ACS GCI Pharmaceutical Roundtable

Moving towards Greener Solvents for Pharmaceutical Manufacturing - An Industry Perspective

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Presentation Overview

• ACS GCIPR introduction and strategic aims
• Key areas of need for greener solvents
• Conclusions and next steps
• Questions
ACS GCI Pharmaceutical Roundtable members as of April 2009

AstraZeneca
Pfizer
MERCK
Wyeth
Schering-Plough
GlaxoSmithKline
Boehringer Ingelheim
Lilly
DSM
BASF
CODEXIS
ACS Green Chemistry Institute
Johnson & Johnson
Novartis
ACS GCI Pharmaceutical Roundtable

• Mission: To catalyze the implementation of green chemistry and engineering in the pharmaceutical industry globally

• Strategic Priorities:
  – Informing and Influencing the Research Agenda
  – Tools for Innovation
  – Education Resource
  – Global Collaboration

  • Influencing solvent manufacturers to develop greener solvent alternatives
  • Developing an industry standard solvent selection guide
  • Process Mass Intensity Benchmarking
Background

• During pharmaceutical process development, solvent selection is a key component in determining the sustainability of future commercial production methods

• Benchmarking has demonstrated that solvents contribute to > 50% of materials used in manufacture of bulk active pharmaceutical ingredients

• Several individual member companies have developed solvent selection guides internally to highlight wider issues associated with using solvents

• ACS GCIPR is developing an industry standard solvent selection guide

• Some barriers remain that hinder increasing the use of alternative greener solvents
Process Mass Intensity (PMI) Benchmarking

- The ACS GCIPR has held two industry wide benchmarking exercises to collect data on the amounts and composition of materials used to make a drug.
  - Decreasing the amount of material is one of the major green chemistry challenges for the pharmaceutical industry
  - Benchmarking reinforces the need for wider use of Greener Solvents
  - PMI measurements should include all steps of a synthetic path from commonly available materials to the final bulk active pharmaceutical ingredient (API)

80% processes analysed are based on full route data
Aim of Presentation

• To recognize the challenges faced by manufacturers of alternative greener solvents

• To provide an understanding of the issues faced by roundtable members when managing the use of some key solvents
  – Chlorinated Solvents, with a focus on Dichloromethane
  – Ethers used as extraction solvents
  – Polar Aprotic solvents, replacements for DMF, DMAc, NMP

• Understanding the pro’s and con’s of currently used solvents

• Highlighting the desire to use greener solvents where appropriate
Chlorinated Solvents

This section will attempt to provide an understanding of

- the driving forces behind the selection of chlorinated solvents for use
- the impacts associated with using chlorinated solvents
Dichloromethane Pro’s

• **Solvation properties**
  – *Ubiquitous solvent* that dissolves a very wide range of pharmaceutical like compounds

• **Relatively inert** to many reactions

• Lack of flammability

• Forms biphasic system with water

• Heavier than water can give some processing advantages
Cons

Issues in using chlorinated solvents in Manufacturing Operations

- In the EU DCM carries the R40: Limited evidence of a carcinogenic effect risk phrase hence is strongly regulated and requires strict control measures.

- Regulations
  - EU: Integrated Pollution Prevention and Control (IPPC)
  - Future EU Water regulations on aqueous discharge of contaminated water
  - US: Hazardous Air Pollutants (HAP)

- Low boiling point and high vapour pressure
  - Emissions from storage tanks in warm ambient temperature climates

- Controlling emissions
  - Use of chlorinated solvents requires abatement technologies which will add to site overheads (capex, opex, energy)
  - Carbon beds (in-situ or off-site regeneration), incineration, cryogenic condensors
# Physical Properties of halogenated solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Regulatory flag</th>
<th>BPt °C</th>
<th>density g/cm³</th>
<th>Hildebrand sol. param. cal¹/₂ cm⁻³/₂</th>
<th>water solubility g/kg</th>
<th>viscosity cP (25°C)</th>
<th>vapor pressure kPa (25°C)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorobenzene</td>
<td>132</td>
<td>1.1</td>
<td>9.5</td>
<td>0.2</td>
<td>0.8</td>
<td>1.2</td>
<td>Unreactive</td>
<td></td>
</tr>
<tr>
<td>Chloroform</td>
<td>61</td>
<td>1.5</td>
<td>9.5</td>
<td>7.95</td>
<td>0.5</td>
<td>26</td>
<td>Essentially inert</td>
<td></td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>40</td>
<td>1.3</td>
<td>9.9</td>
<td>13.0</td>
<td>0.4</td>
<td>58</td>
<td>Unreactive</td>
<td></td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>77</td>
<td>1.6</td>
<td>8.6</td>
<td>0.79</td>
<td>1.1</td>
<td>15</td>
<td>Essentially inert</td>
<td></td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>84</td>
<td>1.3</td>
<td>9.6</td>
<td>8.70</td>
<td>0.8</td>
<td>8.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α,α,α-Trifluorotoluene</td>
<td>102</td>
<td>1.2</td>
<td>0.45</td>
<td></td>
<td></td>
<td></td>
<td>Unreactive</td>
<td></td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>77</td>
<td>0.9</td>
<td>18.6</td>
<td>80</td>
<td>0.4</td>
<td>12.6</td>
<td>More reactivity</td>
<td></td>
</tr>
<tr>
<td>2-Methyl THF</td>
<td>78</td>
<td>0.9</td>
<td>16.7</td>
<td>140</td>
<td>0.5</td>
<td>12.6</td>
<td>More reactivity</td>
<td></td>
</tr>
</tbody>
</table>

Knovel solvents database
Conclusions

• Halogenated solvents are versatile solvents
• Some major EHS regulatory barriers already exist
• Strategic approach is required to
  – *Develop and supply* alternatives to halogenated solvents that perform as well and that are truly greener
  – Continue to increase awareness and understanding in R&D of the consequences (abatement requirements and operational issues) for manufacturing operations when using halogenated solvents
Ethers as extraction solvents

This section will attempt to provide an understanding of the driving forces behind the selection of ethers.
Ethers as extraction solvents

- Need to be insoluble in water
- Have good solubilising properties (many have)
- Ideal boiling point 65-90 °C
  - Too low: emissions, flash point issues
  - Too high: high energy use for stripping operations, long cycle times, potential for decomposition etc.
## Ethers EHS impacts

<table>
<thead>
<tr>
<th>Solvent</th>
<th>B Pt °C</th>
<th>Flash Pt °C</th>
<th>Peroxide Risk</th>
<th>Waste recycling, incineration, VOC, and biotreatment</th>
<th>Environmental Impact fate and effects on the environment</th>
<th>Health acute and chronic effects on human health and exposure potential</th>
<th>Life Cycle Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-Butyl ethyl ether</td>
<td>72</td>
<td>-19</td>
<td>Med</td>
<td>DATA GAPS TO BE FILLED</td>
<td>DATA GAPS TO BE FILLED</td>
<td>DATA GAPS TO BE FILLED</td>
<td>4</td>
<td>Reasonable properties, niche solvent</td>
</tr>
<tr>
<td>t-Amyl methyl ether</td>
<td>85</td>
<td>-11</td>
<td>Low</td>
<td>DATA GAPS TO BE FILLED</td>
<td>DATA GAPS TO BE FILLED</td>
<td>DATA GAPS TO BE FILLED</td>
<td>4</td>
<td>Very good properties, niche solvent</td>
</tr>
<tr>
<td>Dibutyl ether</td>
<td>140</td>
<td>25</td>
<td>Med</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>Boiling Point too high for most purposes.</td>
</tr>
<tr>
<td>t-Butyl methyl ether</td>
<td>55</td>
<td>-32</td>
<td>Low</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>Current best all round choice. Flashpoint on the limit of use for most Pilot Plants and Production facilities</td>
</tr>
<tr>
<td>2-MeTHF</td>
<td>78</td>
<td>-11</td>
<td>Med</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>Good properties with increasing use in member companies</td>
</tr>
<tr>
<td>CPME</td>
<td>106</td>
<td>1</td>
<td>Med</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>Boiling Point too high for widespread use in medicinal chemistry. New solvent to the market</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>35</td>
<td>-45</td>
<td>Med</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>Too volatile and flammable</td>
</tr>
<tr>
<td>Diisopropyl ether</td>
<td>68</td>
<td>-28</td>
<td>High</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>9</td>
<td>High risk of peroxide formation 1000x higher than any ether on this list. Many companies have a policy of not using.</td>
</tr>
<tr>
<td>Ideal Ether</td>
<td>65-90</td>
<td>&gt; -15</td>
<td>Low</td>
<td>DATA GAPS TO BE FILLED</td>
<td>DATA GAPS TO BE FILLED</td>
<td>DATA GAPS TO BE FILLED</td>
<td>4</td>
<td>Currently no ether that meets all of these criteria. An ether meeting these criteria would gain widespread use.</td>
</tr>
</tbody>
</table>

Relative EHS impacts based on GSK’s Solvent Selection Guide
Increasing popularity of 2-MeTHF

A ‘Top 40’ ranking based frequency of use of solvents

Solvent rankings based on number of pilot plant campaigns in which the solvent was used
Ethers: Summary of Key Points

- t-Butyl ethyl ether and in particular t-amyl methyl ether have excellent physical and chemical properties
  - Currently niche solvents with no widespread use in the pharmaceutical industry
  - Data gaps remain to understand the wider EHS and life cycle properties
- 2-MeTHF
  - Increasing popularity
  - The majority of 2-MeTHF is used in early stages
  - Less is used in the API forming step itself.
  - Lack of mammalian toxicity data available.
Dipolar Aprotics

This section will attempt to provide an understanding of
• why we use dipolar aprotic solvents
• the issues with these solvents and the current alternatives
Pros

• Versatile and effective solvent in many reactions that are commonly used in the pharmaceutical industry
  – eg Suzuki and other cross coupling reactions and $S_N^2$ alkylations
• Uniquely effective at dissolving polar materials and salts
• Excellent cleaning solvents
• Low vapour pressure
Cons

- **Use of these materials is becoming restricted by legislation**
  - Many common dipolar aprotics are being classified as human reprotoxins with more likely to be added to the list
    - In the EU, the use of these solvents has to be defended with clear evidence that every reasonable action has been taken to identify a substitute
  - These solvents have very low permitted emissions to air
  - Removal after reaction
  - Listed under ICH solvent guidelines class 2
- **Responsible business practices & sustainability drivers to reduce and remove use of human reprotoxic materials**
  - Already flagged as materials of concern in some member companies
- **What else can we use?**
  - Only a few alternative solvents have been identified
  - Issue may go beyond reactions as NMP and DMF are very good cleaning solvents
The alternatives?

**Acetonitrile**
- Security of supply
- Different solubility characteristics to other dipolar aprotic solvents
- VOC abatement required
- Poor life cycle impact
- Quality issues

**DMSO**
- Disposal / Reaction work up
- Undesirable absorption of chemicals through the skin
- Process Safety issues with hot DMSO

**N-Ethyl pyrrolidinone**
- Currently not enough data is known
- Initial results would suggest R60/R61 will follow

**1,3-Dimethyl-2-imidazolidinone, DMU/DMI**
- May have R60/R61 properties, but no data at present
- Hygroscopic and is oxidized when exposed to air
- Security of supply?
### Physical Properties

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Regulatory flag</th>
<th>BPt °C</th>
<th>FPt °C</th>
<th>density g/cm³ (25°C)</th>
<th>Hildebrand sol. param. cal³/² cm⁻³/²</th>
<th>viscosity cP</th>
<th>vapor pressure kPa (25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl sulfoxide</td>
<td></td>
<td>189</td>
<td>19</td>
<td>1.10</td>
<td>12.0</td>
<td>1.99</td>
<td>0.08</td>
</tr>
<tr>
<td>N,N-Dimethyl formamide</td>
<td></td>
<td>153</td>
<td>-61</td>
<td>0.95</td>
<td>11.6</td>
<td>0.80</td>
<td>0.49</td>
</tr>
<tr>
<td>N-Methyl pyrrolidone</td>
<td></td>
<td>202</td>
<td>-24</td>
<td>1.03</td>
<td>11.3</td>
<td>1.67</td>
<td>0.05</td>
</tr>
<tr>
<td>N,N-Dimethyl acetamide</td>
<td></td>
<td>165</td>
<td>-20</td>
<td>0.94</td>
<td>10.8</td>
<td>0.93</td>
<td>0.17</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td></td>
<td>82</td>
<td>-45</td>
<td>0.78</td>
<td>11.6</td>
<td>0.36</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Many member companies currently opt for NMP out of the polar aprotics

Knovel solvents database
What else?

- PEGS?
- Phase Transfer Catalysis (PTC) – aqueous systems
- Ionic liquids
  - First generation IL’s were promoted as green on the single issue of being non-volatile, but are ecotoxic
  - Newer IL’s are ‘greener’ with sustainable criteria being developed by suppliers
  - Mixtures: recent research suggests that, at least for organic synthesis, IL/Solvent combinations give better performance.
General Issues with ‘neoteric’ green solvents

• Alternatives to VOC’s focus on ‘single issue sustainability’ and actually have very poor Life Cycle Impact data (LCI),
  – for example, ionic liquids where there is little or no LCI data to prove better sustainability
  – Solvents derived from food crops (corn ethanol)
• Lack of mammalian toxicity data – no regulatory guidance (ICH etc.)
• Security of supply
• High Bpt/viscosity materials are difficult to handle in traditional Pharma plants and difficult to remove from products.
• Some IP concerns
Conclusions and next steps

- Finding greener alternatives to chlorinated solvents, ethers and dipolar aprotics remains a key problem
- Alternative solvents have to perform effectively and be sustainable not just resolving single issues

Next Steps
- Roundtable to publicize the ACS GCIPR Solvent Selection Guide
- Open invitation to solvent manufactures to discuss these challenges in more depth at the ACS GCIPR October Meeting in the USA
- Please contact Julie Manley (ACS GCIPR) for more information
  - Website: www.acs.org/gcipharmaaroundtable
  - E-Mail: gcipr@acs.org
Back ups
US hazardous air pollutants (HAP)

- The standard MACT (Maximum Achievable Control Technology) establishes the maximum emission levels covering process vents, storage vessels, waste water, and equipment leaks. It is a very complex and long standard. 
- The MACT standard is applicable if a pharmaceutical manufacturing process unit dedicated to manufacture a single product has the potential to emit 10 tons per year of HAP or 25 tons per year of combined HAP. If it is applicable, the manufacturing unit is called a major source. For the major sources:
  - Control requirements for Process Vents:
    - >= 98 wt% reduction, or
    - < 20 ppmv Total Organic Carbon and 20 ppmv hydrogen halides and halogens
  - Control requirement for storage vessels:
    - >= 90 wt% reduction for 38 m3 < tank volume < 75 m3, and vapor pressure > 13.1 kPa
    - >= 95 wt% reduction for tank volume > 75 m3, and vapor pressure > 13.1 kPa
  - Control requirement for waste water:
    - Remove total partially soluble HAP compounds to < 50 ppmv, or
    - Remove >= 99wt% of total partially soluble HAPs
    - Remove soluble HAP compounds to < 250 ppmv, or
    - Remove >= 90wt% of soluble HAPs
    - Remove >= 95wt% if using enhanced biotreatment for wastewater containing soluble and partially soluble HAPs
  - Control requirement for equipment leaks:
    - Each pump, compressor, agitator, pressure relief device, sampling connection system, open-ended valve or line, valve, connector, instrumentation system in organic HAP service requires measurement of fugitive emissions. The frequency of measurement is dependent on the # of leakers in the system. In addition, there is a very stringent schedule to fix the leakers.
    - As you see, the quantitative emission limit is stringent, but the monitoring/record keeping/reporting side of MACT is very time consuming and resource intensive.
    - Finally, a new regulation is being written for minor sources (i.e., MACT does not apply, but still emits HAPs).
    - Independent of MACT, the US also has Effluent Limitations Guidelines for pharmaceutical manufacturing. For methylene chloride:
      - Indirect discharger: 3.0 mg/L max daily, 0.7 mg/L monthly average
      - Direct discharger: 0.9 mg/L max daily, 0.3 mg/L monthly average
## Freshwater ecotoxicity of Ionic Liquids

<table>
<thead>
<tr>
<th></th>
<th>48 hr <em>Daphnia</em> magna</th>
<th>EC50 mg l⁻¹</th>
<th>72 hr algal</th>
<th>EC50 mg l⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocosalkyl pentaethoxymethyl MeSO₄⁻</td>
<td>1.0</td>
<td>0.088</td>
<td>0.057</td>
<td>0.035</td>
</tr>
<tr>
<td>1-Butyl-3-methyl imidazolium Cl⁻</td>
<td>6.4</td>
<td>36</td>
<td>0.20</td>
<td>0.053</td>
</tr>
<tr>
<td>Trihexyl tetradecyl phosphoniumCl⁻</td>
<td>0.057</td>
<td></td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Methyl trioctyl imidazolium NTf₂⁻</td>
<td>0.20</td>
<td>45</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>1-Butyl-3-methyl imidazolium PF₆⁻</td>
<td>24</td>
<td></td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>19.6</td>
<td>125</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Xylene</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>138</td>
<td>660</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td>25,000</td>
<td>10,000</td>
<td>25,000</td>
<td></td>
</tr>
</tbody>
</table>

NB. Many IL’s also kill bacteria needed for biodegradation.
Bioniqs

• “In common with many novel solvents, ionic liquids as a class have been subject to a certain level of “greenwashing” concerning their purported environmental benefits. We are therefore proud to take the lead in this area by introducing to market our benchmark econiqs certification for green solvents. To qualify for the econiqs branding, a solvent must satisfy all of the following stringent environmentally-relevant criteria:”

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biodegradability</td>
<td>&gt;98% biodegradable by mixed community of natural soil organisms within 14 days, as determined by HPLC and/or ion chromatography</td>
</tr>
<tr>
<td>Sustainable</td>
<td>all precursor materials used in manufacture are available from sustainable, renewable feedstocks</td>
</tr>
<tr>
<td>Non-mutagenic</td>
<td>non-mutagenic as determined by the Ames test (Mutagenicity Index &lt;2, Mutagenic Activity Ratio &lt;2.5).</td>
</tr>
<tr>
<td>Low Toxicity</td>
<td><em>Daphnia magna</em> EC50 &gt;250mg/L</td>
</tr>
<tr>
<td></td>
<td>Green algae (Selanstrum capricornutum) ErC50 &gt;100mg/L</td>
</tr>
</tbody>
</table>

Is this a minimum data set requirement for all alternative solvents?