

## INTRODUCTION

Solvent is usually the largest single component in any given reaction, and greatly affects the chemical environment of the reaction materials, as the photo below of a single dye in multiple solvents illustrates. Only a limited number of ca. 50 solvents are cheaply available on a truly large scale, mostly petrochemical derived. Environmental concerns and increasing regulation mean that fewer solvents are available, especially for manufacturing, and restrictions are tightening. Therefore, early identification of the preferred long-term solvent for a given reaction step is highly desirable and this choice presents both challenges and opportunities.



The primary purpose of a solvent inevitably is that it dissolves substances, allowing molecules to react in the solution phase. But it is also helpful if a solvent is not too solubilising, allowing the product to crystallise whilst retaining impurities in solution – since crystallisation is very much the preferred method of purification on scale-up, especially for active pharmaceutical intermediates (APIs). Indeed, solvents will often be chosen more for their suitability for crystallisation as for their ability to mediate the reaction.

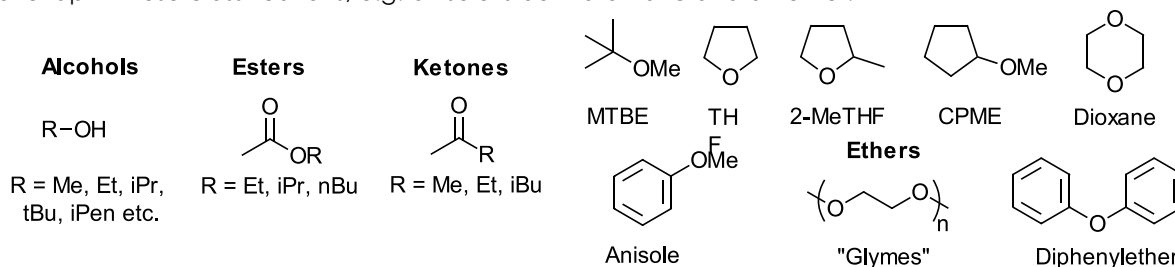
Desirable properties of solvents for manufacture on large scale can be summarised as follows:

- Cheap and commercially available on large scale
- Non-toxic for human health (since operators could regularly be exposed to large quantities)
- Non-polluting to air and water (ozone depletion, green-house gas potential, toxic to fish)
- Low hazard due to physical properties (low static potential, low flammability, high flash point)
- Have a wide boiling range, albeit not too high, but remain liquid on a cold day in N. Europe!
- If not miscible with water, should form a good azeotrope with water
- And lastly, should remain inert in the reaction – this is less common than expected

What follows is a brief survey of solvents commonly used on bulk scale within the pharmaceutical industry for the manufacture of the highly functionalised, high-purity organic compounds that are APIs. Solvent choice inevitably requires a compromise of many conflicting demands – other chemical industries will make different choices. Whilst not discussed here, note that neoteric solvents are also being considered for specific applications within pharmaceutical manufacture, including fluorinated phase solvents, ionic liquids, near-critical water, supercritical CO<sub>2</sub> and novel sustainably sourced bio-derived solvents.

## SOLVENT CLASSES

Solvents can be classified by their structures into the following general types: alcohols, esters, ketones, ethers, chlorinated solvents, aromatics, alkanes, acids, bases and dipolar aprotics, although there is some overlap in these classifications, e.g. anisole is both aromatic and an ether.

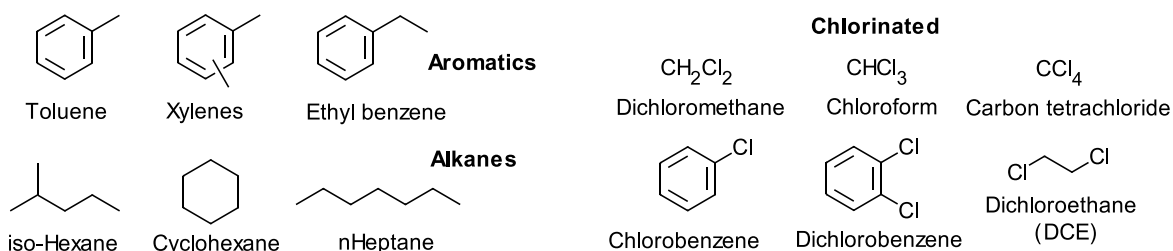


**Alcohols** are ideal solvents in many respects, being cheaply available with good solubilising power and benign physical properties. Due to their low toxicity, and with the shorter alcohols being fully miscible with water, they provide infinite combinations for binary crystallisation solvent systems and are favoured for

the isolation of APIs. However, being protic solvents, they cannot be used in many common types of important reactions, e.g. deprotonations, Grignard reactions, lithiations, certain cross-couplings, etc.

**Esters** and **ketones** are non-protic solvents and so avoid this issue, although neither can be used in some situations due to their particular reactivity. They have less solubilising power than alcohols and are usually immiscible with water. The choice on scale is limited to those shown. Higher homologues are preferred due to having a higher boiling point, which allows faster reactions and provides a greater safety margin in the event of an exothermic reaction. Ethyl acetate and acetone have low flash points and are less stable under reaction conditions, so isopropyl acetate and methyl ethyl (or isobutyl) ketone are preferred.

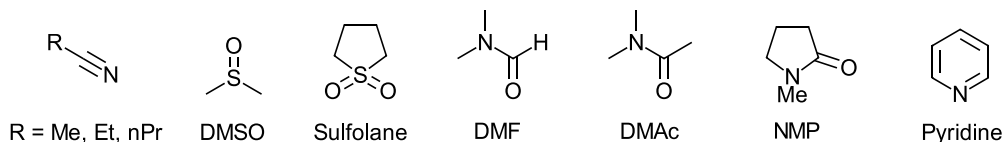
There is a greater choice of **ethers**, which are generally inert except to strongly acidic conditions, but they are also less solubilising than ketones. Tetrahydrofuran is a widely used ether, where its coordinating properties are helpful in metal reactions. Diethyl ether is too volatile to be safely used on plant scale, but can be substituted with MTBE. 2-Methyl-tetrahydrofuran and CPME have come to prominence in recent years, being higher boiling alternatives to THF which are also non-miscible with water and so can be azeo-dried. 1,4-Dioxane is now less used due to its higher toxicity. Aromatic ethers such as anisole and diphenyl ether, and the glymes, are much less used except when needed for niche applications, but like most high boiling solvents, they are difficult to remove from products.



**Chlorinated** solvents are in many aspects ideal reaction solvents, being inert in nearly all cases and tolerant of strongly acidic conditions. They are immiscible with water and have good solubilising power, low flammability and mid-range boiling points, hence they are easily distilled. Unfortunately, their impact on ozone depletion and toxicity in the aqueous environment has resulted in most being banned at full manufacturing scale, leaving little scope for use outside the laboratory. Dichloromethane is the least harmful and too useful to ban entirely, but it is rarely the first choice and alternatives should be sought.

The **aromatic** solvents, toluene and higher homologues, can be substitutes for previously popular chlorinated solvents. They are robust solvents with good overall properties, although high static potential and low polarity. The **alkanes** are similar, inert to nearly everything but with low solubilising power, hence they are often used as anti-solvents in crystallisation protocols. Static risk and toxicity in water are issues which must be managed.

Organic **acids** (formic, acetic, propionic) and **bases** (pyridine, triethylamine) are sometimes used as bulk solvents on manufacturing plants, but odour can be a major issue, and may be regulated to low levels. Inevitably the risk of physical harm to operators, and corrosion to construction materials, is higher when using these corrosive materials. Their reactive nature precludes use in many processes in any case.



Last but by no means least, the diverse group of ever popular **dipolar aprotic** solvents have the solubility of alcohols and acids, but lack an exchangeable proton. This makes them ideal for many reactions in which solubility may be an issue. However, they are water-miscible and, except for acetonitrile, relatively high-boiling, which can make them harder to remove. Toxicity is high for most (except DMSO) and they are less suitable as crystallisation solvents since they are tightly regulated to low residual levels in APIs.

Want to find out more?

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