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Crystallization of Artemisinin from Chromatography Fractions of Artemisia annua Extract

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INTRODUCTION

Artemisinin is an important natural product recommended by World Health Organization (WHO) for the use in combination with other drugs against drug resistant Plasmodium falciparum induced malaria. Artemisinin is obtained mainly from dried leaves of the plant Artemisia annua. Previously, Malwade et al.¹ have proposed and evaluated a three step process for recovery of artemisinin from dried leaves of plant A. annua as shown in Fig. 1. The fractions containing artemisinin obtained after flash column chromatography step were dried and dissolved into dichloromethane prior to crystallization step. The crystallization step included combination of anti-solvent crystallization from dichloromethane and acetone and a cooling crystallization sub-steps which was replicated from Qu et al.² The overall yield of artemisinin by using this crystallization step was found to be very low (47%), which might be due to: (1) poorly selected crystallization steps, (2) the influence of impurities present in the fractions or, (3) a combination of both.

In this work preliminary polythermal solubility measurements and predictions (COSMO-RS) have been done together with Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg, see conference proceedings. For this poster contribution additional isothermal solubility measurements of artemisinin in hexane-ethyl acetate mixtures with varying concentration have been done in order to design crystallization experiments. Effect of impurities present in the fractions³ has been investigated by measuring the solubility of artemisinin in fraction and finally crystallization of artemisinin directly from the chromatography fraction has been demonstrated.

EXPERIMENTAL

Analysis of chromatography fractions
- Artemisinin containing fractions from flash CC combined together
- Analyzed with HPLC-UVD/CAD to determine composition

Artemisinin solubility measurement
- Preliminary polythermal solubility measurements and predictions (COSMO-RS)
- Detailed measurement in combined fraction and hexane-ethyl acetate mixtures at 5, 15 and 25 °C by using isothermal technique to assess effect of impurities

Crystallization experiment
- Solubility data is used to plan crystallization experiments
- Devised plan is depicted in Fig. 3

COMPOSITION OF COMBINED FRACTION

Name of compound | Concentration (mg/ml) | %
--- | --- | ---
Artemisinin (1) | 1.82 | 1.82
Artemisinic acid (2) | 0.015 | 0.015
DHAA (3) | 0.0745 | 0.0745
Artemisinic acid (4) | 0.01 | 0.01
Goumin (5) | 0.0051 | 0.0051
Solvent (Hexane:EA) | 77.65:22.35 v/v | 77.65:22.35 v/v

RESULTS

Effect of impurities on solubility of artemisinin

Artemisinin is obtained mainly from dried leaves of the plant Artemisia annua. Previously, Malwade et al.¹ have proposed and evaluated a three step process for recovery of artemisinin from dried leaves of the plant A. annua as shown in Fig. 1. The fractions containing artemisinin obtained after flash column chromatography step were dried and dissolved into dichloromethane prior to crystallization step.

Concentrations of impurities present in the fraction at concentrations mentioned above do not influence the solubility of artemisinin significantly.

Crystallization of artemisinin from combined chromatography fraction is not influenced by the impurities present in the fraction.

Crystallization profile of artemisinin from combined fraction

<table>
<thead>
<tr>
<th>Step</th>
<th>Artemisinin Conc. (mg/ml)</th>
<th>Ethyl acetate (Vol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point 1 (180ml fraction)</td>
<td>1.82</td>
<td>22.35</td>
</tr>
<tr>
<td>Point 2 (After evaporation, 18ml)</td>
<td>17.81</td>
<td>22.65</td>
</tr>
<tr>
<td>Point 3 (Addition of 50ml hexane)</td>
<td>3.46</td>
<td>5.98</td>
</tr>
<tr>
<td>Point 4 (cooling to 5°C)</td>
<td>2.36</td>
<td>5.98</td>
</tr>
<tr>
<td>Point 5 (Mother liquor)</td>
<td>2.07</td>
<td>5.98</td>
</tr>
<tr>
<td>Yield of artemisin</td>
<td>56.1 wt%</td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES


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