Co-precipitation of Mefenamic Acid and Polyethylene Glycol 4000 Using the Gas Anti-Solvent (GAS) Process

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ABSTRACT
Production of composites of mefenamic acid (MEF) and polyethylene glycol (PEG 4000) by the Gas Anti-Solvent (GAS) technique can be used to modify the dissolution rate of this poorly water-soluble drug. It was found that when using a dichloromethane and ethanol ratio of 80:20 %v/v and a mass ratio of drug and polymer of 1.5:3.5 at 45°C, the highest % drug loading (22.83%) was achieved. A reduction in temperature or an increase in drug and polymer concentration yielded slightly smaller size of composite particles. In addition, it was found that the composites exhibited a higher dissolution rate than the MEF precipitated by the GAS process and could dissolve completely within 3 hours. However, the dissolution rate of the composites was lower than that of the physical mixture of MEF and PEG 4000. This could be attributed to the larger particle sizes of the composites compared to those of the physical mixture, less efficient wetting and lower degree of powder dispersion by PEG in the composites.

Keywords: GAS process, pharmaceutical products, supercritical fluids, composite materials, mefenamic acid, PEG

1. INTRODUCTION
Mefenamic acid (MEF) is a nonsteroidal anti-inflammatory drug (NSAID) possessing analgesic and antipyretic properties. It is typically prescribed for oral administration, with a usual dose of 250 or 500 mg, three times daily. The solubility of MEF in water has been reported to be 20 mg/L [1] and the reported half-life is 2 hours [2]. Various dense gas techniques have been employed to micronize MEF in order to enhance its dissolution rate. Bustami et al. [3] used the aerosol solvent extraction system (ASES) process to precipitate MEF from various organic solvents (methanol, ethanol and
acetone). The drug precipitated as platelets ranging in size from 10-50 \( \mu \text{m} \) when processed at 40°C and 78 bar. It was also found that the powder dissolution rate of the precipitated drug was enhanced due to the particle size reduction. Su et al. [4] employed the batch supercritical anti-solvent (SAS) process to precipitate MEF. Needle-like MEF was observed after the batch SAS process using ethyl acetate as solvent. The degree of crystallinity of the processed MEF was decreased, but the crystal structure remained the same. Hezave and Esmailzadeh [1] were able to micronize MEF via the rapid expansion of supercritical solutions (RESS) process using CO\(_2\) as the supercritical solvent. The mean particle size of precipitates was in the range of 1.9 to 10.4 \( \mu \text{m} \). To date, however, there is no report on the production of MEF and PEG composites using the gas anti-solvent (GAS) process.

In this letter, the GAS technique was employed to produce mefenamic acid-polyethylene glycol composites in order to enhance the drug dissolution rate. The effects of dichloromethane to ethanol solvent ratio, temperature and drug to polymer ratio on the particle size and drug loading were investigated.

2. MATERIALS AND METHODS

Mefenamic acid (Sigma, \( \geq 98.0\% \) purity) and polyethylene glycol 4000 (Sigma, 99.9\% purity) were used as received. Ethanol (EtOH) and dichloromethane (DCM) were purchased from Italmar (Thailand) Co., Ltd. (99.8\% purity) and used as organic solvents. Carbon dioxide (high purity grade, 99.95\% purity, TIG) was used as an anti-solvent. Ethyl acetate (Carlo Erba Reagents, 99.8\% purity) was used to wash the excess drug precipitated on the composites. All chemicals and reagents were used without further purification.

Potassium phosphate monobasic (Sigma, 99\% purity) and sodium hydroxide (Sigma, minimum 98\% purity) were used to prepare the phosphate buffer solution for the dissolution studies.

The schematic diagram of the GAS process and the production of drug-polyethylene glycol composites procedure using the GAS process can be found elsewhere [5]. Production of drug-polymer composites was conducted by charging the vessel (Jerguson sight gauge series no.32) with 5 mL of the drug and polymer solution in ethanol and dichloromethane mixture. The system temperature was controlled to the required temperature within \( \pm 0.1^\circ\text{C} \) accuracy using a recirculation heater (Thermoline Unistat 130). Liquid CO\(_2\) was fed to a syringe pump (ISCO model 260D) and delivered through a preheating coil, which was immersed in the water bath. The precipitation chamber was then brought to the desired pressure by passing CO\(_2\) from the pump through a 0.5 \( \mu \text{m} \) filter from the bottom. The rate of pressurization was set at 10 mL/min at room temperature using pump controller. The pressure of the system was increased up to 90 bar in order to ensure a complete precipitation. Precipitated samples were then washed with CO\(_2\) at 90 bar for approximately 90 mL of CO\(_2\) to remove residual solvent. After washing, the system was depressurized and a sample was taken for further analyses. The morphology of precipitated particles was analyzed by scanning electron microscopy (SEM) (Jeol, JSM-5600LV). Samples were coated with gold using sputter coater prior to analysis. The melting point and heat of fusion of the original materials and precipitates were examined using differential scanning calorimetry (DSC) (TA instruments, SDT 2960). Samples weighing approximately 10 mg were heated in aluminum pans under nitrogen gas flow of 120 mL/min. The heating rate of 10°C/min was used up
to a maximum temperature of 270°C. Before determining the drug loading, the composites were washed with ethyl acetate to eliminate the excess drug (100 mL of ethyl acetate per 0.100g of precipitate). The composites were then dried in a vacuum oven at 50°C overnight. The % drug content (before removing the excess drug) and % drug loading were determined using UV-vis spectroscopy at the wave length of 360 nm as follows:

\[
\text{%drug content} = \frac{\text{mass of the drug in particles}}{\text{Total mass of particles}} \times 100\% \tag{1}
\]

\[
\text{%drug loading} = \frac{\text{mass of the drug in composites}}{\text{Total mass of particles}} \times 100\% \tag{2}
\]

Powder dissolution studies were performed using a magnetic stirrer in 500 mL of phosphate buffer solution at pH 7.6, 37°C and 400 rpm. Accurately weighed samples (approximately 10 mg) were introduced into the dissolution medium. Aliquots (≈ 4 mL) were withdrawn at certain time intervals and passed through a 0.45 μm filter. The amount of MEF in the withdrawn samples was determined by measuring the absorbance at \( \lambda = 360 \) nm using a UV spectroscopy (Shimadzu, Anthelie advance 5).

3. RESULTS AND DISCUSSION

The particle size of the original MEF as received from Sigma was approximately 7.5 μm in length with an aspect ratio (L/D) of 3, as shown in Figure 1(a). Mefenamic acid particles precipitated by the GAS process using 2.5wt% of MEF in a solvent mixture of dichloromethane and ethanol 80:20 %v/v at 45°C were significantly larger than the original material. As is illustrated in Figure 1 (b), the precipitated MEF particles had a rectangular shape: 130 μm long, aspect ratio of 6. Preliminary studies [6] showed that the GAS technique was not able to micronize MEF within the range of operating conditions studied. However, it was found that the processed MEF could dissolve completely in 4 hours while only 82% of the original

![Figure 1](image_url). SEM images of (a) unprocessed MEF, (b) precipitated MEF by GAS, (c) PEG, (d) physical mixture, (e) composites before washing with ethyl acetate, (f) composites after washing with ethyl acetate.
MEF could dissolve.

Prior to the production of MEF-PEG composites, the threshold pressures for independently precipitating MEF and PEG 4000 at various conditions were investigated [6]. In the case of MEF precipitation, the concentration of drug was varied from 1.5 wt% to 3.5 wt% with the use of various solvent ratios between dichloromethane and ethanol ranging from 80:20, 50:50 and 20:80 %v/v. In the case of PEG precipitation, the concentration of polymer was varied from 1.5 wt% to 7.0 wt% with the use of the same solvent mixture. The GAS experiments were carried out at 35°C and 45°C. Conditions for the co-precipitation were then selected to give a small difference in the threshold pressures of the drug and polymer. Table 1 shows the conditions used for producing composite and the % drug loading. It was found that the maximum drug loading obtained in this work was approximately 22.83 %, which was achieved when using the mass ratio of drug and polymer at 1.5:3.5 wt% in the dichloromethane and ethanol solvent (80:20 %v/v) and at 45°C. At the maximum drug loading condition, it was found that PEG was precipitated out first, and then followed by the drug. Even though the difference in precipitation pressures of the drug and polymer at this condition was not the smallest, the highest % drug loading was still obtained. It was also found that a % drug loading higher than 12% could be only obtained when using an 80:20 %v/v solvent mixture of dichloromethane and ethanol. The % drug contents for composites precipitated from the solvent ratio of 80:20 % v/v are also listed in Table 1. It is clearly shown that % drug contents for composites precipitated at 45°C were much higher than those obtained at 35°C. This could be due to the fact that as the temperature increased, the degree of saturation of the solution was decreased and the system was closer to the melting temperature of the polymer. Thus, fewer polymers could precipitate out from the solution. Pasquali et al. [7] also reported the melting point depression of PEG 4000 in the presence of dense CO2. At CO2 pressure above 50 bar, the melting temperature of PEG 4000 is in the range of 42-44°C. In addition, it was found that the particle size and degree of

<table>
<thead>
<tr>
<th>DCM : EtOH volume ratio</th>
<th>MEF : PEG mass ratio</th>
<th>Threshold pressure (bar)</th>
<th>% Drug content</th>
<th>% Drug loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEF</td>
<td>PEG</td>
</tr>
<tr>
<td>T = 35°C</td>
<td>1.5 : 3.5</td>
<td>51.8</td>
<td>51.1</td>
<td>0.7</td>
</tr>
<tr>
<td>80 : 20</td>
<td>2.5 : 7.0</td>
<td>45.5</td>
<td>49.3</td>
<td>-3.8</td>
</tr>
<tr>
<td>80 : 20</td>
<td>3.2 : 3.5</td>
<td>50.1</td>
<td>57.8</td>
<td>-7.7</td>
</tr>
<tr>
<td>50 : 50</td>
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<td>67.4</td>
<td>65.2</td>
<td>2.2</td>
</tr>
<tr>
<td>20 : 80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T = 45°C</td>
<td>1.5 : 3.5</td>
<td>65.6</td>
<td>61.1</td>
<td>4.5</td>
</tr>
<tr>
<td>80 : 20</td>
<td>2.5 : 7.0</td>
<td>58.7</td>
<td>60.0</td>
<td>-1.3</td>
</tr>
<tr>
<td>80 : 20</td>
<td>3.2 : 3.5</td>
<td>63.6</td>
<td>66.7</td>
<td>-3.1</td>
</tr>
<tr>
<td>50 : 50</td>
<td>2.5 : 3.5</td>
<td>77.0</td>
<td>75.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>
aggregation of the composites also increased as the temperature increased.

The effect of MEF to PEG ratio on the particle size was examined by considering MEF to PEG ratios of 1.5:3.5 wt% and 2.5:7.0 wt% in an 80:20 %v/v solvent ratio at 35°C and 45°C. It was found that an increase in the drug and polymer concentration resulted in a slight reduction in particle size and degree of aggregation. This could be attributed to a higher nucleation rate.

The composite precipitated by GAS using drug to polymer ratio of 2.5:7.0 wt% in a solvent mixture of dichloromethane and ethanol 80:20 %v/v and at 45°C was used as a representative sample for further analyses, since the precipitates could be collected in a sufficiently high amount and the drug loading was reasonable high. Figure 1 (e) and (f) show that there was no significant difference in the morphologies of the composites before and after washing with ethyl acetate. However, as is illustrated in Figure 2, the melting peak of MEF was observed only for the composite before washing. These results confirmed that washing with 100 mL of ethyl acetate for every 0.100 g of precipitate could effectively remove the excess drug on the composites.

In addition, the disappearance of the endothermic peak of MEF after washing may be attributed to the transformation of MEF into an amorphous state or the formation of drug-polymer composite. The dissolution profiles in phosphate buffer solution (pH 7.6, 37°C) of the unprocessed MEF, the precipitated MEF by GAS, the physical mixture (with 16 wt% of drug) and the MEF-PEG composites are shown in Figure 3. An enhanced dissolution rate of MEF in the composite was observed when compared with the precipitated MEF by GAS. Although the particle size of the composite was larger than that of MEF precipitated by GAS, the amorphous state of MEF and the hydrophilic property of PEG in the composite could enhance the dissolution rate. It was also found that the composite could dissolve completely within 3 hours, but the unprocessed MEF could only dissolve 82% within 4 hours. However, in this study, the dissolution of the physical mixture was higher than that of the composite. This could be attributed to the smaller particle size of the physical mixture compared to the

Figure 2. DSC curves of (a) unprocessed MEF, (b) unprocessed PEG, (c) composites before washing with ethyl acetate, (d) composites after washing with ethyl acetate.
Figure 3. Dissolution profiles of the MEF–PEG composites, precipitated MEF by GAS, physical mixture and unprocessed MEF in phosphate buffer solution at 37°C, pH 7.6.

4. CONCLUSIONS
Production of MEF-PEG composites was successfully performed by GAS using CO₂ as an anti-solvent. The maximum drug loading obtained was approximately 22.83 %, which was obtained when using the mass ratio of drug and polymer at 1.5:3.5 wt% in an 80:20 %v/v dichloromethane and ethanol solvent and at 45°C. The composites exhibited a higher dissolution rate than the MEF precipitated by the GAS process and could dissolve completely within 3 hours. However, due to the larger particle size of the composites and lower degree of powder dispersion, the dissolution rate of composites produced in this work was lower than that of the physical mixture.

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The authors have declared no conflict of interest.

Symbols used
DCM [-] dichloromethane
EtOH [-] ethanol
MEF [-] mefenamic acid
PEG [-] polyethylene glycol
ΔP [bar] difference in threshold pressures of the drug and polymer
T [°C] operating temperature

REFERENCES
