Solvents

Solvents are liquids that are capable of dissolving or dispersing other substances. They are used in very high volumes in industry and from a number of cradle-to-gate lifecycle studies it is generally recognised that the major contributor to the lifecycle impacts of API synthesis is due to solvents. From a green chemistry point of view, solvents therefore become an area where greatest impact can be achieved by reducing the amount of solvent waste, and minimising human and environmental consequences through the choice and volumes of solvent used.

Learning Objectives

By the end of this module you should:

- Have a broad understanding of why we use solvents;
- Be aware of issues surrounding the use of solvents;
- Be able to identify solvents of concern.

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What are solvents and why do we use them?

Solvents are widely used throughout the chemical industry for example in:

- Synthetic Chemistry: as a reaction medium on both laboratory and industrial scale and in work-up and purifications.
- Analytical Chemistry: for sample extraction and preparation (spectroscopy) and chromatography mobile phase (HPLC, TLC etc.)
- Crystallography: for recrystallisation to purify compounds and prepare crystals suitable for analysis.

Solvents have many other applications other than synthetic chemistry, for example in paints and adhesives, for cleaning (e.g. dry cleaning) and for extraction (e.g. decaffeination of coffee).

Solvents are used as a reaction medium for various reasons including:

- To bring reactants together at suitable concentrations;
- For energy control:
  - Endothermic reactions require energy – heat can be supplied by heating solution;
  - Exothermic reactions – solvent acts as a heat sink preventing runaway reactions;
- For efficient mixing and stirring;
- To allow addition of solid reagents as a solution;

Solvent extraction is also vital part of purification process. Often more solvent is used in work-up than as reaction medium. Partitioning products between an organic phase and an aqueous phase is a very important way of extracting products, although this generates aqueous waste as well as organic waste, both of which require disposal.

Some common classes of solvents are given below.

Solvent Class	Example
Alkanes	Hexane
Aromatics	Toluene
Alcohols	Ethanol

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Solvent Class	Example
Ethers	Diethyl ether
Polar aprotic	Acetonitrile
Chlorinated	Dichloromethane
Ketones	Acetone
Acids	Acetic acid
Bases	Pyridine

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Issues around the use of solvents

At the screening level, as broad a range of solvents as possible will be utilised to determine ideal conditions such as solubility, reaction temperature (as determined by boiling point), partition coefficient *etc*.[1] The use of a full solvent set will indicate which classes of solubilising agents give best results and what solvent properties dominate the solvent effects.

However researchers should be aware of solvents that have been categorised as highly hazardous or worse and their use should be avoided even during screening reactions. The highly hazardous classifications can be due to health, safety or environmental reasons as well as regulatory constraints. In their editorial policy, the journal Organic Process Research and Development discourages research conducted using 'strongly undesirable solvents' such as benzene, carbon tetrachloride, chloroform, HMPA, carbon disulphide.

Solvents that fall into this category include[2]:

- Carcinogenic solvents e.g. benzene, 1,2-dichloroethane (H350).
- Ozone depleting solvents e.g. Carbon tetrachloride (H420).
- Chloroform, due to its toxicity.
- Diethyl ether, due to the safety risks associated with its low flash point; low boiling point; resistivity; ability to form peroxides and low auto-ignition temperature.
- Nitromethane, due to its high energy of decomposition.

Dipolar aprotic solvents are another class of solvents that are subject to an increasing amount of scrutiny. N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc) and 1-Methyl-2-pyrrolidone (NMP) have all been named as substances of very high concern (SVHC) on the REACH Candidate list for Authorisation

As with all chemicals, solvents and their use are subject to legislation: for further study, see Environmental Legislation in the Process Design topic.

1. R. C. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, Towards a holistic approach to metrics for the 21st century pharmaceutical industry, *Green Chem.*, 2015, **17**, 3111-3121.
2. D. Prat, J. Hayler and A. Wells, A survey of solvent selection guides, *Green Chem.*, 2014, **16**, 4546-4551.

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Solvent selection

Frequently a solvent is chosen for a particular reaction due to literature precedent or in-house routine practice. However a more strategic approach should take into consideration the following:

- Inert under reaction conditions
- Chemistry must work!
- Isolation/work-up/crystallisation
- Safety and operability
- Human health issues
- Can the solvent be recovered/recycled?
- Can wastes be incinerated/treated?
- Environment and legislation compliance
- Overall cost burden to final product

Substitutes can also be sought from solvent selection guides (see Solvent Selection Guides in the Guides and Metrics topic.) A number of solvent selection guides have been published with the purpose of promoting the uptake of more sustainable solvents. These guides give the user a quick method of identifying problematic solvents and subsequently recommending preferred alternatives.

Design of Experiments (DoE) and Principal Component Analysis (PCA) can be used as tools to identify solvents to screen, and assist in decision making when looking for replacement solvents.[1]

Other alternative solvents (and solvent-less reactions) are explored in more detail in the solvents topic including water, bio-derived solvents, supercritical fluids and ionic liquids.

1. J. D. Moseley and P. M. Murray, Ligand and solvent selection in challenging catalytic reactions, *J. Chem. Technol. Biotechnol.*, 2014, **89**, 623-632.

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Multiple choice questions

1. What is the major driver for focussing on solvents when addressing the ‘greenness’ of a process?
    1. They are petroleum derived
    2. They are serious pollutants
    3. They make up the largest component (by mass) of a process
    4. They are non-renewable
    5. They are toxic
    6. They are flammable and therefore present a safety hazard
2. Which of these is not a common solvent class?
    1. Alcohols
    2. Aromatics
    3. Chlorinated
    4. Ethers
    5. Ketones
    6. Oils
    7. Polar aprotics
3. Which of the following solvents have been considered ‘strongly undesirable’ and discouraged from being used even in screening reactions?
    1. Diethyl ether
    2. Toluene
    3. Benzene
    4. Carbon tetrachloride
    5. Chloroform
    6. Methanol
    7. HMPA
    8. Pyridine
4. Which of the following solvents are listed as substances of very high concern (SVHC) under REACH?
    1. THF
    2. Cyclohexane
    3. DCM
    4. Xylene
    5. NMP
    6. DMF

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7. Acetonitrile

5. Which of the following solvents can be bio-derived?
    1. Heptane
    2. Ethanol
    3. Ethyl acetate
    4. Limonene
    5. Toluene
    6. DCM

Answers on last page

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Summary and further reading

Solvents are used in large volumes in the chemical industry for example in reactions, work-up procedures and in formulations. There are a number of issues surrounding the use of solvents (including regulatory, environmental, health and safety related factors) and there is a strong drive to move towards the use of more sustainable solvents.

To study this area in more depth, see Solvents

Recommended reading:

W. M. Nelson, *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press, New York, USA, 2003.

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Quiz answers

- Multiple choice questions

1. What is the major driver for focussing on solvents when addressing the ‘greenness’ of a process?
   ***Correct answer**: They make up the largest component (by mass) of a process*
2. Which of these is not a common solvent class?
   ***Correct answer**: Oils*
3. Which of the following solvents have been considered ‘strongly undesirable’ and discouraged from being used even in screening reactions?
   ***Correct answers**:*

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