



From Utility to Risk: Chlorinated Solvents and Their Alternatives in Drug Design

Dr. Bandana Dwivedi¹ and Dr. Shailendra Singh²

¹Department of Chemistry, T.D.P.G. College, Jaunpur (UP)

²Department of Chemistry, T.D.P.G. College, Jaunpur (UP)

ARTICLE INFO	ABSTRACT
Article history: Received 16 October 2021 Received in revised form 20 November 2021 Accepted 23 November 2021 Available online 02 December 2021	The usage of solvents is an integral part of pharmaceutical and medicinal chemistry and is applied at virtually all stages of drug discovery and development such as synthesis, extraction, purification and formation. Chlorinated solvents among other varieties of organic solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane have played a prominent role due to their exceptional solvation properties, chemical stability and good physical characteristics.
Keywords: Chlorinated solvents, drug design, pharmaceutical synthesis, medicinal chemistry,	Their extensive usage has greatly facilitated the development of pharmaceutical research and manufacturing. However, increasing scientific studies revealed that chlorinated solvents may cause serious harm to the health of people and the environment. The issues of toxicity, carcinogenic properties, occupational exposure and long-lasting environmental effects stimulated pharmaceutical companies to seek alternatives to chlorinated solvents. This paper analyzes the shift from usefulness of chlorinated solvents to their hazards and explores the issue of emergence of green solvents in drug designing and pharmaceutical synthesis.

1. Introduction

Nearly all steps involved in drug discovery and development rely on the right solution or reaction medium, which in the pharmaceutical and medicinal chemistry field usually implies utilizing solvents to dissolve active substances and to facilitate separation, reaction and extraction. It is estimated that these processes require solvents to comprise some 80-90% of materials involved in medicinal and pharmaceutical manufacturing processes [1].

In medicinal chemistry, certain chlorinated solvents, such as dichloromethane (DCM), carbon tetrachloride (CCl₄), chloroform, and 1,2-dichloroethane (DCE) historically played a key role because of their remarkable physicochemistry, having a moderate degree of polarity and remarkable solvent strength as well as moderate non-combustibility, suitable for a wide range of applications in the industry [2].

Chlorinated compounds, on account of facilitating efficient procedures for extraction and participating as reagents, were for some decades believed to be inseparable partners for medicinal chemists. Yet, to their overuse and the consequent problems they represent in terms of their toxicity and environment pollution have over the last two decades given rise to the growing number of

evidence linking to such chemicals associated with liver, kidney lesions, neurological disorders and even cancers [3].

At the same time, several evidence reported the long persistences and contaminate the soil and ground water systems [4], in which the green chemistry approach that aims at decreasing and eliminating hazardous chemicals becomes a very important direction.

2. Utility of Chlorinated Solvents in Drug Design

Their ubiquity within medicinal chemistry is generally explained by the useful ensemble of properties they present. The combination of excellent solvating properties with high chemical stability and beneficial physical attributes has rendered chlorinated solvents useful in many of the synthetic transformations involved in the production of medicines.

2.1 Excellent Solvating Ability

There are number of reasons which attribute the use of chlorinated solvents, and one of the primary is the ease with which these substances are able to dissolve the variety of organic compounds which are required. Dichloromethane and chloroform are both classed as intermediates with regard to polarity, which means they are equally competent at dissolving relatively polar and less polar species which can be made up of a vast assortment of molecules.

The same advantage apply to a plethora of compounds such as heterocycles, alkaloids, lipophilic intermediaries and various reagents used in pharmaceuticals [5].

2.2 Chemical Stability and Inertness

Finally, chlorinated solvents are also reasonably inert both chemically. Most of chlorinated solvents neither participate in unwanted side reactions nor readily decompose in the presence of acid or alkali. Such property of many chlorinated solvents becomes highly valuable in a number of multistep reactions where reliable and reproducible experiments under specified conditions are of critical interest [6].

2.3 Favourable Physical Properties

Chlorinated Solvents' other useful characteristics. Chlorinated solvents often offer favorable physical properties, for example, the high volatility of dichloromethane-it has a boiling point of roughly 40° C-allows the solution to evaporate and the reaction to complete more readily than it might with solvents with higher boiling points. This speeds up the research or production process, therefore improving laboratory and plant efficiency.

Table 1. Important Chlorinated Solvents Used in Drug Design

Solvent	Boiling Point (°C)	Major Applications	Relative Toxicity
Dichloromethane	39.6	Extraction, synthesis, purification	Moderate
Chloroform	61.2	Spectroscopy, extraction	High
Carbon Tetrachloride	76.7	Historical cleaning and synthesis	Very High
1,2-Dichloroethane	83.5	Intermediate synthesis	High

That is likely why they have become so prevalent in this drug manufacturing: these solvents strike a useful balance between volatility, solvency and chemical stability. Yet, the same properties make them environmentally lasting and toxic in their workplaces.

2.4 Extraction Efficiency

Due to immiscibility with water and appropriate partition coefficients, chlorinated solvents are widely employed in the technique of liquid-liquid extraction. The high selective extraction properties of these compounds allow a wide use in the separation and purification methods of the compounds [7].

2.5 Compatibility with Pharmaceutical Processes

A similar success has been observed in reactions with a lot of useful transformations for pharmaceuticals like for example reactions in

Friedel-Crafts reactions, halogenation reactions, synthesis of peptide drugs or their purification (purification of active ingredients) [8].

3. Risks Associated with Chlorinated Solvents

Though these chlorinated solvents have made an undeniable mark in drug development, accumulating information about harmful effects raises red flags for their future use.

3.1 Human Toxicity

Generally, most chlorinated solvents easily penetrate the body, either via inhalation, dermal absorption, or inadvertent ingestion. Excessive exposure might lead to CNS depression, impaired renal, and hepatic function, increased respiratory rate, as well as significant and acute disturbances in heart functions [9].

Table 2. Major Health Hazards of Chlorinated Solvents

Solvent	Primary Target Organ	Possible Health Effects
DCM	Liver and CNS	Dizziness, hepatotoxicity
Chloroform	Liver and Kidney	Carcinogenicity, organ damage
CCl ₄	Liver	Severe hepatotoxicity
DCE	Kidney and Liver	Neurological impairment

Based on the established toxicological profiles of these compounds, any benefits they offer in the chemical synthesis application must be seriously evaluated in conjunction with possible risks.

3.2 Carcinogenic Potential

It is established from the various toxicology studies that some chlorinated solvents can act as human carcinogens. In animal tests chloroform can act as a carcinogen and the substance has been put forward as a potential human carcinogen, by the IARC, since 1974, by the German Mak and American MSHA regulations. Carbon tetrachloride has also been considered to act as mutagenic and to be a carcinogen by various researchers [10]. Due to this, most of the regulatory agencies around the world have made the regulations to restrict the use of such products more rigid.

3.3 Environmental Persistence

Another serious problem caused by chlorinated solvents that makes these types of chemical compounds is their persistence in the environment. While many types of solvents can be degraded in nature, the chemical characteristics of chlorine makes some of them persist in groundwater systems or soil. Long persistence leads to severe pollution problems for the remediation of soil, water, etc. Systems [11].

3.4 Atmospheric Effects

Various chlorinated products are released also contribute to atmospheric decomposition. Among them, carbon tetrachloride has the ability to deplete ozone and environmental problem. For instance, it causes the creation of photochemical smog, as well as atmosphere poisonous.

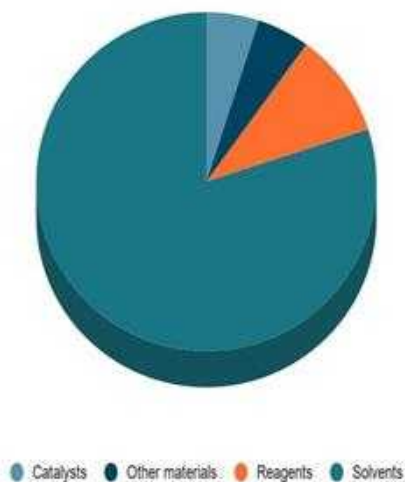
3.5 Occupational Hazards

From an occupational health standpoint, the repeated exposure is a second leading concern. Individuals who work in pharmaceutical and other factories in which chlorinated solvents are used complain of headaches, light headed ness, lung irritation and mental impairment after they have worked with these compounds for a number of years. Even more insidious long-term occupational exposure can even promote long- term cancer risks and health effects [13].

Based on the above observations it appears that while there is still some valid need for these compounds, these factors combine to pose a challenge for the environment as well as the health of the general populace.

4. Solvent Waste Generation in Pharmaceutical Manufacturing

The pharmaceutical industry is known as one of the biggest contributors to solvent waste. As much as 60-80% of the total mass of waste generated in processes utilized by the pharma industry is made up of solvents [14]. It is due to high usage of the solvents that choice of the proper solvent has turned into one of the most important issues to address in Green Chemistry.



Given the tremendous quantities of waste solvent produced by pharmaceutical businesses, the search for more secure and eco-friendly substitutes is more acute than ever. To significantly improve overall green and overall production, process designers

could focus on lowering the consumption of solvents and also by changing harmful to more safer options.

5. Green Chemistry and Sustainable Drug Design

Green chemistry grew as the prevailing scientific and educational paradigm that guided to reduce and avoid the presence and creation of chemicals that may harm humans and ecosystems [15]. Some major principles that this paradigm follows include avoiding waste production and preventing its generation; use the most energy-efficient reactions; use renewable starting materials; and use environment-friendly conditions for the chemical reaction.

In the area of pharmaceuticals production, replacement of solvents became a well-established measure to apply green chemistry in the most efficient way, the fact that, besides protecting the environment, safer solvents reduce workers exposure to hazardous agents and make them compatible for an easier approval by regulatory bodies [16].

6. Alternatives to Chlorinated Solvents in Drug Design

From 2000 to 2019, more efforts have been focused on safe and sustainable solvent systems to be used as substitutes to chlorinated solvent systems without sacrificing any synthetic efficiency.

Alternative Solvent	Source	Advantages	Limitations
Water	Natural	Non-toxic, inexpensive	Limited solubility
Ethanol	Renewable biomass	Biodegradable, safe	Flammability
Ethyl Lactate	Fermentation products	Biodegradable, renewable	Higher cost
Supercritical CO ₂	Carbon dioxide	Non-toxic, recyclable	Specialized equipment
Ionic Liquids	Synthetic salts	Low volatility	Expensive
Deep Eutectic Solvents	Natural components	Biocompatible	Limited industrial data
Glycerol	Biodiesel by-product	Low toxicity	High Velocity

Table 3. Green Alternatives to Chlorinated Solvents

As is clear it may be that there isn't one solution to replace chlorinated solvents in all pharmaceutical processes. The type of green solvents to be used for specific process conditions varies depending on economic costs, and impact on the process and the environment.

7. Water as Green Solvent

Water is considered the most green solvent for several reasons, such as their natural availability, low cost, non-flammability, and largely negligible toxicity. Developments in medicinal chemistry have shown water being useful for many catalytic transformations, as well as for multicomponent reactions, microwave accelerated synthesis, and biotransformations [17].

Water's poor miscibility with numerous drug precursors limits its scope as universally adaptable to all pharmaceutical steps; nevertheless, it's probably one of the most promising substitutes for greener pharma industrial processes.

8. Ethanol and Bio-Based Solvents

Due to its renewable resource origin, low toxicity, biodegradable, simple recovery, and environmental regulations, ethanol has attracted much interest in the area of green-solvent manufacturing processes in pharmaceuticals [22–24].

The most recently reported green replacement, ethyl lactate has proven successful as a replacement for dichloromethane for many extraction and purification processes [18]. By exploiting bio-derived solvents, modern pharmaceutical design and implementation must balance environmental friendliness and synthesis efficiency.

9. Supercritical Carbon Dioxide

Supercritical fluid of CO₂ has properties of liquids and gases, and its extraction performance is high. Supercritical CO₂ has been used in the field of drug delivery as the tool of particle size control, encapsulation of drugs, the purification process and the process of the crystal reformation [19].

The primary benefit of its use, like non-toxicity, noncombustible and reusable in nature, can contribute to environmentally sound processes [26].

But the special equipment which required pressure above 0.073 mPa is still limited to applying in this area.

10. Ionic Liquids and Deep Eutectic Solvents

Ionic liquids are a class of salts which are liquid in room and moderate temperatures, have a very high vapor pressure, and very low stability towards thermal decomposition and adjustable properties [20], have proved to be suitable in organic synthesis, catalysis, and in pharmaceutical applications.

Similarly, deep eutectic solvents, and natural deep eutectic solvents are novel alternative media due to lack of toxicity, abundant resources and excellent dissolving properties. Based on reports [21], their enhanced solubility and increased stability of low solubility drugs and natural products were investigated.

11. Comparative Assessment of Chlorinated Solvents and

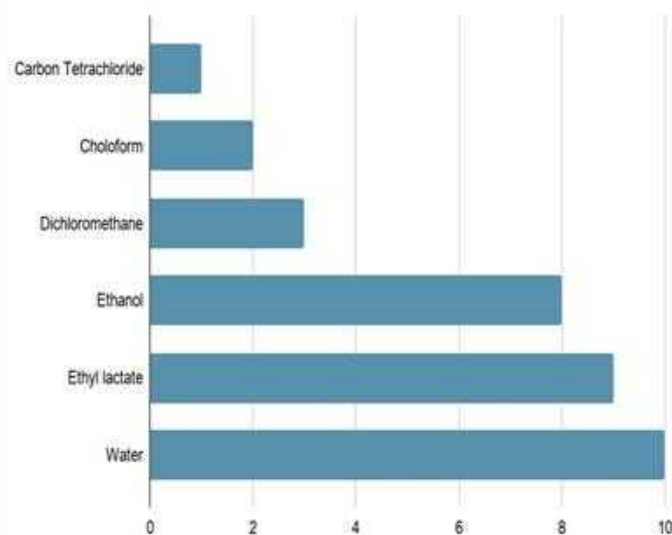
Parameter	Chlorinated Solvents	Green Alternatives
Toxicity	High	Low
Environmental persistence	High	Low
Biodegradability	Poor	Good
Renewability	Non-renewable	Mostly renewable
Worker safety	Moderate to poor	Good
Regulatory acceptance	Decreasing	Increasing
Waste generation	High	Reduced

Their Alternatives Table 4. Comparative Assessment

Relative Sustainability Ranking

Relative sustainability of solvent systems.

Illustrative sustainability scores (1–10) based on toxicity, renewability and environmental compatibility.



Overall, the evaluation confirms the increased preference of green solvents in pharmaceutical development. While chlorinated solvents still maintain relevance in niche scenarios, the environmental and human safety advantages associated with cleaner solvent options will drive their widespread adoption in next generation drug discovery endeavors.

12. Conclusion: -

Since chlorinate solvents possess good solvating properties and stability in chemical reaction and are of versatile use in all aspects in modern pharmaceuticals. The importance of using chlorinate solvent in the fields of drug design and synthesis, in medicine is well known.

Nevertheless, an extensive body of literature has shown many advantages, while, it is accompanied with great drawback including the toxicity of health hazard, Occupational Safety and Health Administration's Permissible Exposure Limit, a threat to carcinogens, as well as environmental non-degradability and non-bioaccumulated etc.

Between 2000 and 2019, solvent substitution in drug discovery process has undergone a revolutionary upheaval driven by the guiding of the green chemistry chemistry paradigm. Water, ethanol, ethyl lactate, supercritical carbon dioxide, ionic liquids, and deep eutectic solvents have received attention and demonstrated their capacity to lessen the environmental impact to satisfy an acceptable synthetic efficacy. Consequently, switching from chlorinated solvent to greener solvent signifies more than simply switching the reaction environment.

It represents a larger paradigmatic shift, where in modern drug design, innovative efficient development and efficiency need to balance in with environmental sustainability and human safety. The ongoing improvement and deployment of eco-friendly solvent systems will have considerable future influences to drug design and pharmaceutical production.

References: -

1. Nelson WM. Green Solvents for Chemistry: Perspectives and Practice. Oxford University Press; 2003.
2. Anderson NG. Practical Process Research and Development. Academic Press; 2000.
3. Constable DJC, et al. Green Chem. 2007;9:411–420.
4. Fortunak JM, et al. Future Med Chem. 2009;1:571–583.
5. Sheldon RA. Green Chem. 2007; 9:1273–1283.
6. Dunn PJ, Wells AS, Williams MT. Green Chemistry in the Pharmaceutical Industry. Wiley-VCH; 2010.
7. Butters M, et al. Chem Rev. 2006;106:3002–3027.
8. Zhang W. Chem Rev. 2006; 106:2583–2603.
9. Fortunak JM. Curr Opin Drug Discov Devel. 2007; 10:651–659.
10. International Agency for Research on Cancer (IARC). Monograph on the Evaluation of Carcinogenic Risks to Humans. 2016.
11. United States Environmental Protection Agency (EPA). Toxicological Review of Dichloromethane. Washington DC; 2011.
12. World Health Organization (WHO). Guidelines for Drinking-Water Quality. Geneva; 2011.
13. United Nations Environment Programme (UNEP). Environmental Effects of Ozone Depletion. Nairobi; 2014.
14. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Chlorinated Solvents. Atlanta; 2017.
15. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. Oxford University Press; 1998.
16. Gupta P, Mahajan A. RSC Adv. 2015;5:26686–26705.
17. Li CJ, Chen L. Chem Soc Rev. 2006;35:68–82.
18. Clark JH, Tavener SJ. Org Process Res Dev. 2007; 11:149–155.
19. DeSimone JM. Science. 2002; 297:799–803.
20. Plechkova NV, Seddon KR. Chem Soc Rev. 2008;37:123–150.
21. Jeliński T, Przybyłek M, Cysewski P. Pharmaceuticals. 2019; 11:75.
22. Prat D, Hayler J, Wells A. Green Chem. 2014;16:4546–4551.