. The properties of spray dried particles namely morphology, surface characteristics, particle size, crystallinity, dissolution rate and compactibility were evaluated.

Results: Spray drying process significantly changed the morphology of acetaminophen crystals from acicular (rod shape) to spherical microparticle. Differential scanning calorimetry (DSC) and x-ray powder diffraction (XRPD) studies ruled out any polymorphism in spray dried samples, however, a major reduction in crystallinity up to 65%, especially for those containing 5% w/w PVP was observed. Spray dried acetaminophen particles especially those obtained in the presence of PVP exhibited an obvious improvement of the dissolution and compaction properties. Tablets produced from spray dried samples exhibited excellent crushing strengths and no tendency to cap.

Conclusions: The findings of this study revealed that spray drying of acetaminophen from hydroalcoholic solution in the presence of small amount of PVP produced partially amorphous particles with improved dissolution and excellent compaction properties.

Introduction

The importance of the solid-state structure with regards to the physico-mechanical properties of pharmaceuticals has already been reported (1-3). Preparation of amorphous form is a possible approach to improve the physico-mechanical behaviors of pharmaceutical solids. Compared to a crystalline solid, the amorphous material can have advantages such as enhanced dissolution rate, bioavailability and tableting properties (4, 5). Amorphous solids can be produced by common pharmaceutical processes including melt quenching, super critical fluid, freeze drying, long period milling and spray drying (6). Spray drying of solutions is known as the most important industrial method to facilitate the production of amorphous material.

Due to poor solubility of acetaminophen in water, spray drying of its aqueous suspensions has been widely used in pharmaceutical industry to improve its physico-mechanical properties (7, 8). Spray drying of a material from suspension often yields crystalline products due to crystalline material that remains in suspension. In fact, spray dried particles obtained from a suspension are agglomerates of original crystals, while spray drying the solution is a crystallization process which could lead to production of partially or completely amorphous materials due to rapid solidification of droplets (9).
Many amorphous solids are thermodynamically unstable and can spontaneously transform into a crystalline state if exposed to sufficient moisture and heat (10, 11). It has been shown that addition of some polymers, known as stabilizing polymer, such as PVP, can prevent or minimize such these transformations (12-14). This effect has been attributed to adsorption of PVP onto the surfaces of the drug crystals.

The production of amorphous acetaminophen by spray drying technique from aqueous solution in the presence of 50% w/w chitosan (based on acetaminophen weight) has already been reported (15). However, the use of high amount of polymer (more than 50%) and low drug concentration in dispersions have been the drawback for this study.

Garekani et al showed that PVP is an effective additive during crystallization of acetaminophen and significantly changed the crystal habit and physico-mechanical properties of obtained particles by adsorption onto the surfaces of acetaminophen crystals via hydrogen bonding (16-19). Therefore, PVP may act as an effective additive to improve both stability and physico-mechanical properties of acetaminophen during spray drying.

In the present study, spray drying of acetaminophen is carried out from hydroalcoholic solution in the presence of small amounts of PVP, maximum 5% w/w based on acetaminophen weight. The solid states and physico-mechanical properties of spray dried particles were also investigated. To the best of our knowledge, there is no study regarding the use of hydroalcoholic solution for spray drying of acetaminophen.

The use of hydroalcoholic solution for spray drying of acetaminophen has several advantages. Ethanol is one of the safest and cheapest organic solvents for acetaminophen. Solubility of acetaminophen in ethanol is 10 times higher than water (20). The solubility of acetaminophen in hydroalcoholic solution (25% V/V) is 50 mg/ml and therefore a solution with rather high solid content can be obtained. Besides, during spray drying process, this solvent is much less flammable compared to pure ethanol. Also the evaporation rate of hydroalcoholic solution is higher than water. Therefore, due to faster solidification during spray drying, the production of amorphous material is facilitated.

Materials and Methods

Materials

Acetaminophen was obtained from Temad Co., Iran. PVP-K30 was obtained from BASF, Germany. Ethanol 96% was obtained from Zakaria Co, Iran.

Methods

Hydroalcoholic solutions (25% v/v ethanol/water) of acetaminophen (5% w/v) were prepared in the presence of different amounts of PVP K30 (0, 1.25, 2.5 and 5%w/w, based on acetaminophen weight). These solutions were spray dried under the obtained optimal conditions of inlet drying air of 160 °C, outlet drying air of 85 °C, feed rate of 45 g/min and atomizing air pressure of 0.5 bar. Spray drying of these solutions was performed using a Mini Spray Dryer B-290, (BUCHI, Switzerland). The solutions were fed through a two fluid pressure atomizers at the top of the spray dryer by means of a peristaltic pump. The spray dryer was operated in co-current air flow and the powder was collected using a cyclone.

Process yield of spray drying

After spray drying process, the production yield was calculated using the following equation:

\[
\% \text{Process Yield} = \left( \frac{\text{Weight of obtained sample}}{\text{Total solid content of each formulation}} \right) \times 100
\]

(Equation 1)

Particle size measurement

Optical microscope (Olympus BX60, Japan) was used in order to determine the size of particles. Tiny amounts of spray dried samples were spread on glass slides and Martin’s diameter of minimum 100 particles was measured using a micrometer fitted on eyepiece.

Scanning electron microscopy (SEM)

Electron micrographs of acetaminophen particles were obtained using a scanning electron microscope (Oxford S360, UK). Voltage of 15 kV was selected for accelerating the electrons from electron gun onto the specimen. The specimens were mounted on a metal stub with double side adhesive tape and coated with gold in an argon atmosphere using Sputter Coater SC 7620, prior to observation.

Assessment of crystallinity of spray dried samples

Differential scanning calorimetry (DSC)

A differential scanning calorimeter (Mettler Toledo DSC 822, Switzerland) was used to determine the melting points and fusion enthalpy of samples. The equipment was calibrated using indium. Acetaminophen samples (3-5 mg) were heated at 10°C/min in sealed aluminum pans under nitrogen atmosphere. The melting points and enthalpies of fusion of samples were calculated by the instrument. Percentage of relative crystallinity of samples was calculated by the following equation (15).

\[
\% \text{ Relative crystallinity} = \left( \frac{\Delta H_s}{\Delta H_{s0}} \right) \times 100
\]

(Equation 2)
The onset of melting point, the enthalpy of fusion and percent of crystallinity for untreated acetaminophen and spray dried samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Onset of Melting point</th>
<th>ΔH (J/g)</th>
<th>% Crystallinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated acetaminophen</td>
<td>170.6 ±0.2</td>
<td>198.9±3.3</td>
<td>100</td>
</tr>
<tr>
<td>Spray dried acetaminophen in absence of PVP</td>
<td>169.2±0.3</td>
<td>169.9±4.1</td>
<td>85.42</td>
</tr>
<tr>
<td>Co-spray dried acetaminophen + 1.25% PVP</td>
<td>167.4±0.1</td>
<td>116.6±2.7</td>
<td>58.60</td>
</tr>
<tr>
<td>Co-spray dried acetaminophen + 2.5% PVP</td>
<td>165.1±0.4</td>
<td>94.6±3.2</td>
<td>47.55</td>
</tr>
<tr>
<td>Co-spray dried acetaminophen + 5% PVP</td>
<td>164.4±0.3</td>
<td>72.2±5.2</td>
<td>36.31</td>
</tr>
</tbody>
</table>
Sadeghi et al

Physico-mechanical Properties of Acetaminophen


Figure 1. Scanning electron micrograph of a) untreated acetaminophen crystals, b) spray dried acetaminophen in absence of polyvinylpyrrolidone, c) co-spray dried acetaminophen in presence of 2.5% polyvinylpyrrolidone, d) co-spray dried acetaminophen in presence of 5% polyvinylpyrrolidone

DSC studies

Figure 2 shows DSC thermograms of untreated acetaminophen and spray dried samples. In Table 2 the values of enthalpy of fusion and relative amounts of crystallinity calculated based on equation 2 are presented.

XRPD studies

The XRPD spectra of untreated acetaminophen and spray dried samples are shown in Figures 3 a-d. The area under a peak exactly at 18° 2θ and the relative amount of crystallinity based on equation 3 is presented in Table 3.

Dissolution test

The MDT values for untreated acetaminophen and spray dried samples are presented in Table 4.

Compaction study

The influence of compression force on crushing strengths of tablets made from spray dried acetaminophen obtained in the absence or presence of PVP are shown in Figure 4. Effect of compression force on the crushing strengths of tablets made from physical mixtures of acetaminophen with different contents of PVP (2.5% and 5% w/w) are also presented in Table 5.

Discussion

The percentage yield of spray drying process varied between 35.7% and 65.1%, depending on the concentration of PVP (Table 1). The lowest yield was obtained for the samples spray dried from solution containing no PVP and the highest yield was obtained for the samples produced from solution containing 5% PVP. Regarding Table 1, it can be deduced that there is a direct relationship between the percentage of yield and the concentration of PVP used in the solutions.

This could be explained by the data of particle size analysis. Table 1 clearly shows that the mean particle size of samples increased with the increase in PVP concentration. For instance, the mean particle size of spray dried samples increased from 11 to 18.5 µm when the concentration of PVP increased from 0 to 5% w/w. The increase in mean

Figure 2. DSC thermograms of: A) untreated acetaminophen and spray dried samples obtained in presence of: B) 0%, C) 1.25%, D) 2.5% and E) 5% polynynlpyrrolidone
The relative amount of crystallinity for acetaminophen samples obtained based on the area under a curve in XRPD spectra

<table>
<thead>
<tr>
<th>Sample</th>
<th>Area under a peak at 18° 2θ</th>
<th>%Crystallinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated acetaminophen</td>
<td>2411.76</td>
<td>100</td>
</tr>
<tr>
<td>Co-spray dried acetaminophen + %1.25 PVP</td>
<td>1581.89</td>
<td>65.59</td>
</tr>
<tr>
<td>Co-spray dried acetaminophen + %2.5 PVP</td>
<td>1365.99</td>
<td>56.63</td>
</tr>
<tr>
<td>Co-spray dried acetaminophen + %5 PVP</td>
<td>790.34</td>
<td>32.77</td>
</tr>
</tbody>
</table>

The relative crystallinity of acetaminophen following spray drying process was determined based on the area under a peak exactly at 18° 2θ. The relative crystallinity increased with the increase in the amount of PVP from 0 to 5%. The spray dried samples obtained in the presence of PVP exhibited a significant reduction in the area under the peak, indicating a decrease in the relative crystallinity of acetaminophen. This decrease in crystallinity was attributed to the presence of amorphous regions in the spray dried samples due to weakening and disruption of crystal lattice and order. Garekani et al. reported that crystallization of acetaminophen from a mixture of water and ethanol in the presence of PVP resulted in a reduction in melting point and enthalpy of fusion of samples. The relative crystallinity values for untreated acetaminophen and spray dried samples are shown in Figures 3 a-d. These figures exhibit essentially similar diffraction patterns (20 values) for all samples suggesting that spray dried particles did not undergo any structural modifications (Figure 3). However, a major reduction in relative intensities of their peaks (particularly samples containing 2.5 and 5% PVP) may be due to reduction in crystallinity and presence of amorphous state in the samples. It has been reported that PVP is a strong crystal growth inhibitor for acetaminophen (30). It was also demonstrated that there is a potential binding between acetaminophen and PVP in their aqueous solutions via hydrogen bonding (19). Therefore, it is expected that in the presence of higher concentration of PVP, acetaminophen particles with less crystallinity are produced. The area under a peak exactly at 18° 2θ and the relative amount of crystallinity based on equation 3 are presented in Table 3. These results clearly show that the spray drying caused a major reduction in crystallinity of acetaminophen. The spray dried samples obtained in the absence of PVP exhibited about 35% reduction in crystallinity. Increase in the amount of PVP in the samples decreased the crystallinity to more extent so that the co-spray dried particles obtained in the presence of 5% PVP, exhibited only 32% crystallinity. In a similar study, XRPD technique was used to quantify the relative crystallinity of acetaminophen in co-precipitated or co-crystallized with PVP obtained from different solvents (21). It was concluded that along with the increase in the amount of PVP, the
degree of crystallinity dramatically decreased. The degree of crystallinity of acetaminophen in the solid dispersions was 1.99-76.16%, based on the PVP content.

Overall, the results of DSC and XRPD studies were in good agreement and both studies showed that partially amorphous or semi-crystalline acetaminophen could be obtained following a spray drying process of acetaminophen from hydroalcoholic solutions in the presence of PVP. The production of partially amorphous acetaminophen particles are explained in following paragraphs.

Rapid evaporation rate of vehicle during spray drying due to nature of hydroalcoholic solvent and the use of high inlet temperature (160°C) facilitated the rapid solidification of spray droplets and contributes to production of amorphous phase. As it was mentioned above, PVP is a strong crystal growth inhibitor for acetaminophen, therefore, it was most likely that during spray drying from hydroalcoholic solution, rapid solidification of acetaminophen droplets in the presence of PVP changed the morphology and solid state characteristics of acetaminophen crystals and reduced the crystallinity of obtained particles. However, spray drying process itself could also lead to formation of the amorphous parts in the obtained particles mainly by rearrangement of the physical state. Takahashi et al reported that spray drying of acetaminophen with high ratios of chitosan produced completely amorphous state (15). It has been reported that spray drying of valdecoxib and PVP K30 (at ratio 1:1 or more) from methanol produced amorphous solid (27). Production of amorphous lactose using spray drying technique in the presence of polyethylene glycol has been reported by Corrigan et al who used DSC and XRPD to show the presence of amorphous state in spray dried samples (2).

The preliminary stability studies for particles stored 6 months at ambient condition showed no significant changes in their DCS and XPRD spectra, indicating no significant changes in their crystallinity (data are not shown). However, the stability studies at various temperatures and relative humidity are being evaluated and the results will be published later.

The MDT values for untreated acetaminophen and spray dried samples are presented in Table 4. This table clearly indicates that there is a marked enhancement in the dissolution rate of spray dried samples specially for those obtained in the presence of PVP, compared to untreated acetaminophen. Untreated acetaminophen showed a MDT of 19.7 min while the particles obtained in the presence of 5% PVP exhibited a MDT of 2.8 min. The enhancement in dissolution rate of spray dried particles may be explained by three different reasons:

1- Reduction in crystallinity of acetaminophen and formation of amorphous phase in spray dried samples (Tables 2 and 3) tend to increase the dissolution rate of acetaminophen. Amorphous form is a high-energy state that would improve the dissolution rate of low soluble drug substances (27).
Physico-mechanical Properties of Acetaminophen

Sadeghi et al

Table 4. The calculated MDT ± SD for different acetaminophen samples

<table>
<thead>
<tr>
<th>sample</th>
<th>Untreated acetaminophen</th>
<th>Spray dried acetaminophen</th>
<th>Co-spray dried acetaminophen + 1.25% PVP</th>
<th>Co-spray dried acetaminophen + 2.5% PVP</th>
<th>Co-spray dried acetaminophen + 5% PVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDT (min)</td>
<td>19.7±2.3</td>
<td>10.9±1.7</td>
<td>6.8±1.1</td>
<td>5.2±1.4</td>
<td>2.8±0.6</td>
</tr>
</tbody>
</table>

Table 5. Effect of compression force on the crushing strengths of tablets made from physical mixtures of acetaminophen and different amounts of PVP (2.5% and 5% w/w):

<table>
<thead>
<tr>
<th>Compression force (kN)</th>
<th>2.5% w/w PVP</th>
<th>5% w/w PVP</th>
<th>5% w/w PVP</th>
<th>5% w/w PVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3±1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>6±2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>5±2</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*very weak tablets with no measurable hardness

Figure 4. Effect of compression force on crushing strengths of tablets made from spray dried acetaminophen samples obtained in presence of different amounts of PVP.

Several studies have already indicated that the presence of amorphous state in particles enhances the dissolution rate of some drugs (14, 31).

2- Reduction in particle size. Scanning electron micrographs (Figure 1a- d) shows that untreated acetaminophen particles have acicular shape with 33 µm length and 7 µm width. The particles obtained in the absence or presence of 2.5% or 5% w/w PVP had an agglomerated structure consisting of microparticles with diameter of 3-4 µm. Presence of these microparticles in the samples could be another reason for the dissolution enhancement of acetaminophen from spray dried samples. A decrease in particle size increases the surface area of acetaminophen particles exposed to the dissolution media and subsequently increases the dissolution rate.

3- The presence of PVP in the samples increased the wettability. PVP is a water soluble polymer and increases the wettability of acetaminophen particles. Table 4 clearly shows that with increase in the amount of PVP in particles, the dissolution rate increased. Similar results reported by Garekani et al (18) showed that crystallized acetaminophen in the presence of small amount of PVP exhibited a marked enhancement in dissolution rate of acetaminophen and this was attributed to the adsorption of PVP on the surface of acetaminophen crystals.

The influence of compression force on crushing strengths of tablets made from spray dried acetaminophen obtained in the absence or presence of PVP are shown in Figure 4. Effect of compression force on the crushing strengths of tablets made from physical mixtures of acetaminophen with different contents of PVP (2.5% and 5% w/w) are also presented in Table 5. Compression of untreated acetaminophen at all compression forces produced extremely weak tablets with no measurable crushing strengths and a high tendency to cap. Figure 4 shows that the spray dried acetaminophen particles especially those obtained in the presence of PVP exhibited an obvious improvement in their compaction properties compared to untreated acetaminophen. Acetaminophen particles which were spray dried in the absence of PVP exhibited a minor enhancement in their compaction properties and produced tablets with maximum hardness of 25 N with tendency to cap. However, co-spray dried samples obtained in the presence of PVP exhibited a major improvement in their compaction properties and produced tablets with excellent crushing strength and lack of tendency to cap. Figure 4 clearly shows that an increase in the amount of PVP in spray dried samples resulted in a profound increase in the crushing strength of tablets. The high crushing strength of tablets is indicative of stronger interparticulate bonding between particles. This may be attributed to the presence of PVP in particles which is known as a good binder, or may be due to the solid state characteristics of these particles. Data related to crushing strengths of physical mixtures of sieved fractions of PVP and acetaminophen compressed at different compression forces (Table 5), clearly indicate that the crushing strengths of tablets even at 5% w/w PVP content were less than 10 N, whereas particles spray dried in the presence of 5% PVP produced tablets with crushing strengths more than 100 N (Figure 4). Therefore, these results indicate that improvement in compaction properties of spray dried acetaminophen obtained in the presence of PVP was due to the solid state characteristics and the
The results describe the formation of small amounts of PVP (maximum 5% w/w based on acetaminophen weight) produced partially amorphous particles with improved dissolution and excellent compaction properties. Acetaminophen particles obtained in the presence of PVP had agglomerated structure consisting of spherical microparticles with the size of 3-4 µm.

DSC and XRPD experiments indicated a marked reduction in crystallinity of spray dried particles especially for those containing 5% w/w PVP.

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## References

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