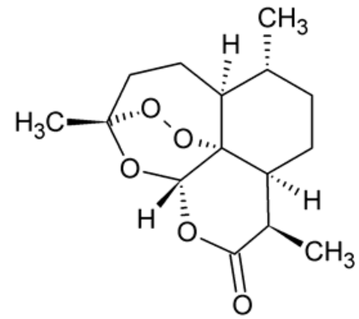
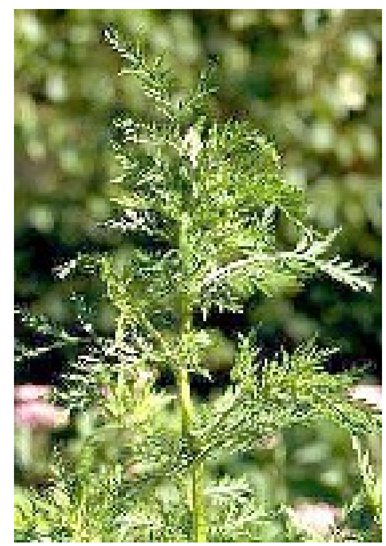


Comparative assessment of feasibility and environmental performance of different solvents for extraction of the natural antimalarial compound Artemisinin

Alexei Lapkin, P.K. Plucinski, M. Cutler

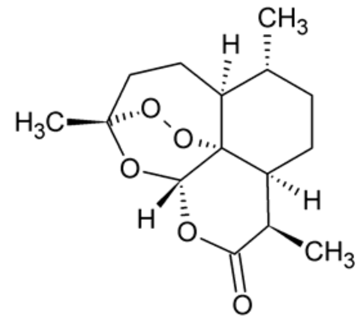
Catalysis and Reaction Engineering Group
Department of Chemical Engineering
University of Bath, UK.

FSC Development Services Ltd



Artemisinin Conference • 24-26 June 2007

Extraction of Natural Products: Antimalarials
(motivation)



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

Solvents	**Processes**
• Steam ✘	Batch •
• Ethanol	Batch Percolation •
• Hexane / Petroleum Ether	Semi-Continuous •
• Natural oils ✘	Continuous •
• $scCO_2$	Conventional or MV Heating •
• HFC-134a?	
• Ionic Liquids?	Secondary Purification Step? •

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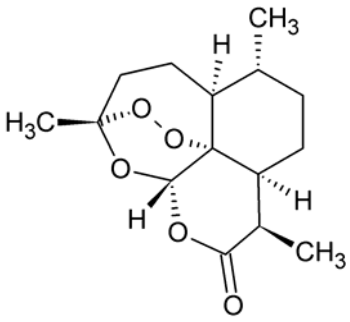
Extraction of Natural Products: Antimalarials
(motivation)



- 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)

Complete LCA	**L**ife **C**ycle **A**ssessment difficult in the absence of precise data, comparing mature and emerging technologies is not easy
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

Graedel, T.E. *Pure Appl. Sci.* **2001**, *73:8*, 1243-1246.
Lapkin, A.; Joyce, L.; Crittenden, B. *Env. Sci. Technl.* **2004**, *38*, 5815-5823.
Lapkin. A. Sustainability performance indicators. In “Renewables-Based Technology: Sustainability Assessment”. J. Dewulf, Ir H. van Langenhove (Eds), John Wiley & Sons, 2006, pp. 39-53.

Comparative Assessment
(criteria & method)

Stakeholders	Drivers	Indicators
Patients	price, efficiency, side effects, availability of medicines	€·kg^{-1} (artemisinin) or $·kg^{-1} (artemisinin)
Growers of *Artemisia annua*	price of fresh/dry leaf *Artemisia annua*, availability of processing facilities, potential to switch to other crops	kg (artemisinin) · ha^{-1} €·kg^{-1} (artemisinin)
Owners of extraction facilities	capital and running cost of processing technology, quality/price of final product, safety, other crops, environmental impact	€·kg^{-1} (artemisinin) kg (CO_2) · kg^{-1} (artemisinin) €m capital costs kg (artemisinin) · ha^{-1} other products (from *Artemisia* and other crops)

Comparative Assessment
(criteria & method)

Stakeholders	Drivers	Indicators
Technology developers	quality of produced extract, compliance with regulations enabling implementation, safety, environmental impact, cost, other crops	€·kg^{-1} (artemisinin) €m capital costs kg (CO_2) · kg^{-1} (artemisinin) other markets safety, hazard to environment and human health
Pharmaceutical industry	availability of artemisinin at the correct price and purity	€·kg^{-1} (artemisinin)
WHO and NGOs	availability and price of artemisinin, environmental and social impact of technologies in local areas	€·kg^{-1} (artemisinin)

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: LD_{50} & LC_{50} MSDS data
- Risk: MSDS categories
- Environmental performance: green house gases emissions, assumption of complete capture and re-use of solvents (HFC134a - loss is quantified)

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Extraction technologies on trial

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

} no phase change, diluted extract solution

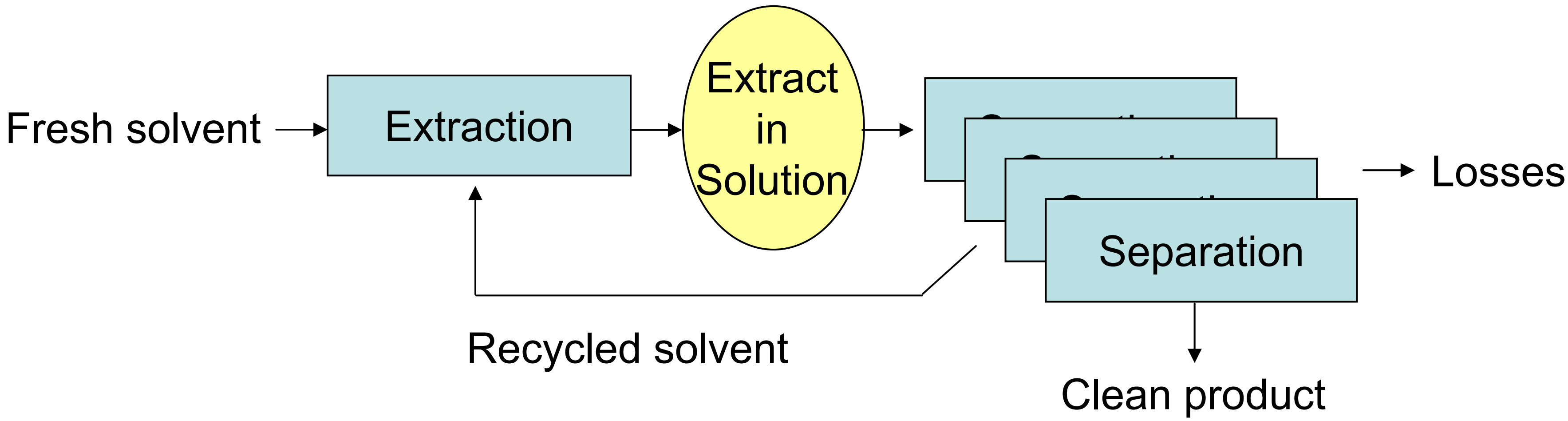
- scCO_2
- HFC-134a

} with phase change, concentrated extract

A.Lapkin, P.K. Plucinski, M. Cutler, Comparative assessment of technologies for extraction of artemisinin, *J. Nat. Prod.*, 69 (2006) 1653-1664. doi: 10.1021/np060375j

Extraction with liquid solvents *vs* extraction by compressed gases

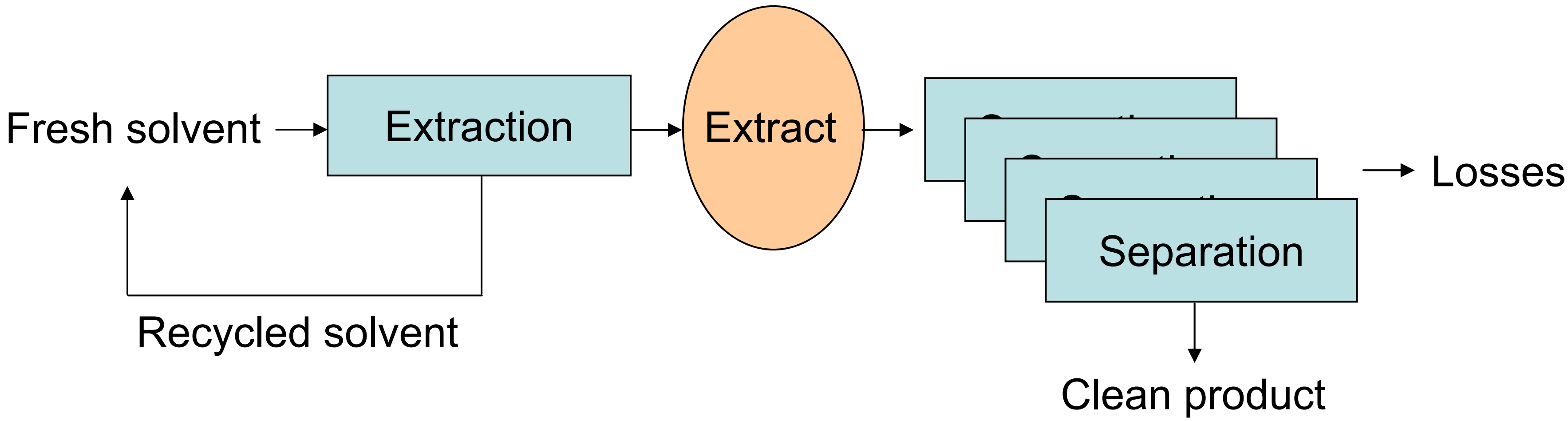
- In extraction by hexane, petroleum ether, ethanol or any other liquid solvent there is no *phase change* of the solvent; extracted product(s) must be separated from the final liquor.



Losses: solvent, product, other products, agents/materials used in separations.

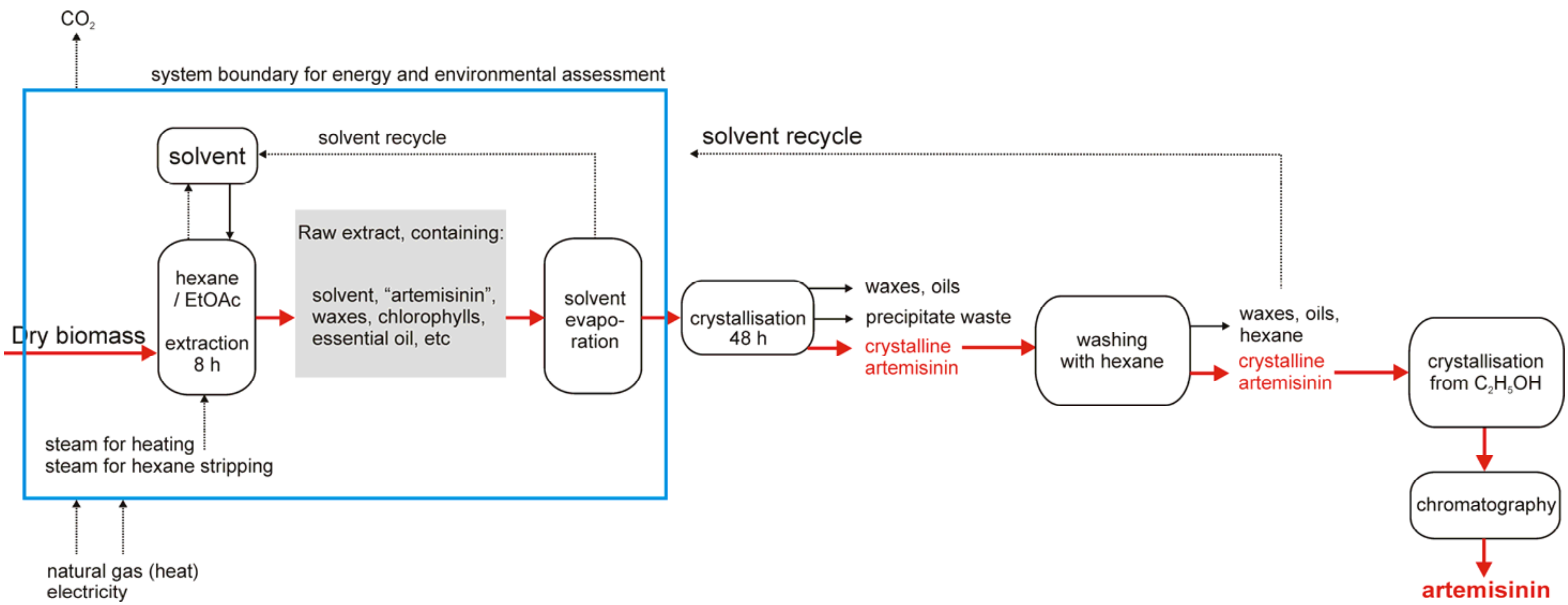
Extraction with liquid solvents *vs* extraction by compressed gases

- In extraction by compresses 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



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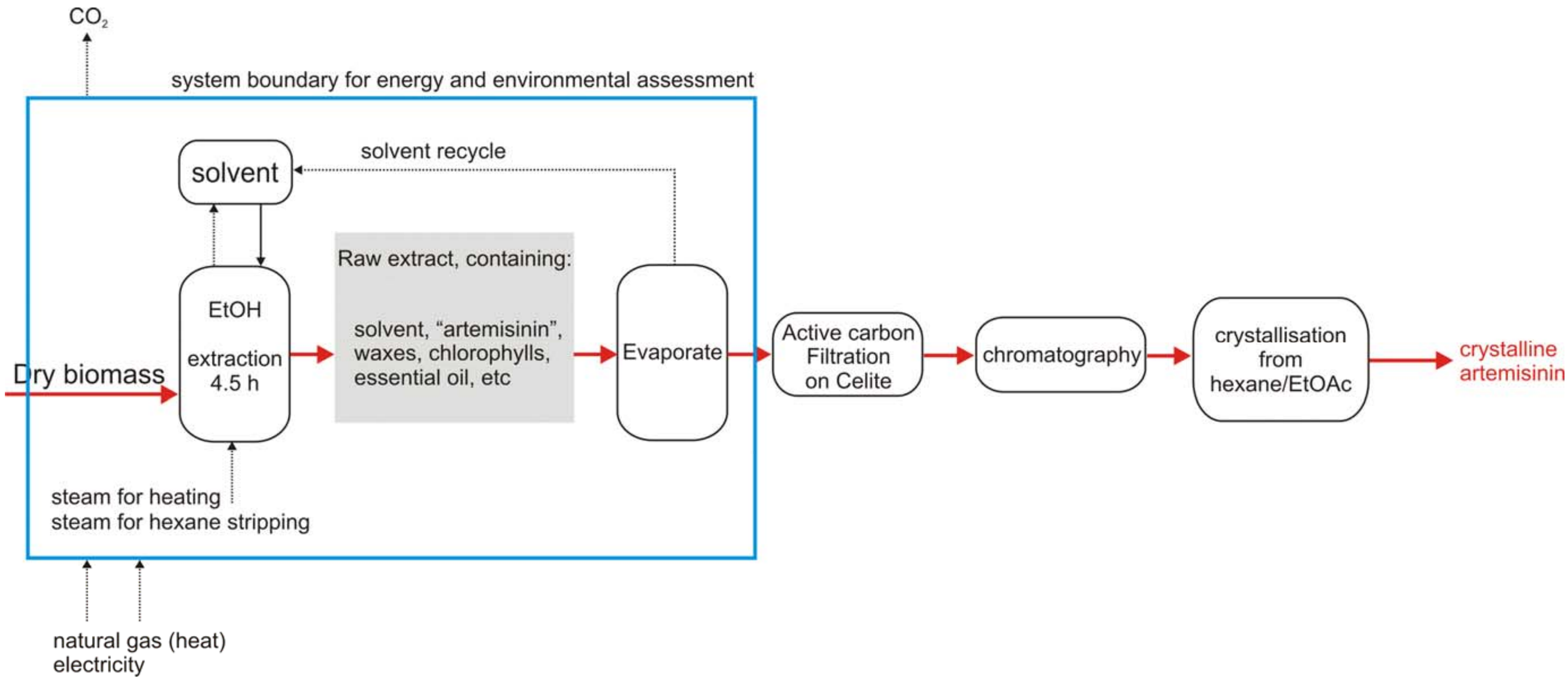
Ethanol Extraction



- 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.

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Rodrigues, R. A. F.; Foglio, M. A.; Júnior, S. B.; Santos, A. d. S.; Rehder, V. L. G. *Quim. NoVa* **2006**, *29*, 368-372.

Ionic liquids Extraction
(Bioniqs Ltd, UK)

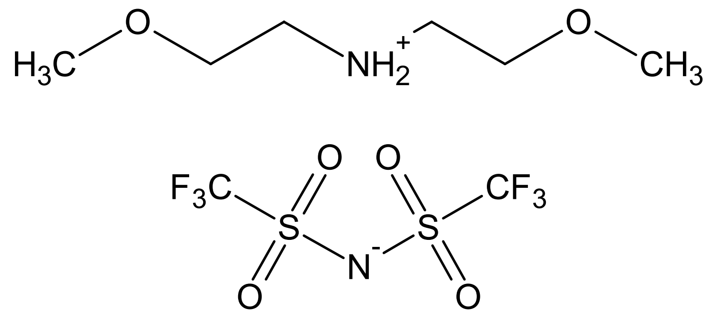
Ionic Liquids (ILs) – organic salts with melting point below 100 ºC.

Key properties:

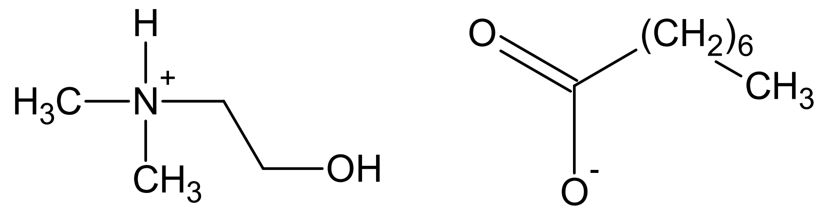
- Low vapour pressure
- Non-flammable
- Large variation of cations and anions
- Potential for design for function

Challenges:

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



bis(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)amide



N,N-dimethylethanolammonium octanoate

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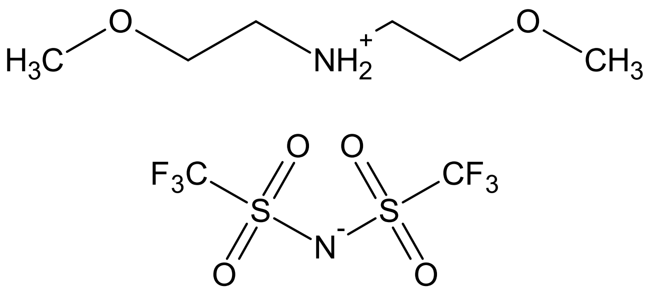
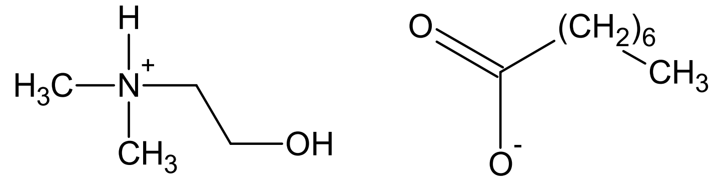
Ionic liquids Extraction

Ionic Liquids (ILs) Suppliers:

Merck
BASF
Solvents Innovation
…

Ionic liquids Extraction
(Bioniqs Ltd, UK)





bis(2-methoxyethyl)ammonium
bis(trifluoromethylsulfonyl)imide

N,N-dimethylethanolammonium octanoate

Parameter	**Value**
Solubility in EtOAc @ 20 ºC / $g{\cdot}L^{-1}$	100
Solubility in hexane @ 40 ºC / $g{\cdot}L^{-1}$	0.46
Solubility in hexane/EtOAc (5 %vol) / $g{\cdot}L^{-1}$	33
110 $g{\cdot}L^{-1}$	**82 $g{\cdot}L^{-1}$**

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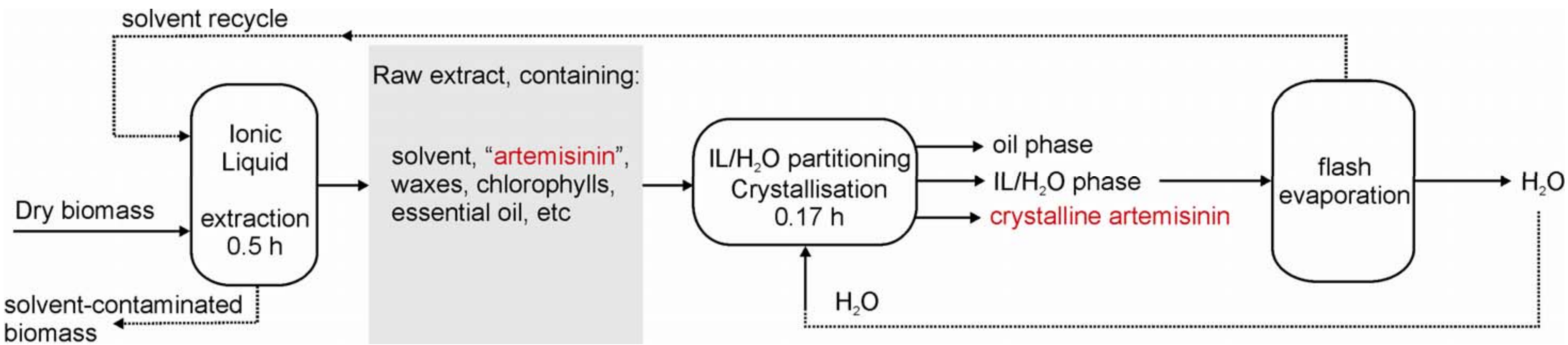
Ionic liquids extraction
(potential process)

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

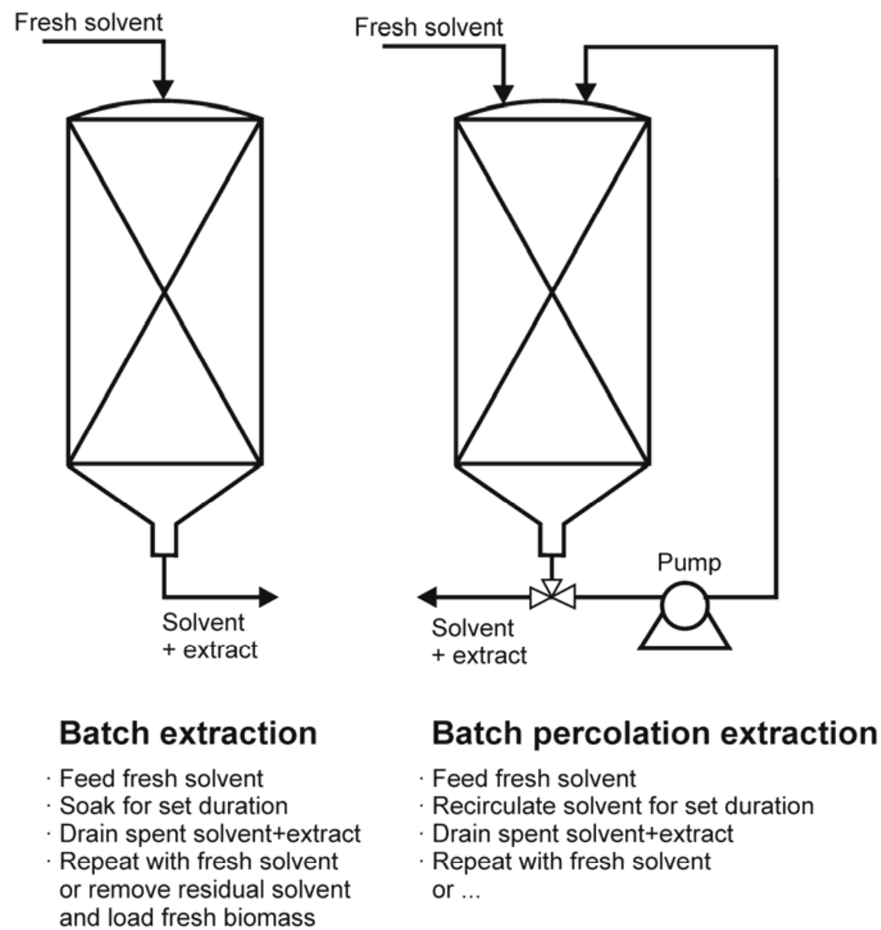


Main drawback: need for water in partitioning (high latent heat of water).
Unknown: degree of recovery of IL from spent biomass, fate of IL in environment.

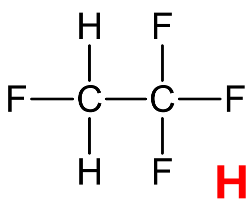
Mini conclusion 1: liquid solvents
(hexane, ethanol & ILs)

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.

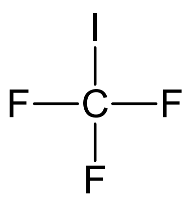
Extraction into IL is very fast and requires only one step. Separation from primary extract is simple.



$scCO_2$ & Hydrofluorocarbons Extraction

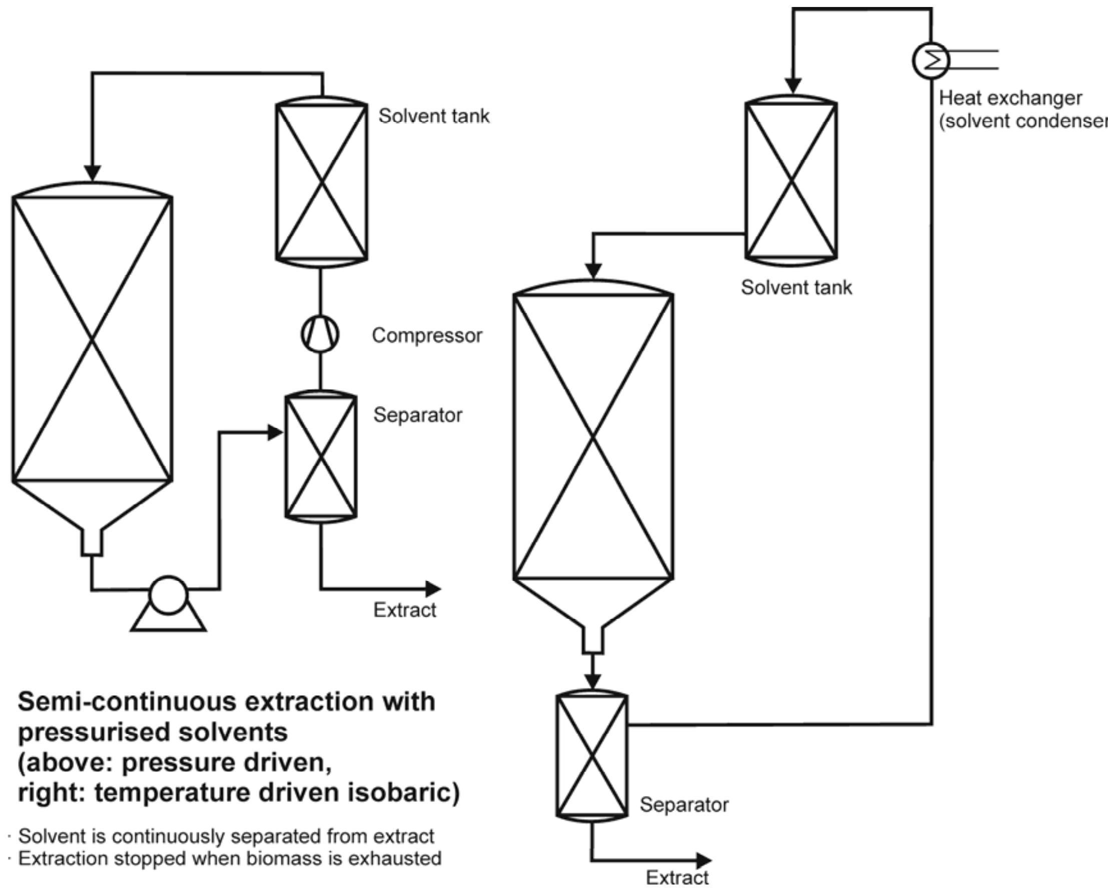


HFC-134a



Iodotrifluoromethane

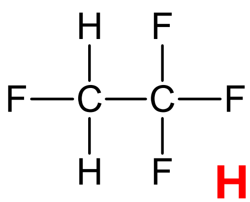
CO_2 **Carbon dioxide**



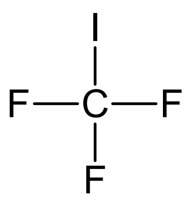
Semi-continuous extraction with pressurised solvents (above: pressure driven, right: temperature driven isobaric)

- Solvent is continuously separated from extract
- Extraction stopped when biomass is exhausted

$scCO_2$ & Hydrofluorocarbons Extraction



HFC-134a



Iodotrifluoromethane

CO_2

Carbon dioxide

- High pressure of $scCO_2$ process
  ➔ high operating and capital cost
- 134a global warming potential is 1300 x CO_2
  ➔ must have complete recovery
- ITFM's decomposition products are toxic
  ➔ regulatory and H&S must be resolved

Efficiency, Duration and Costs
(main criteria)

Method	T / ºC	P / MPa	Solvent to dry leaf / kg : kg	Extraction cycle / h	Efficiency / %
Hexane	**30-40**	**0.1**	**4 : 1**	**8-10**	**60**
EtOH	20	0.1	5 : 1	7	**73**
$scCO_2$	30-50	15-30	N/A	**3-6**	**82**
HFC-134a	15-40	0.4-1.2	N/A	6	62
[DMEA][oct]	20	0.1	6.3 : 1	**2.5**	**64**
[BMEA][Tf_2N]			**0.9 : 1**	6	**79**

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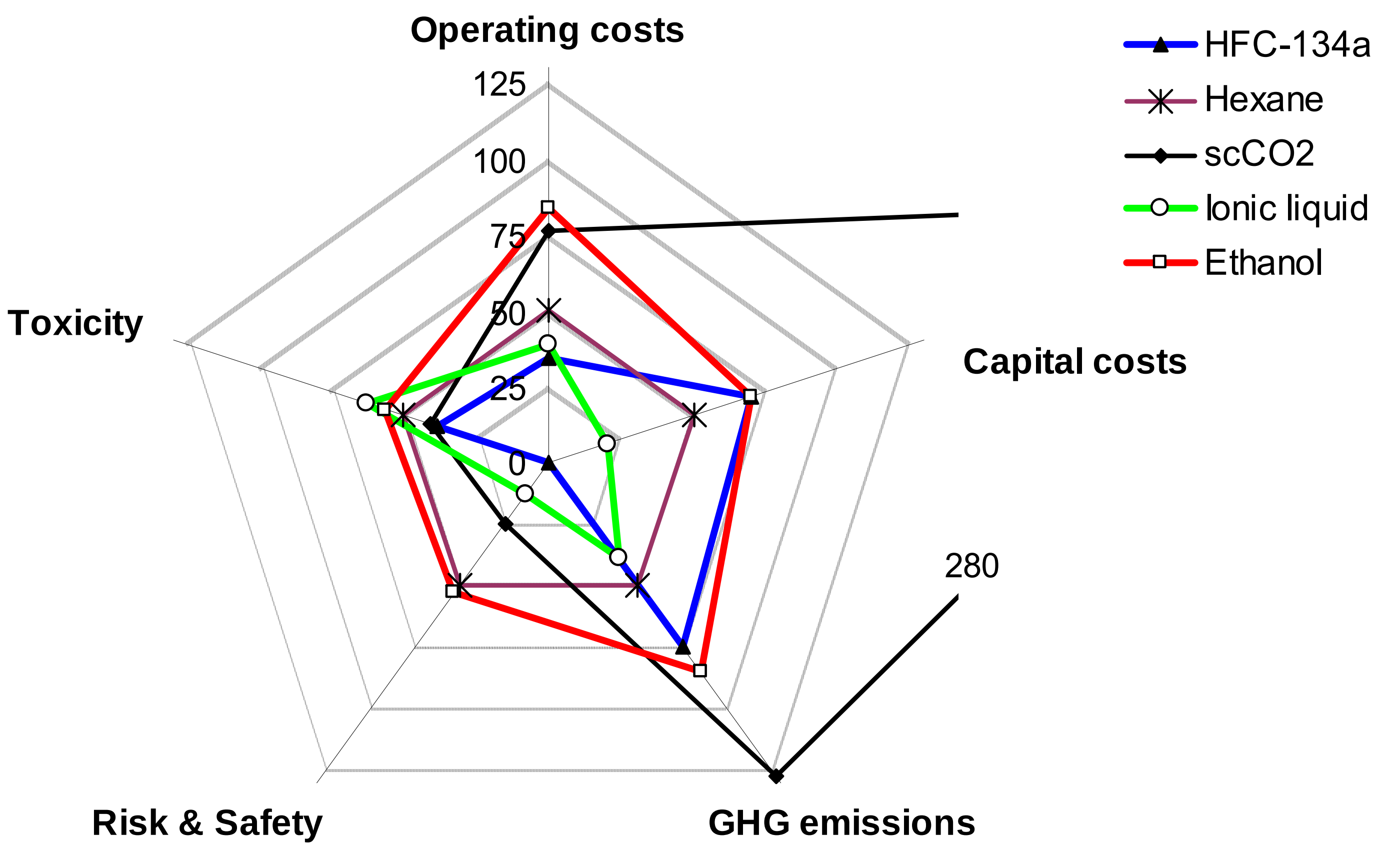
Efficiency, Duration and Costs
(main criteria)

	Energy efficiency / GJ·kg (artemisinin)$^{-1}$	GHG emissions / CO_2 kg·kg (artemisinin)$^{-1}$	Running cost / €·kg^{-1} artemisinin	Capital cost for $2.5 \cdot 10^6$ kg (biomass)·annum^{-1} / m€
Hexane	**1.3**	**87**	**28**	**0.7**
Ethanol	2.3	148	47	1.0
Ionic liquids	**0.9**-6.3	**56**-407	**22**	**0.3-1.0**
$scCO_2$	3.5	221	42	4.1
HFC-134a	**0.9**	**131**	**19**	**1.0**

!!! 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.

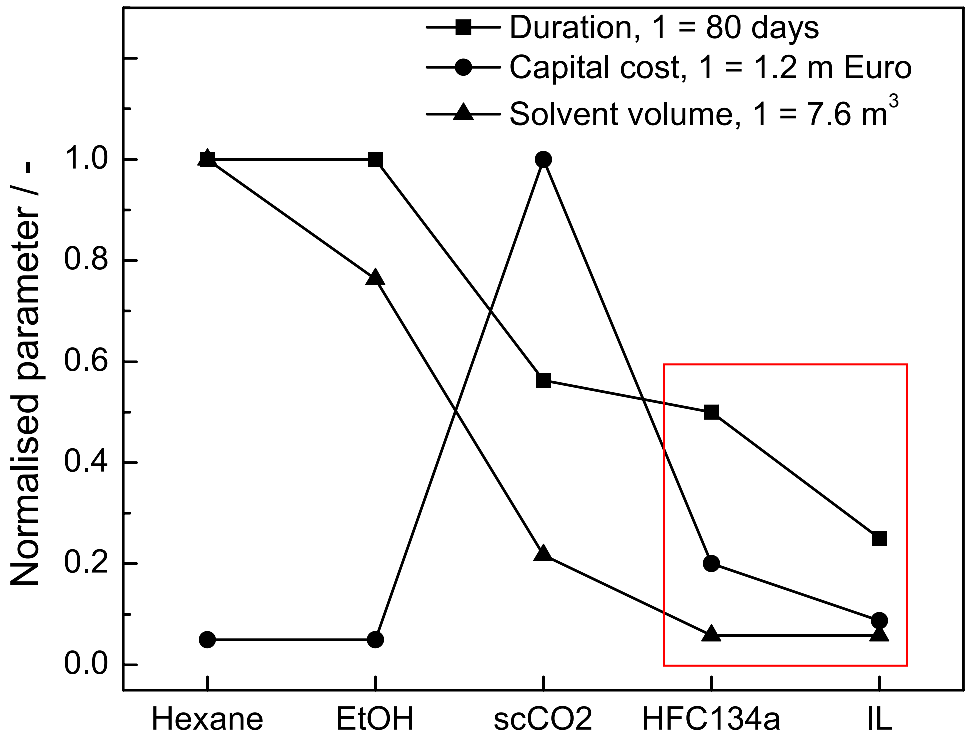
Multi-objective Assessment



- 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.

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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.
- $scCO_2$ 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.

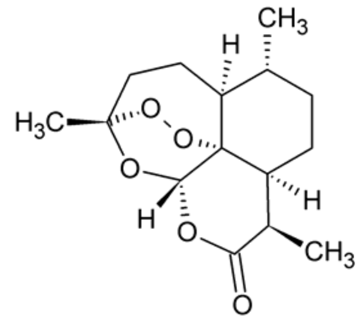
Acknowledgements

This study was funded by Malaria Medicines Ventures (MMV, Switzerland).

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

Simon Gardner, Andrew Lindley and Amy Elliott at **Ineos Fluor**
Dr. Adam Walker at **Bioniqs Ltd**
Thomas Chapman and Colin Newbould at **Essential Nutrition Ltd**
Prof. S.P.S. Khanuja at **CIMAP (India)**
Drs. Bhupinder Khambay and Maz Nicola at **Rothamsted Research UK**
Dr. Ian Flockhart at **Botanical Developments Ltd**
Anthony Ellman, Colin Hill, Peter Wilde and Prof. Michaela von Freyhold,
Drs. Chris Preston (**GlaxoSmithKline**), and Maggie Smallwood (**University of York**).

A.Lapkin, P.K. Plucinski, M. Cutler, Comparative assessment of technologies for extraction of artemisinin, *J. Nat. Prod.,* 69 (2006) 1653-1664. doi: 10.1021/np060375j



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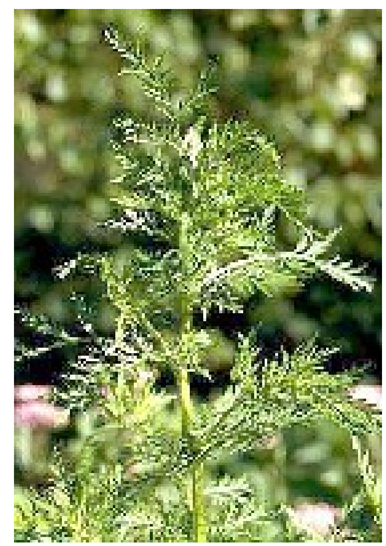

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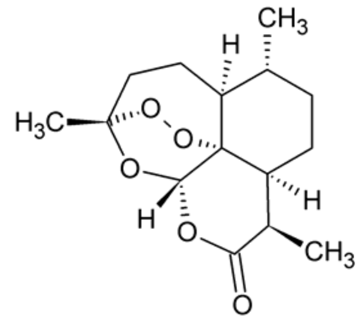
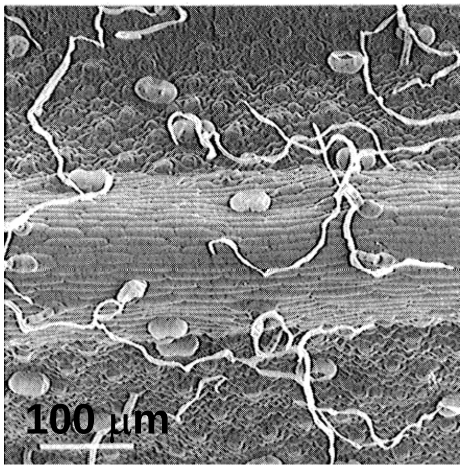
Properties of Artemisinin
(specificity of artemisinin extraction)

Parameter	Value
Molecular weight / g·mol^{-1}	282.3
Melting point / ºC	156-157
Thermal stability in non-polar solvents / ºC	150
Solubility in H_2O @ pH 7 / g·L^{-1}	0.063
Solubility in H_2O @ pH 7, 37 ºC / g·L^{-1}	0.048*
Solubility in EtOH @ 21 ºC / g·L^{-1}	12
Solubility in EtOAc @ 20 ºC / g·L^{-1}	100
Solubility in hexane @ 40 ºC / g·L^{-1}	0.46
Solubility in hexane – EtOAc (5 %vol) / g·L^{-1}	33
Octanol/H_2O partitioning coefficient / log P	2.94





Glandular trichoms on Artemisia A. leaf

Int. J. Plant Sci. 154(1):107–118. 1993.

Main growing and processing regions:

Vietnam and China

Emerging regions:

East Africa, India

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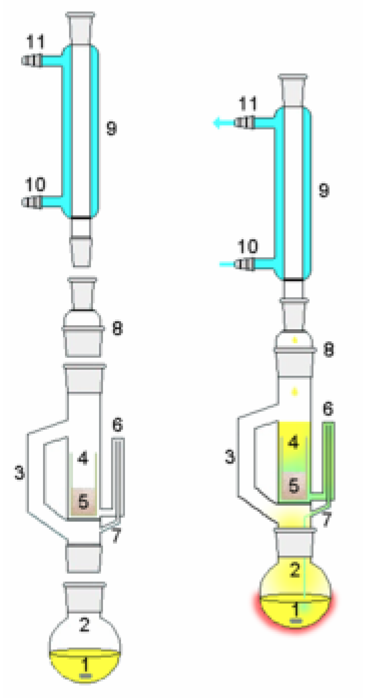
Conventional Batch "Hexane" Extraction

Scaled-up Soxhlet extraction
Vietnam



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

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