2026 Volume: 01 Issue: 07 ISSN 1671-2838 Page No: 263-280

Pharmaceutical Care and Research

https://pcrjournal.com

Review Article

Volume: 01
Issue: 07

A REVIEW SOLVENT RECOVERY AND RECYCLING IN PHARMACEUTICAL MANUFACTURING

Sanskruti. S. Mali[1], Dr. Prasad V. Patrekar[2], Shrirang V. Kharmate[3*], Satyajeet R. Jagdale[4], Pradeep C. Patil[5], Pratibha P. Shingade[6].

[1]Student, [2]Principal, [3]Assistant Professor, [4]Assistant Professor, [5]Assistant Professor, [6]Assistant Professor.

Eklavya College of Pharmacy, Tasgaon, Maharashtra, India.

Article Received: 23 August 2026
Article Revised: 11 September 2026
Published on: 01 October 2026

***Corresponding Author: Shrirang V. Kharmate**
Assistant Professor, Eklavya College of Pharmacy, Tasgaon, Maharashtra, India.

DOI: https://doi-doi.org/101555/ijpcr.9770

ABSTRACT

Organic solvents are a key component of pharmaceutical manufacturing and constitute 50-90% of the total mass of non-active substances employed in the production of active pharmaceutical ingredients (APIs). Although solvents are not usually used as such in the reaction, their high consumption leads to huge amount of wastes being generated, which makes the pharmaceutical manufacturing the most wasteful branch of the chemical industry with the E-factors of 25-100 kg of waste per kilogram of the product. Traditionally, only 28% of the waste pharmaceutical solvents were being recovered and reused whereas the rest of the waste was burnt, which led to enormous energy consumption, generation of greenhouse gases, and expenses. Solvent recovery methods include batch and continuous distillation, azeotropic and pressure-swing distillation, pervaporation, organic solvent nanofiltration, and adsorption. In addition, the paper discusses physical and chemical properties which define solvent separation, solvent design guidelines, and quality of the solvent recovery process required for successful implementation of the solvent recovery process in the pharmaceutical process. Examples of case studies of industry leaders such as Pfizer, Bristol-Myers Squibb, and Novartis provide evidence of the environmental and economic benefits of the solvent recovery. Life-cycle emission reduction is reported at 74-98% and the cost savings of 69-99% for a particular waste stream. Payback periods of the solvent recovery systems for several solvent streams recovery are 1.8-4.5 years, which guarantees internal rate of return exceeding investment hurdle rates. Consequently, solvent recovery and recycling are efficient approaches to reduce pharmaceutical wastes, energy consumption, emissions, and the cost of pharmaceutical production.

KEYWORDS: Solvent recovery, solvent recycling, green chemistry,ICH Q3C, guidelines for solvent selection.

1. INTRODUCTION

1.1 Importance of Solvents in Pharmaceutical Manufacturing

Solvents are the major constituent by mass of an active pharmaceutical ingredient (API).Although a solvent normally is not a reactant in a reaction, it plays various important roles in the synthesis process such as providing a reaction medium, facilitating heat dissipation in exothermic reactions, reducing the viscosity of the reaction mixture, and allowing selective extraction and purification of the API. It is estimated that solvents constitute 50% to 90% of the total mass consumed and about 60% of the process energy consumed in the production of an API[1].

The sequential/batch process for the production of pharmaceutical drugs involves a number of unit operations in the form of a liquid phase reaction where solvents act as reaction media, as well as media for subsequent purification, crystallization and cleaning processes. Due to the sequential character of API production through the use of numerous solvents on each stage of the process and the non-consumptive character of solvents, the pharmaceutical industry belongs to those industries having the highest E-factor (the amount of waste/kg of the product) – up to 25 to 100 kg/kg of waste within the chemical industry [2]. According to the US TRI reporting system, in a year there is more than 88-90 million kg of solvent waste from the pharmaceutical industry, out of which about 75-83 % is made up by organic solvent, and out of the top 10 solvents used, 83% of the total solvent waste is generated [3].

1.2 The Reasons for Usage of Huge Amounts of Solvents

Reaction Medium: Organic reactions taking place during drug production occur in the homogeneous liquid phase and thus require a considerably greater amount of solvent compared to the amount of the reactants.

Multi-step Synthesis: The process of synthesis of an active pharmaceutical ingredient involves several reactions, and each step requires its own amount of the solvent. Thus, the solvent-to-product ratio becomes rather high in such cases.

Purification & Crystallization: Recrystallization of the API in the pharmaceutical quality occurs repeatedly, and thus the amount of solvent used is rather large in order to dissolve the ingredient and re-precipitate it.

Dilution due to safety concerns: Solvent contributes to the dilution of exothermic species in order to minimize the risk of uncontrolled chemical reactions.

Equipment and flexibility: Operations in liquid phase provide a high degree of equipment flexibility and allow using one and the same reactor trains for many different reactions. However, such flexibility is achieved due to the large amount of solvent required for the rinsing of the reactors.

Historical/regulatory inertia: once a synthetic procedure and its solvents have been proven and registered by regulatory authorities, changing solvents would involve additional costly proving; therefore, historical (and not necessarily optimal) solvents continue being used in large quantities.[4]

Solvent recovery – reusing the recovered solvent instead of buying new material and incinerating the waste – is an implementation of two out of the Twelve Principles of Green Engineering formulated by the American Chemical Society: prevention of waste versus treatment and maximization of mass and energy efficiency. In this review, we discuss advantages of solvent recovery from technical, economical and ecological point of view based on comparisons of solvent selection guides, solvent recovery process design and optimization, solvent recovery system approaches, industrial practice and solvents chemistry basics. [5].

2. Types and Classification of Solvents Used in Pharmaceutical Manufacturing

Selection of solvent is not only about dissolution of the reactant. Macroscopically solvents can be classified by their physical parameters such as boiling temperature, density and relative dielectric constant. Microscopically the classification includes the values of dipole moment, polarizability and number of hydrogen bond donors/acceptors. "Like dissolves like" empirical rule has been quantified with solubility parameters (Hildebrand, Hansen), solvent chromic polarity scale (Kamet-Taft, Reichardt's $E_I(30)/E_I^N$), thus allowing quantitive comparison and replacement of solvents. Chemically solvents can be classified by the nature of intermolecular interactions and divided into molecular liquids (the majority of currently used solvents, including volatile organic compounds, or VOCs), ionic liquids (molten salts) and atomic liquids (low-melting metals) [6]. Regulation-wise, solvents are classified according to the toxicological risk of each solvent by ICH Q3C residual solvent guideline. This is the most widespread classification in the industry because it determines the allowed level of residual solvent in a final drug product. [7]

Table 1: Classification of residual solvents based on the ICH Q3C(R7) guideline.

ICH Class	Definition	Representative Solvents	Regulatory Limit
Class 1	To be avoided — known human carcinogens or environmental hazards	Benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, 1,1,1-trichloroethane	2–1500 ppm (very tightly restricted)
Class 2	To be limited — non-genotoxic animal carcinogens or agents of other significant, often reversible toxicity	Acetonitrile, methanol, dichloromethane, hexane, toluene, pyridine, tetrahydrofuran, N-methyl pyrrolidone	PDE-based limits, typically 50–4500 ppm
Class 3	Low toxic potential; no health-based exposure limit needed	Ethanol, acetone, ethyl acetate, isopropanol, 1-butanol, heptane, triethylamine	≤5000 ppm (0.5%) without special justification
Not classified	Insufficient toxicological data available	2-Methyltetrahydrofuran, isopropyl ether, petroleum ether	Manufacturer must justify residual level

With respect to the functional aspects of solvents employed in various unit operations in the pharmaceutical industry, the following classification based on the chemical nature of solvents is possible (Table 2). [8]

Table 2: Functional classification of solvents employed in the pharmaceutical industry.

Functional Category	Typical Solvents	Primary Use
Protic / alcohols	Methanol, ethanol, isopropanol, n-butanol	Reaction medium, recrystallisation, washing
Esters	Ethyl acetate, isopropyl acetate, n-butyl acetate	Extraction, chromatography, crystallization
Ketones	Acetone, methyl ethyl ketone, methyl isobutyl ketone	Recrystallisation, cleaning, extraction
Ethers	THF, diethyl ether, MTBE, 2-methyl-THF	Organometallic reactions, extraction
Hydrocarbons	n-Hexane, heptane, toluene, xylene	Extraction, non-polar reaction medium
Chlorinated solvents	Dichloromethane, chloroform	Extraction, chromatography (increasingly restricted)
Dipolar aprotic	DMF, DMAc, NMP, DMSO	Nucleophilic substitution, coupling reactions
Water / aqueous	Water, aqueous buffers	Work-up, biphasic and biocatalytic reactions

3. Solvent Selection Guides and Ranking Systems

Several leading pharmaceutical companies and pharmaceutical consortia have produced solvent selection guidelines intended to aid chemists to choose safer and sustainable solvents: Pfizer, GlaxoSmithKline (GSK), AstraZeneca (AZ), Sanofi, and the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCI-PR), then followed by IMI-CHEM21 consortium. Each of the developed guidelines has been affected by the specific corporate philosophy and includes such criteria as safety, occupational health, environmental performance, and quality as well as industrial factors like boiling point, freezing point, density, and recyclability [9].

3.1 Structural Differences Between Guides

Pfizer: a simple two-page guideline that divides solvents into three classes – preferred, acceptable, and undesirable and recommends replacement of undesirable solvents.

AstraZeneca: table with evaluation of 46 solvents on basis of ten criteria (2 safety, 1 health, 7 environmental including life cycle).

GlaxoSmithKline: two criteria on safety, one on health, three criteria on environment (including life cycle) plus regulatory warning signs.

GCI-PR: one criterion on safety, one on health, and three criteria on environment (air, water, waste).

Sanofi: four level system: recommended, recommended for substitution, requested for substitution, banned. One of the few that provides explicit preference ranking.

CHEM21: consensus-based harmonized guideline that was introduced in order to eliminate discrepancies among earlier company-specific guidelines.

The four guides were then combined and normalized to produce a simpler preference ranking for 51 commonly used solvents into recommended, problematic, hazardous and highly hazardous categories. Consensus was obtained in 39% of the cases while 39% were near agreement. 8% (2-

methyltetrahydrofuran, chlorobenzene, acetonitrile, N-methyl pyrrolidone) showed significant discrepancy, which was at least partially resolved by regulatory classification (for example, CMR—carcinogenic, mutagenic, reprotoxic hazard statement EU GHS). 33% of the solvents could not be ranked due to actual discrepancy in institutional criteria preferences. [10]

3.2. Consequences for Solvent Recovery

Firstly, solvents that have been classified as hazardous or highly hazardous such as (DMF, DMAc, NMP, benzene, 1,2-dichloroethane, diethyl ether) will be ideal candidates for substitution. If substitution is not possible then they will be subjected to harsher recovery techniques since the procurement and disposal costs will be minimal. Secondly, the degree of ease of recovery of the solvents is dependent on factors such as boiling point difference, formation of azeotropes and miscibility, and is thus another green design factor. During process design, chemists should choose solvent pairs that will make distillation easier. Solvents with a boiling range of about 70-139 degrees celsius offer a balance between ease of recycling via distillation and generation of volatile organic compounds [11].

4. Challenges

4.1 Environmental Problems

Greenhouse gas and CO2 emission: The incineration which is one of the primary methods of disposing used organic solvents produces large amounts of CO2 and other combustion products; Life cycle assessments have established that CO2 accounts for 74-99% of emissions of solvents from production to disposal.

Air, water and soil pollution: Volatile organic compounds result in photochemical smog formation while the inadequately treated waste effluents cause aquatic toxicity, biological oxygen demand and ozone layer depletion for chlorinated solvents.

Resource depletion: Manufacturing solvents is resource intensive; the cumulative energy demand (CED) for manufacturing various solvents ranges between 40MJ/Kg for methanol and above 270 MJ/kg for tetrahydrofuran [12].

4.2 Health and Safety Issues

Occupational exposure: The majority of process solvents pose health risk being flammable, irritating, neurotoxic, hepatotoxic or reproductive toxicants including DMF, DMAc, NMP which are also reprotoxic and fall into the category of the substances of very high concern on the REACH candidate list.

Explosion/fire hazard: The usage of low flashpoint solvents (diethyl ether, THF, hexane) requires rigorous containment, nitrogen purging, and proper grounding of equipment.

Peroxide formation: ethers (diethyl ether, di-isopropyl ether) can form explosive peroxides upon prolonged storage. [13]

4.3 Economic and Regulatory Issues

Costs associated with the purchase, storage, and disposal of hazardous waste of the pure solvent are an operational expense.

Regulatory constraints: regulatory measures such as the Reach regulation have put restrictions on the use of some solvents (toluene, dichloromethane, and chloroform) above certain concentration levels and hence reformulation and process modification.

Solvent Residue Limitations: limitations according to ICH Q3C require that drug products should not have any residual solvents to a very low level [14].

5. Solvent Recovery and Recycling: Definitions and Basic Principles

5.1 Solvent Recovery

Solvent Recovery: the separation of a used solvent from a mixture of by-products, contaminants, water, or co-solvents to recover pure solvent. This is done based on the difference in physical properties (boiling points, polarity, molecule size, or selectivity to a membrane or adsorbent) [15].

5.2 Solvent Recycling

Solvent Recycling involves using the recovered solvent again for performing useful work. It is the general term for the practice of using recovered solvent again in various applications, including use in the same process where it was originated (closed loop recycling) or use of the solvent in another process in the same facility, or even transfer to third parties as generic solvent for use in non-pharmaceutical activities. In other words, solvent recovery is only one of the steps in the process of recycling. [16]

5.3 Basic Principle of Solvent Waste Management

The basic principle of management of solvent waste is the waste management hierarchy, where priority is given to the prevention/reduction of the solvent waste at its origin of generation; recovery and reuse/recycling of any remaining amount; followed by the treatment and disposal of waste solvent (through incineration with energy recovery). It has been proved through the life cycle assessment (LCA) analysis that recovery and reuse/recycling of solvent waste prevents emissions not only from manufacturing of the same quantity of new solvent but also emissions from incineration of the same quantity of waste solvent. This gives double advantage for solvent recovery. [17]

Table 3: Solvent Recovery vs Solvent Recycling.

Aspect	Solvent Recovery	Solvent Recycling
Definition	Physical separation/purification of solvent from a waste mixture	Overall management practice of returning recovered solvent to productive use
Scope	A unit operation (e.g., distillation, pervaporation)	A system-level strategy including recovery, quality release, and reuse decision
Output	Purified solvent stream meeting a defined specification	Solvent placed back into a process, sold, or repurposed
Objective	Achieve required purity and remove impurities/water	Close the material loop and minimize net virgin-solvent demand
Example	Batch distillation of an IPA/water waste stream	Distilled IPA returned to the same crystallization step at a Pfizer manufacturing site

6. Process of Solvent Recovery

Generalized Solvent Recovery Process which applies to all types of pharmaceutical waste solvents includes the following steps:

Solvent waste segregation and collection: Different solvent waste streams originating from various unit processes are segregated as far as possible since mixing incompatible or very different solvent waste streams makes their further treatment difficult and costly.

Pre-treatment: Gross solids, residuals of catalysts (activated carbon, palladium) and immiscible water and organic layers are separated from the process flow before it is fed to the primary treatment facility.

Primary recovery: A major proportion of the solvent is stripped from the high-boiling fraction and water by processes like distillation, typically batch-wise or continuously.

Secondary recovery: In situations where the required level of purity cannot be achieved solely through the process of distillation (as in the case of an azeotrope), a complimentary process such as pervaporation, membrane separation or adsorption is used.

Quality testing: The recovered solvent is analyzed for identity, purity, moisture, unreacted solvents and other impurities.

Reuse/recycling: Recovered solvent, if within specifications, may be reused/re-cycled back to its parent process, used in a low-grade process or sold as generic solvent; recovered solvent not up to specification standards can be reprocessed or incinerated [18].

7. Solvent Recovery Process Technologies

The process of distillation is used in almost 95 percent of the applications related to solvent recovery in industry, and also is the most common process used for solvent recovery in the pharmaceutical industry, owing to consistent recovery and purity levels [19].

7.1 Distillation-Based Methods

Simple/Batch distillation: applicable to binary or dilute solvent separations wherein the solvent boils much lower than impurities.

Fractional Distillation: uses packed/trayed columns in separation of solvents with similar boiling point.

Vacuum distillation: decreases the temperature of separation in order to prevent degradation of heat sensitive solvents or products. [20]

7.2 Membrane-Based Methods

Pervaporation (PV): it includes passage of one component (for example, water) in a vapour state through a selective but non-porous membrane (silicone or zeolitic membrane) due to the effect of vacuum or sweep gas in the permeate side. Owing to its solution-diffusion operating mechanism as opposed to vapor-liquid equilibrium, pervaporation is able to break azeotropes that cannot be separated by conventional distillation. Moreover, pervaporation is more energy efficient than azeotropic distillation in performing the same dehydration operation. [21]

Organic solvent nanofiltration (OSN)/solvent-resistant nanofiltration (SRNF): pressure-driven membrane processes that enable separation of dissolved components (active ingredient, catalyst, genotoxic impurities) from an organic solvent using size exclusion technique, hence, allowing solvent recovery and separation of high molecular weight solutes. [22]

7.3 Adsorption-Based Methods

Adsorption: use of solid sorbents (activated carbon, synthetic resin, zeolites), which selectively absorb either the solvent or impurities from the waste liquid; sorbents' regeneration (thermal desorption or solvent washing). The fixed bed adsorption is becoming increasingly popular compared to batch adsorption since it reduces the solvent and adsorbent consumption as well as cleaning of containers filled with adsorbents [23].

Table 4: Comparison of main solvent recovery techniques used in pharmaceutical industry.

Recovery Technique	Principle	Best Suited To	Key Limitation
Batch/fractional distillation	Separation by relative volatility	Mixtures with sufficiently different boiling points	Cannot break azeotropes; energy intensive
Azeotropic / pressure-swing distillation	Entrainer addition or pressure-shift of azeotropic composition	Azeotropic mixtures (e.g., THF–water, ethanol–water)	Additional equipment/entrainer; higher capital cost
Pervaporation	Selective diffusion through a dense membrane	Dehydration/polishing after primary distillation; azeotrope-breaking	Membrane fouling; limited throughput at large scale
Organic solvent nanofiltration	Size-based rejection through a solvent-stable membrane	Removing high-MW impurities/catalysts from bulk solvent	Membrane solvent compatibility; flux decline over time
Adsorption (fixed-bed)	Selective binding to a solid sorbent, then regeneration	Trace impurity removal, decolorization, catalyst removal	Sorbent regeneration cost; capacity limits
Liquid-liquid extraction	Partitioning between two immiscible liquid phases	Recovering solvent from dilute aqueous waste	Generates a secondary waste stream (extractant)

8. Process Intensification and Software Tools for Recovery Design

8.1 Process Intensification

The idea behind process intensification is that multiple separation functions can be integrated in fewer pieces of equipment without losing its effectiveness. Thus, for example, a dividing wall column can be a substitution for two distillation columns in series with savings of operation and capital expenses in 20-50 percent of total cost and maintaining the capability of separating a multi-component mixture [24]. Switchable hydrophilicity solvents (SHSs) possessing the ability to alter polarity in the presence of CO2 and water are considered as a prospective technology in the field of distillation-free solvent recovery with significant energy savings, but still are at the initial stage of development in the industry [25].

8.2 R-SWEET and Related Toolboxes

Rowan University developed R-SWEET (Recovery of Solvent Waste Environmental and Economic Toolbox) - Excel based program combining Aspen Simulation Workbook (distillation simulations), pervaporation model and life-cycle inventories produced by Semipro and Eco solvent. With the help of R-SWEET program one can receive recommendations for solvent separation process selection considering thermodynamic properties of the binary mixture; simulate distillation and pervaporation processes of solvent recovery; calculate avoided Life-Cycle Emissions (LCEA) and Operating Cost Savings (OCS) in dependence of the reflux ratio and feed stage; and conduct the full cost analysis including pay-back period and IRR. One of the conclusions drawn from case studies using R-SWEET program was that heuristics applied in the design of distillation could lead to under- or overdesigning of a recovery column: the use of optimal reflux ratio calculated by the program in comparison with conventional heuristics (1.1-1.5x minimum reflux ratio) led to up to 49 percent increase in avoided emissions and up to 56 percent decrease in cost savings [26].

8.3 Superstructure-Based Optimization

The latest approach to formulate the problem of solvent recovery at the systems level allows creating the generic network of the solvent removal, recovery, purification and refining process with possible technologies (sedimentation, precipitation, centrifugation, distillation, aqueous two-phase extraction, pervaporation, microfiltration, ultrafiltration and nanofiltration) at each step in the form of a mixed-integer non-linear (or linear) programming problem solution of which gives the optimal solvent recovery route according to cost and emissions minimization considering constraints without sequential and iterative engineering judgments'. The system-level solvent recovery roadmap includes: problem formulation, superstructure generation, optimization, economic analysis (pay-back / IRR calculation using capital cost estimated using scaling laws) and sustainability analysis (LCA (ISO 14040/14044), Sustainable Process Index, Energy analysis, Techno-Ecological Synergy and GREENSCOPE of EPA) [27].

9. Solvent Recycling: Quality Testing and Reuse Criteria

To ensure that the recovered solvent is fit for further use in validated processes, it should be proven that the recovered solvent corresponds to the specified quality standard since any impurities present in the previous batch might influence reaction performance and pose the risks for patient safety.

10. Parameters Typically Tested

Identification: Identification via IR spectroscopy or refractive index/GC retention time.

Purity/Assay: Quantitative GC is the main analytical tool for measuring the purity of solvents and the residual solvents.

Residual by-products/Cross contamination: Analysis to confirm that the residual impurities from the previous stage of manufacturing or from the previous batch in the multipurpose facility are below acceptable limits.

Color/Observation: It's a simple yet effective analysis method for assessing degradation or contamination.

Non-volatile residue/TDS: Critical when the recovered solvent is contaminated with solid materials, salts, and catalysts.

pH/acid/alkali: particularly relevant to alcohols and esters, which can hydrolyze and oxidize when stored.

11. Reuse Criteria

The reclaimed solvent is considered to be reusable in the originating process provided that it satisfies, at least, the same specification as the equivalent virgin solvent used in the process or the scientifically proven lower specification for the application. Examples of reuse include in-process reuse (e.g. IPA reuse in the celecoxib process at Pfizer), demotion of use from critical to non-critical application like cleaning, resale as 'generic' or industrial grade solvent to another company or rejection, reprocessing and disposal of material failing to satisfy specifications despite reprocessing. As there will be always some residual solvents left in the drug substance or drug product, a solvent recovery process should also consider the ICH Q3C(R7) Permitted Daily Exposure levels. The solvent recovery process should be validated and documented as part of process validation. [28]

12. Case Studies: Industrial Applications and Techno-Economic Results

Industrial cases illustrate the potential benefits of solvent recovery by applying LCA and techno-economic analysis to quantify the benefit of a solvent recovery process addition to an already existing manufacturing process.

10.1 Bristol-Myers Squibb, Pfizer, and Novartis

Bristol-Myers Squibb (pilot-scale oncology API): the process step required dehydration of a THF-water intermediate mixture via constant volume distillation, consuming much THF as an entrainer.

Addition of pervaporation unit to distillation process allowed THF recovery and reuse in the process, reducing THF virgin material consumption and amount of THF required for incineration — 94% life-cycle emissions reduction (≈64.3 kg waste/kg API).

Pfizer (commercial-scale celecoxib, API for Celebrex): the large amounts of isopropanol (IPA) and water consumed in the final crystallization process were recovered through distillation-pervaporation-distillation process, achieving the purity needed for in-line reuse, the secondary waste was distilled and resold as a generic solvent — 91% life-cycle emissions reduction (≈24.1 kg waste/kg API).

Novartis (synthetic intermediate for a hypertension drug): Heck coupling reaction resulted in the formation of product mixtures which had to be purified by palladium removal using batch adsorption on activated carbon, generating huge amounts of waste of methanol-based solvent and spent adsorbent. Replacement of the batch adsorption with fixed bed adsorption on synthetic resin brought down the requirements of virgin solvent and adsorbent – with 91% of life-cycle emissions reductions (≈10.3 kg waste/kg intermediate).

Table 5: Summary of solvent recovery cases analyzed through cradle-to-grave LCA.

Case Study	Process Step	Recovery Technology Introduced	Emission Reduction
Bristol-Myers Squibb	THF/water dehydration (oncology drug, pilot-scale)	Pervaporation added to existing constant-volume distillation	94%
Pfizer	IPA/water recovery (celecoxib crystallization)	Distillation–pervaporation–distillation train; sale of generic solvent	91%
Novartis	Pd removal (Heck-coupling intermediate)	Fixed-bed adsorption replacing batch carbon adsorption	91%

From the above case studies it is clear that the reductions of the emissions due to reduced generation of the solvents and reduced combustion far exceed additional energy consumption required to operate the solvent recovery equipment. For BMS, the solvent recovery equipment actually decreased energy consumption of the process as less steam was consumed after reducing the amount of THF entrainer which needed heating and distillation. [29]

10.2 Pfizer Kalamazoo Low-Volume Waste Stream Study

Detailed case study, including actual data from the manufacturing process of Pfizer in Kalamazoo, MI, examined single, flexible, packed column batch distillation skid for the recovery of the solvents in three different low volume API waste streams: selectin (Revolution®), 72 wt.% acetonitrile / 28 wt.% acetone at 84,500 kg/yr.; nelfinavir (Varicent®), 86 wt.% IPA / 14 wt% THF at 78,700 kg/yr; and hydrocortisone (Tryptic-S®), 79 wt.% toluene / 8 wt% acetone / 10 wt% water / 3 wt% other organics at 296,000 kg/yr.

Table 6: Techno-economic and LCA results for the shared multi-purpose recovery skid with three low volume waste streams.

Case (API)	Waste Stream	Emissions Reduction	Cost Reduction	Payback / IRR
Selamectin	84,500 kg/yr acetonitrile/acetone	74%	83% ($234,000/yr)	8.8 yr / 8.7% (alone)
Nelfinavir	78,700 kg/yr IPA/THF	61%	69% ($99,000/yr)	n/a / −1.3% (alone)
Hydrocortisone	296,000 kg/yr toluene/acetone/water	98%	99% ($271,000/yr)	7.9 yr / 11.0% (alone)
All three (combined skid)	459,200 kg/yr total	85.3% overall	86.3% overall ($584,000/yr)	4.5 yr / 27.9%

In combining all three recovery units into one single recovery skid, overall life-cycle emissions were reduced by 85.3%, overall energy use was cut by 87.0%, and operating costs decreased by 86.3%. Combined investment payback period was 4.5 years, IRR during 10-year period was 27.9%, which represents a significant improvement compared to any individual waste stream analysis (Irr of nelfinavir was negative of −1.3%), and illustrates the feasibility of scheduling multiple waste streams using one recovery skid [20]. Life-Cycle Impact Assessment (Recipe method, Semipro) revealed reductions of 82.4% (human health), 85.1% (ecosystems), and 87.1% (resource depletion) impact categories, where the main contributors to this effect included lower toluene production and combustion. Sensitivity study of reflux ratio and feed stage optimization, performed on the same three case studies showed that selection of software-optimized reflux ratio over the heuristic one resulted in 21.4%–49.2% increase in lifecycle emissions saved and 21.4%–56.5% in operating cost reduction. In addition, all three cases combined resulted in IRR > 0. [30]

13. Legislation, Policy, and the Drivers of Solvent Recovery

Historically, regulations have been the primary motivating factor for solvent recovery in industry.

Table 7: Regulation Drivers of Industrial Solvent Recovery.

Year	Instrument	Jurisdiction	Relevance to Solvent Recovery
1973	Environmental Action programmed	European Community	First EC framework targeting waste reduction and recovery
1973	Polluter Pays Principle	European Community	Assigned clean-up costs to polluters, incentivizing waste minimization
1975	Framework Directive on Waste	European Community	Defined “waste”/“disposal”; promoted recovery and recycling
1976	Resource Conservation and Recovery Act (RCRA)	United States	Cradle-to-grave regulation of hazardous solid waste
1984	Hazardous and Solid Wastes Amendments (HSWA)	United States	Banned direct landfilling of hazardous liquid waste, spurring incineration and recovery
1989/2015	Environmental Protection Law	China	Established (and later tightened) pollutant discharge and monitoring standards
2008	Waste Framework Directive	European Union	Five-step waste hierarchy: prevention, reuse, recycling, recovery, disposal

14. Advantages of Solvent Recovery

Environmentally Friendly: eliminates both emissions from the production of the virgin solvent and emissions from the incineration of the solvent waste; reductions in the life-cycle emissions of 74-98% have been reported for some specific case studies from the pharmaceutical industry.

Reduction in Carbon Footprint: due to the combustion in the process of virgin solvent production and incineration, the process of solvent recovery eliminates such emissions.

Savings from operational costs: reduces the cost of purchasing the original solvent and incineration of the solvent waste; operational savings of 69-99% have been made for individual waste streams having excellent payback period of 1.8-4.5 years in case of multi-stream skid solutions.

Environmental regulatory compliance and sustainability objectives: will help in achieving the environmental regulation (like REACH) and sustainability goals of organizations.

Reduced reliance on the use of raw materials: it will help in reducing the dependence of the organization on the suppliers of the solvent due to its reuse.

Savings on energy use: this is because the solvent recovered does not need any kind of synthesis and the other changes made by the organization during the incorporation of the solvent recovery process can result in savings on energy use.

Reduction in waste generated: reduces the generation of waste by the company.

15.Challenges of Solvent Recovery

Azeotropes: many systems of solvents/water and solvents/solvents are azeotropic in nature, thus rendering conventional distillation unsuitable for separation.

Waste streams containing multiple components: pharmaceutical solvent waste streams typically consist of multiple solvents along with solids, catalysts, and other chemicals whose composition varies from batch to batch. Therefore, it is difficult to create an effective recovery method for such waste streams.

High costs of capital and operations: distillation columns, pervaporation membranes, and adsorption units are capital-intensive equipment that have to be justified by low pharmaceutical intermediate production.

Risk of contamination in multiproduct facility: equipment used for recovery of solvents for multiple pharmaceutical products increases the risk of product contamination by improper cleaning.

Need for qualification and validation of reused solvent: any recovered solvent used in GMP process needs qualification and validation with respect to its use in the process.

Membrane fouling: membranes used in pervaporation and nanofiltration could be fouled or even damaged due to contact with pharmaceutical wastewater streams.

Energy balance: while solvent recovery saves the resources used to produce new solvents, it consumes energy itself (in form of steam and electricity) which should be optimized in order to save energy spent on the process of high boiling point or complex solvents' recovery, e.g. THF.

Disadvantages of the general guides to solvent selection: as different guides provided by different companies award points according to different criteria and cut-offs, it may be difficult to reach an agreement whether the quality of recovered solvent is green enough for chemical reactions. [32]

16. Environmental Impact and Life-Cycle Assessment

Life-Cycle Assessment (LCA) is the most extensive method for solvent's environmental impact evaluation because it takes into account all the emissions that occur outside the boundaries of pharmaceutical plant – during solvent manufacture and its off-site incineration. In other words, LCA analysis evaluates not only emissions from inside the gate-to-gate boundary of the plant, but also emissions from the manufacture and destruction phases of solvents' lifecycle. It was calculated using Semipro and Eco solvent that cumulative energy demand (CED) for 1 kg of commonly used solvents varied between 40 MJ-eq (methanol) and 270 MJ-eq (THF), CO2 comprises 74-99% of all emissions during solvent's life cycle.

As the case studies analysis has shown, solvent recovery is not quite beneficial from an environmental point of view, if one speaks about gate-to-gate analysis – that means emissions which occur inside the boundary of battery limits of the manufacturing plant. Only the cradle-to-grave analysis, which includes reduction of emissions from solvent manufacture and destruction phases, shows the magnitude of potential environmental benefits which could reach up to 70% reduction of process emissions, when taking into account that solvents constitute 50-90% of mass in API manufacture.

Solvent selection guides prepared by GSK, Pfizer, Sanofi, ACS Green Chemistry Institute, CHEM21 consortium serve as a complementary tool to LCA approach since they allow chemists to choose, at the stage of design, those solvents which are easy to recover and inherently safe (for example, by avoiding use of halogenated and dipolar aprotic amide solvents and using alcohols and esters). [33]

17. Green and Neoteric Solvents: Prospects and Limits

In addition to molecular solvents, there are other types of "neoteric" or alternative solvents, such as supercritical fluids (primarily supercritical CO2), fluorosis (perfluorinated) solvents, and room temperature ionic liquids (RTILs) which are seen as more sustainable alternatives since they offer tunable solvating ability, zero vapor pressure, or easy recyclability. Nevertheless, based on the analysis of 577 molecular substances reported as solvents in solvent selection handbooks and in computer assisted solvent design databases, very few of the neoteric solvents are commercially viable and novel molecular solvents; the majority of compounds presented as "green" were known materials and claims of greenness lacked toxicological, ecotoxicological, and life-cycle justification. There is no solvent that is inherently or absolutely green - as much as there is no universal solvent ("alkahest") - and therefore solvent selection, including solvent recovery and recycling, should always be evaluated on a case-by-case basis taking into consideration application conditions, scale and disposal.

As far as the classes of so-called neoteric solvents – ionic liquids, deep eutectic solvents, fluorosis fluids, and supercritical fluids – they have not become widely used to replace traditional molecular solvents due to high costs, viscosity and difficulty of recovery, and in case of ionic liquids, due to lack of reliable toxicological/ecotoxicological information although these solvents are considered as archetypical green solvents. "Bio solvent" platforms utilizing biomass-based materials such as 2-methyltetrahydrofuran, dihydrolevoglucosenone (Cyrene®), Solera, levulinic acid derivatives etc. are seen currently as the most realistic platform towards sustainable solvents but encounter challenges such as feedstock availability and diversity, as well as energy/fertilizer input necessary for biomass production and processing. In general, the main conclusion regarding solvent recovery programs is that recycling and reuse of well-characterized and appropriately chosen solvents can be the most sustainable option for pharmaceutical producers in the near future instead of searching for new neoteric solvents which is rather speculative since it relies on non-proven distillation-free technology and does not provide clear life-cycle benefits. [34]

18. CONCLUSION

Despite being absolutely necessary in pharmaceutical production, due to the high volume and high energy usage in API synthesis process, solvents make the biggest contribution to the environmental footprint of this industry. Solvent wastes disposal creates environmental, occupational health and safety, and regulatory problems and usually leads to material and energy losses in the form of incineration. Solvent recovery and solvent recycling as a process of solvent reuse represent one of the most efficient and economic ways of mitigating such footprint.

There are several methods of solvent recovery, such as various types of distillation, pervaporation, membrane-driven nanofiltration, adsorption process which can be applied in combination; however, to ensure quality and reusability of the recovered solvents, it is necessary to perform rigorous quality checks for each batch before returning them back to the process. For example, solvent recovery in industrial companies such as Bristol-Myers Squibb, Pfizer, Novartis led to reduction of lifecycle emissions up to 90%. In addition, the results of techno-economic assessment of low-volume waste streams demonstrate that even if the projects aimed at low-volume streams are unprofitable individually (payback period from 1.8 to 4.5 years), if they are combined into one multi-purpose recovery skid, they become highly advantageous and economically attractive (high internal rate of return). Such advantage becomes evident only when the cradle-to-grave approach to the environment is taken into account.

The various solvent selection guidelines agree on the recommendation regarding the "recommended" and "highly hazardous" solvents; however, they do not agree on roughly one-third of the commonly used solvents; hence, the decision of the priority of solvent recovery must be made on a case-by-case basis by consulting the individual guides and the claims on "green" or "neoteric" solvents have to be considered cautiously. However, despite the various challenges that solvent recovery faces from both

technical, economic and regulatory standpoints, the evolution of environmentally safer solvents, the development of membrane and adsorption techniques as well as the advances in solvent selection and superstructure optimization software indicate the direction towards the sustainable future of solvent application in the pharmaceutical industry. The reuse of a well-characterized solvent is a very sustainable approach based on the available information.

20. REFERENCES

1. Constable DJ, Jimenez-Gonzalez C, Henderson RK. Perspective on solvent use in the pharmaceutical industry. Organic process research & development. 2007 Jan 19;11(1):133-7.
2. Sheldon RA. The E factor: fifteen years on. Green Chemistry. 2007 Nov 22;9(12):1273-83
3. Burlinson D, Koehrn K, Subramanian KR, Lu A. Are Environmental Regulations Working? A Visual Analytic Approach to Answering Their Impact on Toxic Emissions. In EnvirVis@ EuroVis 2016 Jun 6 (pp. 17-21).
4. Britton J, Raston CL. Multi-step continuous-flow synthesis. Chemical Society Reviews. 2017 Mar 6;46(5):1250-71.
5. Moura MB, Monteiro H, Alves C, Fernandes C, Amorim AC, Duarte AR, Burke AJ. The Bucherer-bergs reaction in deep eutectic solvents: Accessing Spiro-Oxindole-Hydantoins. Journal of Molecular Liquids. 2026 Feb 18:129390.
6. Reichardt C. Solvents and solvent effects: an introduction. Organic process research & development. 2007 Jan 19;11(1):105-13.
7. **7.**. Guideline Jimenez-Gonzalez C, Ponder CS, Broxterman QB, Manley JB. Using the right green yardstick: why process mass intensity is used in the pharmaceutical industry to drive more sustainable processes. Organic Process Research & Development. 2011 Jul 15;15(4):912-7.IH. Impurities: Guideline for residual solvents Q3C (R5). Current Step. 2005 Nov;4:1-25
8. Slater, C.S., Savelski, M.J., Carole, W.A., & Constable, D.J.C. (2010). Use of solvents and waste problems. In Green chemistry in the pharmaceutical industry (pp. 49–82). Wiley-V
9. Byrne FP, Jin S, Paggiola G, Petchey TH,
10. Prat D, Hayler J, Wells A. A survey of solvent selection guides. Green Chemistry. 2014 Sept 23; 16(10): 4546-51.
11. Slater CS, Savelski MJ. A method to characterize the greenness of solvents used in pharmaceutical manufacturing. Journal of Environmental Science and Health, Part A. 2007 August 31; 42(11): 1595-605.
12. Capello C, Fischer U, Hungerbühler K. What is a green solvent? A comprehensive framework for the environmental assessment of solvents. Green Chemistry. 2007 August 28; 9(9): 927-34.
13. Barton P.I. Solvent recovery opportunities in the pharmaceutical industry. Current Opinion in Drug Discovery and Development. 2000 November 1; 3(6): 707-13
14. Sheldon RA. The E-factor

15. Ahmad BS, Barton PI. Solvent recovery targeting. AIChE journal. 1999 Feb;45(2):335-49
16. Aboagye EA, Chea JD, Yenkie KM. Systems level roadmap for solvent recovery and reuse in industries. Iscience. 2021 Oct 22;24(10).
17. Savelski MJ, Slater CS, Tozzi PV, Wisniewski CM. On the simulation, economic analysis, and life cycle assessment of batch-mode organic solvent recovery alternatives for the pharmaceutical industry. Clean technologies and environmental policy. 2017 Dec;19(10):2467-77
18. Manso-Álvarez, V., Hamad-Piqué, A., Bonet-Ruiz, J., Curcó, D., & Plesu Popescu, A. E. (2022). Valorization of valuable solvents
19. Shores BT, Sieg PE, Nicosia AT, Hu C, Born SC, Shvedova K, Sayin R, Testa CJ, Wu W, Takizawa B, Ramanujam S
20. Ciaciuch A, Sulewski M. Recovery of the organic solvents from the multicomponent mixture in the process of the fractional distillation and the vacuum distillation. Structure and Environment. 2024;16(2):111-21.
21. Sah, A., & Kumar, A. (2020). Recent advances in the application of silica membranes in pervaporation processes for solvent dehydration and recovery. Materials, 13(15), 3354
22. Goyal P, Sundarrajan S, Ramakrishna S. A review on mixed matrix membranes for solvent dehydration and recovery process. Membranes. 2021 Jun 11;11(6):441.
23. Subramanian D, Ritter JA. Equilibrium theory for solvent vapor recovery by pressure swing adsorption: analytical solution for process performance. Chemical engineering science. 1997 Sep 1;52(18):3147-60.
24. Rajawat A, Subramanian S, Ramakrishna S. Progress on silica pervaporation membranes in solvent dehydration and solvent recovery
25. Winterton N. The green solvent: a critical perspective. Clean Technologies and Environmental Policy. 2021 Nov;23(9):2499-522.
26. Cavanagh EJ, Savelski MJ, Slater CS. Optimization of environmental impact reduction and economic feasibility of solvent waste recovery using a new software tool. Chemical Engineering Research and Design. 2014 Oct 1;92(10):1942-54.
27. Chea JD, Lehr AL, Stengel JP, Savelski MJ, Slater CS, Yenkie KM. Evaluation of solvent recovery options for economic feasibility through a superstructure-based optimization framework. Industrial & Engineering Chemistry Research. 2020 Mar 9;59(13):5931-44.
28. Guideline Jimenez-Gonzalez C, Ponder CS, Broxterman QB, Manley JB. Using the right green yardstick: why process mass intensity is used in the pharmaceutical industry to drive more sustainable processes. Organic Process Research & Development. 2011 Jul 15;15(4):912-7. IH. Impurities: Guideline for residual solvents Q3C (R5). Current Step. 2005 Nov;4:1-25.
29. Raymond MJ, Slater CS, Savelski MJ. LCA approach to the analysis of solvent waste issues in
30. Aboagye EA, Chea JD, Yenkie KM. A systems-level roadmap for solvent recovery and reuse in industries. Iscience. 2021 Oct 22;24(10).

31. Raymond MJ, Slater CS, Savelski MJ. An LCA approach for analyzing solvent waste issues in the pharmaceutical industry. Green Chemistry. 2010 Oct 1;12(10):1826-34.
32. Chea JD, Christon A, Pierce V, Reilly JH, Russ M, Savelski M, Slater CS, Yenkie KM. Framework for solvent recovery, reuse and recycling in industries. Computer Aided Chemical Engineering. 2019 Jan 1; 47:199-204.
33. Raymond MJ, Slater CS, Savelski MJ. An LCA approach for analyzing solvent waste issues in the pharmaceutical industry. Green Chemistry. 2010 Oct 1;12(10):1826-34.
34. Winterton N. The green solvent: a critical perspective. Clean technologies and environmental policy. 2021 Nov;23(9):2499-522.