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**Editorial**

# Basic Approaches for the Selection of Solvents in Pharmaceutical Industries

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Commonly used solvents in pharmaceutical industries are water, ethanol, acetone, ethers, n-butanol etc. Solvents are used for various purposes. They are used for extraction, as medium and to dissolve the solutes. Due to their chemical nature, in some instances, they pose toxicity, causes adverse effects and cause damage to the environment. Solvents are classified in various categories such as inorganic, organic, and green solvents. They are also grouped as oxygenated solvents, halogenated solvents, and hydrocarbon solvents. Green solvents are the prime focus and the most used solvents in pharmaceutical industry. Different types of solvent are characterized with various properties such as viscosity, biocompatibility, physiochemistry, extraction potential, biodegradability, renewability, hydrophobicity, polarity, conductivity, hydrophilicity, and solubilizing-stabilizing abilities. The most suitable solvents include organic solvents having good properties including volatility, acid-base properties, low boiling point, suitable density, etc. Solvents have important roles in solubility, bioavailability, and crystallization. According to recent trends, solvents other than green solvents are a major source of pollution. Therefore, solvents that affect environment should be avoided in pharmaceutical industry.[1]

Chemical processing industries engaged in pharmaceutical manufacturing use organic solvents to produce complex intermediates that lead to an active pharmaceutical ingredient (API). The aim to develop a robust process to produce intermediates and active pharmaceutical ingredients at high purity, with known and consistent quality, and high yields. It is also important to ensure volume efficiencies,

operability, safety, and less environmental impacts as possible.[2]

ICH provides guidelines and recommended the acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.[3]

Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity and solubility. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements.

Residual solvents are classified into various categories such as class 1, class 2 and class 3 solvents.

Class 1 solvents to be avoided in common use since these are known human carcinogens, strongly suspected human carcinogens and causes environmental hazards. The list of some class 1 solvents with concentration limit are list in the table-1.

**Table 1: Class 1 Solvents:**

| Solvent | Concentration limit (ppm) | Concern |
|---|---|---|
| Benzene | 2 | Carcinogen |
| Carbon tetrachloride | 4 | Toxic and environmental hazard |
| 1,2-Dichloroethane | 5 | Toxic |
| 1,1-Dichloroethene | 8 | Toxic |
| 1,1,1-Trichloroethane | 1500 | Environmental hazard |

The use of class 2 solvents to be limited. These are non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. These Solvents suspected of other significant but reversible toxicities. The list of some class 2 solvents is given in the table 2.

**Table 2: Class 2 Solvents**

| Solvent | PDE (Permitted daily exposure) (mg/day) | Concentration limit (ppm) |
|---|---|---|
| Acetonitrile | 4.1 | 410 |
| Chlorobenzene | 3.6 | 360 |
| Cyclohexane | 38.8 | 3880 |
| Dichloromethane | 6.0 | 600 |
| Hexane | 2.9 | 290 |
| Methanol | 30.0 | 3000 |
| N-Methylpyrrolidone | 5.3 | 530 |
| Tetrahydrofuran | 7.2 | 720 |
| Toluene | 8.9 | 890 |
| Xylene | 21.7 | 2170 |

Class 3 solvents are with low toxic potential. There is no need of health-based exposure limit. These solvents have PDEs of 50mg or more per days. Some of the common class 3 solvents includes Acetic acid, Acetone, Anisole, 1-Butanol, 2-Butanol, Butyl acetate, tert-Butylmethyl ether, Dimethyl sulfoxide, Ethanol, Ethyl acetate, Ethyl ether, Ethyl formate, Formic acid, Heptane, Isobutyl acetate, Isopropyl acetate, Methyl acetate, 3-Methyl-1-butanol, Methylethyl ketone, Methylisobutyl ketone, 2-Methyl-1-propanol, Pentane, 1-Pentanol, 1-Propanol, 2-Propanol and Propyl acetate.

ICH Q3C defines options for the definition of acceptance criteria for class 2 solvents

OPTION 1: tabulated limits, calculated based on a TDI (Tolerable Daily Intake) of 10 g of the product.

OPTION 2: Products that are administered in doses greater than 10 g per day should be considered under Option 2.

There are some solvents for which no adequate toxicological data was found. Example of such solvents are 1,1-Diethoxypropane, Methylisopropyl ketone, 1,1-Dimethoxymethane, Petroleum ether, 2,2-Dimethoxypropane, Trichloroacetic acid, Isooctane, Trifluoroacetic acid, and Isopropyl ether.

Selection of solvents for the purpose of manufacturing of pharmaceuticals is the important step in pharmaceutical industries.

Therefore, the basic knowledge of limits and toxicities will help in optimum use of solvents. The aim is to reduce use of solvents that have toxicities and adverse effect on the environments. Various steps should be taken and policies to be made for the use and managements of solvents.

**References:**

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