Comparative assessment of feasibility and environmental performance of different solvents for extraction of the natural antimalarial compound Artemisinin

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FSC Development Services Ltd

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Extraction of Natural Products: Antimalarials (motivation)

- Current method: hexane/petroleum ether extraction. Is there anything better?

**Solvents**
- Steam ×
- Ethanol
- Hexane / Petroleum Ether
- Natural oils ×
- scCO$_2$
- HFC-134a?
- Ionic Liquids?

**Processes**
- Batch ●
- Batch Percolation ●
- Semi-Continuous ●
- Continuous ●
- Conventional or MV Heating ●
- Secondary Purification Step? ●
Extraction of Natural Products: Antimalarials
(motivation)

• Current method: hexane/petroleum ether extraction. Is there anything better?

Aims of the study:

• to review most reliable data on artemisinin extraction,
• to compare technologies in terms of efficiency, economics, environmental performance, scalability, mobility,
• to identify where improvements must be made.
### Comparative Assessment
**(criteria & method)**

<table>
<thead>
<tr>
<th>Complete LCA</th>
<th>Life Cycle Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>difficult in the absence of precise data, comparing mature and emerging technologies is not easy</td>
</tr>
</tbody>
</table>

| Energy        | does not take into account toxicity, hazard, can show path for incremental process improvement |

| Mass intensity | does not take into account toxicity, energy sources are converted into mass |

| Health & Risk | essential and must accompany other metrics |
Comparative Assessment
(criteria & method)

Multiobjective hierarchical metrics approach:

• identify stakeholders & most relevant issues,
• define problem specific indicators,
• communicate results in the form relevant to stakeholders.

Calcs: abridged life cycle impact assessment

## Comparative Assessment
(criteria & method)

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Drivers</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>price, efficiency, side effects, availability of medicines</td>
<td>€·kg⁻¹ (artemisinin) or $·kg⁻¹ (artemisinin)</td>
</tr>
<tr>
<td>Growers of <em>Artemisia annua</em></td>
<td>price of fresh/dry leaf <em>Artemisia annua</em>, availability of processing facilities, potential to switch to other crops</td>
<td>kg (artemisinin) · ha⁻¹ €·kg⁻¹ (artemisinin)</td>
</tr>
<tr>
<td>Owners of extraction facilities</td>
<td>capital and running cost of processing technology, quality/price of final product, safety, other crops, environmental impact</td>
<td>€·kg⁻¹ (artemisinin) kg (CO₂) · kg⁻¹ (artemisinin) €m capital costs kg (artemisinin) · ha⁻¹ other products (from <em>Artemisia</em> and other crops)</td>
</tr>
</tbody>
</table>
## Comparative Assessment
### (criteria & method)

<table>
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<th>Drivers</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology developers</td>
<td>quality of produced extract, compliance with regulations enabling implementation, safety, environmental impact, cost, other crops</td>
<td>€·kg(^{-1}) (artemisinin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>€m capital costs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>kg (CO(_2)) · kg(^{-1}) (artemisinin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other markets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>safety, hazard to environment and human health</td>
</tr>
<tr>
<td>Pharmaceutical industry</td>
<td>availability of artemisinin at the correct price and purity</td>
<td>€·kg(^{-1}) (artemisinin)</td>
</tr>
<tr>
<td>WHO and NGOs</td>
<td>availability and price of artemisinin, environmental and social impact of technologies in local areas</td>
<td>€·kg(^{-1}) (artemisinin)</td>
</tr>
</tbody>
</table>
Comparative Assessment  
(criteria & method)

How the assessment was done:

• Gate-to-gate process system boundary

• Actual performance data; **best operating conditions for each solvent**

• Running costs: electricity and natural gas

• Capital costs: “Guide for capital cost estimation”, includes solvent inventory

• Health data: LD₅₀ & LC₅₀ MSDS data

• Risk: MSDS categories

• Environmental performance: green house gases emissions, assumption of complete capture and re-use of solvents (HFC134a - loss is quantified)
Extraction technologies on trial

- Hexane/petroleum ether (benchmark)
- Ethanol
- Ionic Liquids

- \( \text{scCO}_2 \)
- HFC-134a

\{ no phase change, diluted extract solution \}

\{ with phase change, concentrated extract \}

Extraction with liquid solvents vs extraction by compressed gases

- In extraction by hexane, petroleum ether, ethanol or any other liquid solvent there is no *phase change* of the solvent; extracted product(s) must be separated from the final liquor.

![Diagram of extraction process]

Losses: solvent, product, other products, agents/materials used in separations.
Extraction with liquid solvents vs extraction by compressed gases

- In extraction by compressed gases, the solvent is liquid (or supercritical) when in contact with biomass, and in the gaseous state, when extract needs to be separated.
Conventional Batch “Hexane” Extraction

- 3 portions of fresh solvent per batch; 1.5 h each (under percolation)
- separation of artemisinin by crystallisation, 48 h
- loss of solvent with spent biomass
- explosion hazard, human and bio toxicity, long process
• More polar solvent extracts carbohydrates, but less waxes
• Potential problem of stability of artemisinin in ethanol
• Very high latent heat of evaporation. Hence, high cost of heating.

Ionic liquids Extraction
(Bioniqs Ltd, UK)

Ionic Liquids (ILs) – organic salts with melting point below 100 ºC.

Key properties:
- Low vapour pressure
- Non-flammable
- Large variation of cations and anions
- Potential for design for function

Challenges:
- Toxicity must be studied
- Purity
- Cost
- Recycling/reuse, or biodegradability?
- Separation of solutes from ILs

![Chemical structures of Ionic Liquids](attachment:image.png)

- bis(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)amide
- N,N-dimethylethanolammonium octanoate
Ionic liquids Extraction

Ionic Liquids (ILs) Suppliers:

Merck
BASF
Solvents Innovation
...
Ionic liquids Extraction  
(Bioniqs Ltd, UK)

\[
\text{H}_3\text{C-O-CH}_2\text{N}^+\text{H}_2\text{O-CH}_3
\]

\[
\text{F}_3\text{C-SO}_2\text{SO}_2\text{N}^-\text{SOF}_3\text{CF}_3
\]

\[
\text{H}_3\text{C-N}^+\text{CH}_3\text{OH}
\]

\[
\text{O}-(\text{CH}_2)_6\text{CH}_3
\]

bis(2-methoxyethyl)ammonium  
bis(trifluoromethylsulfonyl)imide  
N,N-dimethylethanolammonium octanoate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility inEtOAc @ 20 °C / g·L(^{-1})</td>
<td>100</td>
</tr>
<tr>
<td>Solubility in hexane @ 40 °C / g·L(^{-1})</td>
<td>0.46</td>
</tr>
<tr>
<td>Solubility in hexane/EtOAc (5 %vol) / g·L(^{-1})</td>
<td>33</td>
</tr>
<tr>
<td>110 g·L(^{-1})</td>
<td>82 g·L(^{-1})</td>
</tr>
</tbody>
</table>
Ionic liquids extraction (potential process)

ILs allow fast recovery of artemisinin from primary extract, as well as simultaneous recovery of essential oil: clean three-phase separation.

Main drawback: need for water in partitioning (high latent heat of water). Unknown: degree of recovery of IL from spent biomass, fate of IL in environment.
Mini conclusion 1: liquid solvents (hexane, ethanol & ILs)

Hexane & ethanol extraction are very similar: require several portions of fresh solvent due to low solubility, and also require long extraction times. Separation from primary extract is difficult.

Extraction into IL is very fast and requires only one step. Separation from primary extract is simple.
scCO₂ & Hydrofluorocarbons Extraction

HFC-134a

Iodotrifluoromethane

CO₂

Carbon dioxide
scCO₂ & Hydrofluorocarbons Extraction

- High pressure of scCO₂ process
  - high operating and capital cost
- 134a global warming potential is 1300 x CO₂
  - must have complete recovery
- ITFM’s decomposition products are toxic
  - regulatory and H&S must be resolved

HFC-134a
Iodotrifluoromethane
CO₂ Carbon dioxide
## Efficiency, Duration and Costs
(main criteria)

<table>
<thead>
<tr>
<th>Method</th>
<th>T / °C</th>
<th>P / MPa</th>
<th>Solvent to dry leaf / kg : kg</th>
<th>Extraction cycle / h</th>
<th>Efficiency / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>30-40</td>
<td>0.1</td>
<td>4 : 1</td>
<td>8-10</td>
<td>60</td>
</tr>
<tr>
<td>EtOH</td>
<td>20</td>
<td>0.1</td>
<td>5 : 1</td>
<td>7</td>
<td>73</td>
</tr>
<tr>
<td>scCO₂</td>
<td>30-50</td>
<td>15-30</td>
<td>N/A</td>
<td>3-6</td>
<td>82</td>
</tr>
<tr>
<td>HFC-134a</td>
<td>15-40</td>
<td>0.4-1.2</td>
<td>N/A</td>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>[DMEA][oct]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.1</td>
<td>6.3 : 1</td>
<td>2.5</td>
<td>64</td>
</tr>
<tr>
<td>[BMEA][Tf₂N]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.9 : 1</td>
<td>6</td>
<td>79</td>
</tr>
</tbody>
</table>
### Efficiency, Duration and Costs
(main criteria)

<table>
<thead>
<tr>
<th></th>
<th>Energy efficiency / GJ·kg (artemisinin)$^{-1}$</th>
<th>GHG emissions / CO$_2$ kg·kg (artemisinin)$^{-1}$</th>
<th>Running cost / €·kg$^{-1}$ artemisinin</th>
<th>Capital cost for 2.5·10$^6$ kg (biomass)·annum$^{-1}$ / m€</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>1.3</td>
<td>87</td>
<td>28</td>
<td>0.7</td>
</tr>
<tr>
<td>Ethanol</td>
<td>2.3</td>
<td>148</td>
<td>47</td>
<td>1.0</td>
</tr>
<tr>
<td>Ionic liquids</td>
<td>0.9-6.3</td>
<td>56-407</td>
<td>22</td>
<td>0.3-1.0</td>
</tr>
<tr>
<td>scCO$_2$</td>
<td>3.5</td>
<td>221</td>
<td>42</td>
<td>4.1</td>
</tr>
<tr>
<td>HFC-134a</td>
<td>0.9</td>
<td>131</td>
<td>19</td>
<td>1.0</td>
</tr>
</tbody>
</table>

!!! Best case scenario for ILs is very promising even when water partitioning is used.

HFC134a loss: 300ppm each run = annual loss < 5% of inventory, 10.2 t.
• ILs extraction has the potential to outperform hexane in all criteria
• HFC134a will always suffer from GHG emissions rating; cost will increase due to need to comply with EU monitoring regulations
Feasibility of a Mobile Extractor
(a ‘back-of-a-truck’ plant?)

Main criteria: how long it would take to process given amount of biomass?
what is the capital cost?
how much solvent must be carried with the plant?

IL and HFC134a appear to be most promising systems for developing a mobile plant.
Conclusions

• New technologies (HFC-134a and ionic liquids) are potentially equal or better in extraction efficiency, extraction time, and costs than hexane.

• Both technologies are also safer and are potentially more environmentally benign (accepting that care has to be taken to ensure complete recycling and capture of the solvents).

• HFC-134a is a proven technology for the extraction of a wide range of other natural products.

• Ionic Liquids show considerable promise. The immediate problem of regeneration of the ionic liquid solvent and solvent recovery from the biomass is now being investigated.

• scCO₂ has high efficiency and speed of extraction. Its limitation is the higher capital and running costs, together with the need for experienced management due to the higher operating pressures and rig complexity.
Acknowledgements

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The following people have made significant contribution to this work by providing data, technical advice and their time:

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## Properties of Artemisinin
(specificity of artemisinin extraction)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Molecular weight / g·mol⁻¹</td>
<td>282.3</td>
</tr>
<tr>
<td>Melting point / °C</td>
<td>156-157</td>
</tr>
<tr>
<td>Thermal stability in non-polar solvents / °C</td>
<td>150</td>
</tr>
<tr>
<td>Solubility in H₂O @ pH 7 / g·L⁻¹</td>
<td>0.063</td>
</tr>
<tr>
<td>Solubility in H₂O @ pH 7, 37 °C / g·L⁻¹</td>
<td>0.048*</td>
</tr>
<tr>
<td>Solubility in EtOH @ 21 °C / g·L⁻¹</td>
<td>12</td>
</tr>
<tr>
<td>Solubility in EtOAc @ 20 °C / g·L⁻¹</td>
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<td>33</td>
</tr>
<tr>
<td>Octanol/H₂O partitioning coefficient / log P</td>
<td>2.94</td>
</tr>
</tbody>
</table>

Glandular trichoms on Artemisia A. leaf

**Main growing and processing regions:**
Vietnam and China

**Emerging regions:**
East Africa, India
Conventional Batch “Hexane” Extraction

Scaled-up Soxhlet extraction
Vietnam

http://en.wikipedia.org/wiki/Soxhlet_extractor