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Strategic Solvent Management in Pharmaceutical Manufacturing: A Green Chemistry Metrics Framework for Operational and Economic Decision-Making

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Abstract:
Background: *Solvent use represents one of the major contributors to material consumption and waste generation in pharmaceutical manufacturing. Effective solvent management is therefore essential for improving both environmental sustainability and operational efficiency. Green chemistry metrics such as Process Mass Intensity (PMI), E-factor, and Solvent Intensity (SI) provide quantitative tools to evaluate process performance and identify waste hotspots. However, the integration of these metrics into plant-level managerial decision-making remains limited. This study investigates strategic solvent management in pharmaceutical manufacturing through an industrial case analysis at Zavieh Darouyi Teb Ariana (ZDTA). The aim was to evaluate solvent utilization across key production stages and assess the environmental and economic implications of improved solvent recovery strategies.*
Materials and Methods: *In this industrial case study, operational data related to solvent consumption, recovery efficiency, waste generation, and production output were collected from reaction, crystallization, and purification stages within the ZDTA manufacturing facility. Green chemistry indicators including Process Mass Intensity (PMI), E-factor, and Solvent Intensity (SI) were calculated to evaluate environmental performance. Pareto analysis was applied to identify major solvent waste sources, and sensitivity analysis was performed to examine the impact of different solvent recovery rates on process efficiency. In addition, solvent procurement, recovery operation, and waste treatment costs were analyzed to assess the economic implications of solvent management practices.*
Results: *The analysis identified crystallization as the primary environmental hotspot, showing the highest PMI (8.3) and E-factor (2.6) among the evaluated stages. Pareto analysis indicated that crystallization and reaction together contributed to the majority of solvent waste generation. Sensitivity analysis revealed a strong nonlinear relationship between solvent recovery efficiency and environmental performance; increasing the recovery rate from 55% to 75% significantly reduced both E-factor and overall material intensity. Economic assessment showed that solvent procurement accounted for approximately 60.6% of total solvent-related operational costs.*
Conclusion: *Strategic solvent management plays a critical role in improving the environmental and economic performance of pharmaceutical manufacturing systems. The findings demonstrate that increasing solvent recovery efficiency can substantially reduce waste generation, material consumption, and operational costs. Integrating green chemistry metrics into plant-level operational analysis provides a practical framework for supporting data-driven sustainability decisions in pharmaceutical production.*
Key Word*: Solvent management; Green chemistry metrics; Pharmaceutical manufacturing; Process Mass Intensity; E-factor.*

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I. Introduction

The pharmaceutical industry is widely recognized as one of the most resource-intensive sectors within the chemical manufacturing landscape. Among the various inputs used in pharmaceutical production, organic solvents constitute the largest material component of most processes. Solvents are extensively employed in reaction media, crystallization, extraction, purification, and cleaning operations, often accounting for a substantial proportion of total mass input. Studies indicate that solvents may represent up to 80–90% of the total material usage in pharmaceutical manufacturing, making them a dominant contributor to both environmental impact and operational costs (Constable et al., 2007; Dunn et al., 2010).

The heavy reliance on solvents leads to significant volumes of chemical waste and emissions. Compared with other chemical sectors, pharmaceutical manufacturing typically exhibits relatively high waste generation rates, commonly measured using the Environmental factor (E-factor). While bulk chemical processes often achieve E-factors below 5, pharmaceutical processes frequently report values ranging from 25 to 100, largely due to extensive solvent consumption, multi-step syntheses, and relatively low overall yields (Sheldon, 2007; Sheldon, 2012). As a result, solvent management has emerged as a critical challenge for enhancing sustainability, improving operational efficiency, and ensuring regulatory compliance in pharmaceutical production.

In response to these challenges, the principles of green chemistry have increasingly guided process design and manufacturing strategies. Green chemistry emphasizes waste prevention, the use of safer solvents and auxiliaries, energy efficiency, and the design of inherently safer chemical processes (Anastas & Warner, 1998). Within pharmaceutical manufacturing, quantitative metrics such as Process Mass Intensity (PMI), E-factor, and solvent intensity have become essential tools for evaluating environmental performance and identifying process optimization opportunities (Jiménez-González et al., 2011). These indicators provide a transparent and systematic framework for assessing material efficiency and have been widely adopted by leading pharmaceutical companies and industrial consortia.

Despite the availability of these metrics, their integration into routine operational and strategic decision-making remains limited in many pharmaceutical facilities. Solvent selection, procurement, recovery, and waste management decisions are often driven primarily by cost considerations, supply reliability, and established operational practices rather than by a comprehensive sustainability framework. Addressing this gap requires management approaches that systematically incorporate environmental performance metrics into production planning and decision processes.

Recent research highlights the importance of sustainable manufacturing strategies and green supply chain management within the pharmaceutical sector. Approaches such as solvent substitution, closed-loop recovery systems, process intensification, and continuous manufacturing have been proposed to reduce solvent consumption and environmental impact (Clark & Tavener, 2007; Alfonsi et al., 2008). However, the successful implementation of such strategies typically requires plant-specific evaluation and integrated decision frameworks that simultaneously consider technical feasibility, economic constraints, safety requirements, and environmental performance.

Industrial case studies play a crucial role in advancing sustainable pharmaceutical manufacturing by providing empirical data and demonstrating practical applications of sustainability metrics. Case-based research enables detailed analysis of solvent usage patterns, identification of inefficiencies, and development of tailored management strategies suited to specific operational contexts.

In this context, the present study examines solvent utilization and management practices within a pharmaceutical manufacturing environment, focusing on a case study of Zavieh Darouyi Teb Ariana (ZDTA). By analyzing solvent consumption patterns, recovery practices, and waste generation across selected production processes, this research quantifies environmental performance using established green chemistry metrics, including PMI and E-factor. Furthermore, the study proposes an operational decision-making framework that integrates green chemistry indicators with managerial considerations such as cost efficiency, safety, regulatory compliance, and process performance.

Accordingly, the objectives of this research are twofold:

1. To evaluate solvent use efficiency and environmental impact in pharmaceutical manufacturing using quantitative sustainability metrics; and
2. To develop a strategic solvent management framework that supports informed and sustainability-oriented operational decision-making.

By bridging the gap between green chemistry assessment tools and managerial practice, this study contributes to the expanding literature on sustainable pharmaceutical manufacturing and offers practical guidance for improving resource efficiency in industrial pharmaceutical processes.

II. Literature Review

Sustainable solvent management in pharmaceutical manufacturing lies at the intersection of green chemistry, process engineering, and operations management. While substantial progress has been made in developing green chemistry metrics and solvent selection tools, their systematic integration into managerial decision-making at the plant level remains limited. This section reviews the relevant literature in four subsections: (1) solvent intensity and environmental performance in pharmaceutical manufacturing, (2) green chemistry metrics and solvent assessment frameworks, (3) operational and strategic solvent management approaches, and (4) research gaps and the contribution of the present study.

Solvent Intensity and Environmental Performance in Pharmaceutical Manufacturing

Pharmaceutical production is characterized by high material intensity, with solvents constituting the dominant mass fraction of process inputs. Empirical analyses indicate that solvents can account for approximately 70–90% of the total mass used in active pharmaceutical ingredient (API) synthesis and downstream purification processes (Constable et al., 2007; Dunn et al., 2010). This extensive solvent usage contributes significantly to the relatively high waste generation rates observed in pharmaceutical manufacturing compared with other chemical sectors (Sheldon, 2012).

Material efficiency in pharmaceutical processes is commonly evaluated using the Environmental factor (E-factor) and Process Mass Intensity (PMI). Industrial reports and academic case studies consistently demonstrate that typical PMI values for pharmaceutical APIs are substantially higher than those observed in bulk or commodity chemical production. The primary driver of this difference is the extensive use of solvents in reaction media, crystallization, extraction, and purification stages (Jiménez-González et al., 2011; Sheldon, 2017). Consequently, solvent reduction has been widely recognized as one of the most effective strategies for improving the environmental performance of pharmaceutical manufacturing processes.

Recent life cycle assessment (LCA) studies further highlight the environmental significance of solvent use. Research shows that solvent production, transportation, recovery, and incineration contribute substantially to greenhouse gas emissions and other environmental burdens associated with pharmaceutical manufacturing (Wernet et al., 2016; Parvatker & Eckelman, 2019). These findings emphasize the need for systematic solvent management strategies that address not only process-level efficiency but also upstream and downstream environmental impacts.

Green Chemistry Metrics and Solvent Assessment Frameworks

The principles of green chemistry emphasize waste prevention, the use of safer solvents and auxiliaries, energy efficiency, and inherently safer chemical processes (Anastas & Warner, 1998). In response to these principles, several quantitative tools and frameworks have been developed to support solvent evaluation and selection.

Two of the most widely used metrics for assessing material efficiency are Process Mass Intensity (PMI) and the E-factor:

$$PMI = \frac{\text{Total mass input}}{\text{Mass of product}}$$

$$E\text{-factor} = \frac{\text{Mass of waste}}{\text{Mass of product}}$$

These metrics provide a straightforward and transparent method for quantifying resource efficiency and identifying opportunities for process improvement.

Beyond mass-based metrics, solvent selection guides have been developed by several pharmaceutical companies and industry consortia to classify solvents according to toxicity, environmental impact, and safety considerations. For example, solvent selection frameworks developed by pharmaceutical companies rank solvents based on health, safety, and environmental criteria, helping researchers and process engineers identify more sustainable alternatives (Henderson et al., 2011; Prat et al., 2016). Such guides have had a significant influence on solvent selection practices in medicinal chemistry and early-stage process development.

More recent studies have introduced multi-criteria solvent assessment models that combine environmental hazard data, life cycle indicators, and regulatory considerations (Byrne et al., 2016; Capello et al., 2007). Despite these advances, most solvent selection tools remain primarily designed for research and development environments rather than for large-scale industrial operations with complex economic and operational constraints.

Operational and Strategic Solvent Management in Industrial Contexts

From a managerial perspective, solvent management extends beyond solvent selection to encompass procurement strategies, solvent recovery and recycling systems, waste treatment infrastructure, and regulatory compliance. Studies in sustainable manufacturing and green supply chain management highlight the importance of integrating environmental considerations into operational decision-making processes (Seuring & Müller, 2008; Sarkis et al., 2011).

Within pharmaceutical manufacturing, several operational strategies have been proposed to improve solvent efficiency:

- Implementation of solvent recovery and distillation systems to increase recycling rates
- Process intensification and reaction telescoping to reduce solvent consumption
- Adoption of continuous manufacturing technologies to enhance material efficiency

- Deployment of digital monitoring systems for real-time tracking of resource consumption

Recent research also highlights the growing role of digitalization and Industry 4.0 technologies in improving environmental transparency and resource efficiency within chemical and pharmaceutical industries (Bag et al., 2021; Centobelli et al., 2022). Advanced data analytics and digital monitoring tools enable more accurate measurement of material flows and facilitate data-driven operational decisions.

Despite these developments, empirical studies that quantitatively connect green chemistry metrics (e.g., PMI, solvent intensity) with operational decision frameworks at the plant level remain relatively scarce. Much of the existing research either focuses primarily on technical process optimization or addresses sustainability from a high-level managerial perspective without incorporating detailed chemical performance metrics.

This disconnect limits the ability of plant managers to make data-driven decisions that simultaneously optimize environmental performance, economic efficiency, and operational feasibility.

Research Gaps and Contribution of the Present Study

Although the literature provides robust tools for measuring environmental performance and evaluating solvent hazards, several important gaps remain:

- Limited integration of green chemistry metrics into operational decision-making models at the plant level
- Scarcity of empirical case studies using real industrial data from pharmaceutical manufacturing facilities
- Insufficient linkage between solvent recovery performance, economic costs, and environmental indicators within a unified decision framework

These gaps highlight the need for research that bridges technical sustainability metrics with practical managerial decision processes. The key research gaps identified in the literature are summarized in Table 1.

Table 1. Research Gaps in Strategic Solvent Management Literature

Research Stream	Representative Recent Studies	Key Contributions	Limitations Identified	Research Gap Addressed in This Study
Green chemistry metrics in pharmaceutical manufacturing	Sheldon (2017); Parvatker & Eckelman (2019); Li et al. (2023)	Development and industrial adoption of metrics such as PMI, E-factor and material efficiency indicators to evaluate sustainability of pharmaceutical processes	Metrics are often used only for environmental reporting and benchmarking rather than integrated operational decision-making tools	This study integrates PMI, E-factor and solvent intensity directly into managerial solvent decision processes within ZDTA
Solvent selection guides and solvent sustainability tools	Prat et al. (2016); Byrne et al. (2020); Henderson et al. (2021)	Development of solvent selection guides and multi-criteria solvent sustainability ranking frameworks based on safety, health and environmental factors	Primarily applied during laboratory-scale or early process development; limited validation in full-scale pharmaceutical manufacturing environments	Industrial validation of solvent sustainability evaluation using real production data from ZDTA
Sustainable manufacturing and green operations management	Centobelli et al. (2020); Bag et al. (2021); Dubey et al. (2022)	Integration of environmental sustainability into operations management, supply chains and production systems	Studies generally focus on managerial strategies without incorporating chemical process-level performance indicators	Linking solvent-level chemical performance indicators with operational management strategies in pharmaceutical manufacturing
Life cycle and environmental assessment of pharmaceutical production	Parvatker & Eckelman (2019); Wernet et al. (2020); Chen et al. (2023)	Application of life cycle assessment (LCA) to quantify environmental impacts of pharmaceutical manufacturing and chemical processes	Many studies operate at sectoral or system-level analysis and rarely provide plant-level managerial guidance	Development of a plant-level solvent management framework informed by environmental performance indicators
Digitalization and data-driven sustainability in chemical industries	Centobelli et al. (2022); Kamble et al. (2023); Sharma et al. (2024)	Demonstrates the role of Industry 4.0 and data-driven decision systems in improving sustainability and operational efficiency	Limited application to solvent-intensive pharmaceutical production processes	Implementation of a data-driven solvent management decision framework using real operational data from ZDTA

The present study addresses these limitations through a detailed industrial case study of Zavieh Darouyi Teb Ariana (ZDTA). Specifically, the research:

- Applies green chemistry metrics (PMI, E-factor, and solvent intensity) to real operational data from pharmaceutical manufacturing processes
- Integrates environmental performance indicators with operational and economic considerations
- Develops a structured decision-making framework for strategic solvent management at the plant level

By linking chemical performance metrics with managerial decision processes, this study contributes to both the green chemistry and sustainable operations management literature while providing practical insights for improving solvent efficiency in pharmaceutical manufacturing.

III. Methodology

This study adopts a quantitative industrial case study approach to investigate strategic solvent management in pharmaceutical manufacturing. The methodology integrates green chemistry performance metrics with operational decision-making considerations and applies them within the real industrial context of Zavieh Darouyi Teb Ariana (ZDTA). The primary objective is to evaluate solvent consumption patterns, quantify environmental performance using established green chemistry indicators, and develop a managerial framework that supports more sustainable solvent management decisions at the plant level.

The methodological framework consists of three main stages:

1. Collection of operational and solvent-related data from selected production processes at ZDTA.
2. Calculation of environmental performance metrics, including Process Mass Intensity (PMI), E-factor, and Solvent Intensity (SI).
3. Integration of environmental performance indicators with operational and economic considerations to support strategic solvent management decisions.

Conceptual Model

The conceptual model guiding this research is illustrated in Figure 1. The model establishes a link between operational solvent data from ZDTA, green chemistry performance metrics, and managerial decision-making processes. In this framework, solvent usage data obtained from pharmaceutical production operations are translated into quantitative environmental indicators, which are subsequently evaluated alongside operational and economic factors to support strategic solvent management decisions.

In the proposed model, solvent consumption patterns within ZDTA production processes serve as the primary input for environmental performance evaluation. These operational inputs are converted into sustainability indicators such as PMI, E-factor, and Solvent Intensity, enabling the quantitative assessment of material efficiency and waste generation. The resulting environmental performance outcomes are then analyzed in conjunction with operational variables including production yield, solvent recovery efficiency, and cost implications.

The integration of these dimensions allows managers to identify improvement opportunities such as solvent substitution, recovery optimization, or process modification, thereby supporting more sustainable and economically viable solvent management strategies.

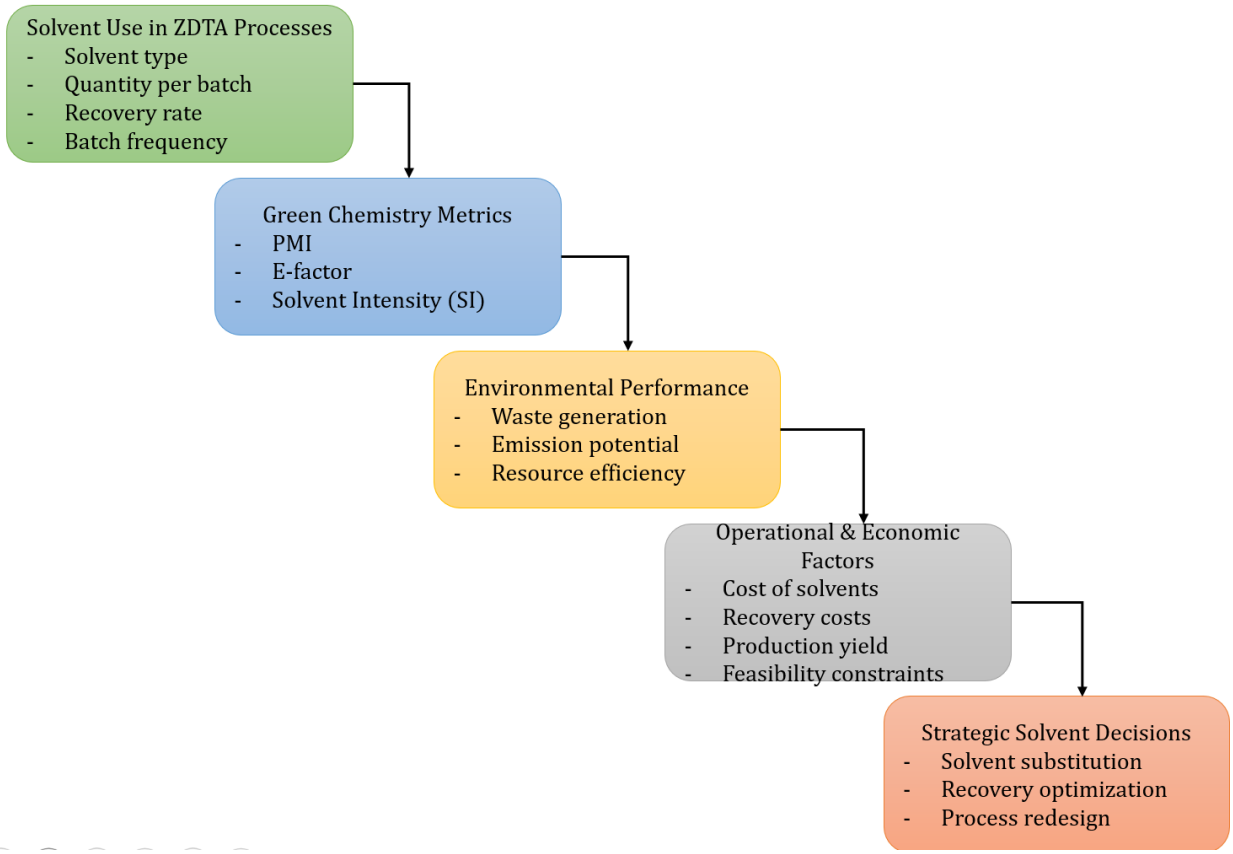

Figure 1. Conceptual model for strategic solvent management in pharmaceutical manufacturing (case of ZDTA)

As illustrated in Figure 1, the case study of ZDTA serves as both the data source and the application environment in which the proposed solvent management framework is evaluated.

Data Collection

Operational data were collected from selected pharmaceutical production processes at Zavieh Darouyi Teb Ariana (ZDTA). The analysis focuses on solvent-intensive stages of pharmaceutical manufacturing, including reaction, crystallization, washing, and purification processes. These stages typically represent the largest contributors to solvent consumption and waste generation in pharmaceutical production.

The required data were obtained from internal production documentation, including batch production records, material balance sheets, and environmental monitoring reports. To ensure confidentiality and protect proprietary information, all collected industrial data were aggregated and anonymized before analysis.

The dataset includes the following variables:

- Type of solvent used in each production stage
- Quantity of solvent used per batch
- Production output per batch
- Solvent recovery rate
- Amount of solvent waste generated
- Cost of solvent procurement and waste treatment

These data provide the basis for calculating environmental performance indicators and assessing solvent management efficiency within the selected production processes.

Green Chemistry Metrics and Data Analysis

To evaluate the environmental performance of solvent use in pharmaceutical production, three widely recognized green chemistry indicators were calculated: Process Mass Intensity (PMI), E-factor, and Solvent Intensity (SI).

Process Mass Intensity (PMI) measures the overall material efficiency of a manufacturing process and is defined as:

$$PMI = \frac{\text{Total mass of input materials}}{\text{Mass of product}}$$

A lower PMI value indicates higher material efficiency and reduced resource consumption.

E-factor represents the amount of waste generated per unit of product and is calculated as:

$$E\text{-factor} = \frac{\text{Mass of waste generated}}{\text{Mass of product}}$$

This metric is widely used in the chemical and pharmaceutical industries to assess waste generation and environmental burden.

Solvent Intensity (SI) specifically quantifies the contribution of solvents to total material consumption:

$$SI = \frac{\text{Total mass of solvent used}}{\text{Mass of product}}$$

This indicator provides a focused measure of solvent dependency within pharmaceutical production processes.

These metrics were calculated for the baseline production processes at ZDTA using the collected operational data. The results were then analyzed to identify major sources of solvent consumption and waste generation within the selected processes.

In addition, improvement scenarios—such as enhanced solvent recovery rates or solvent substitution options—were evaluated to estimate their potential impact on environmental performance indicators. By integrating the calculated green chemistry metrics with operational and cost considerations, the analysis provides a decision-support perspective for strategic solvent management in pharmaceutical manufacturing.

IV. Results and Discussion

This section presents the empirical findings of the solvent management analysis conducted in the case study company, Zavieh Darouyi Teb Ariana (ZDTA). The objectives of this section are threefold:

(1) to evaluate the baseline environmental performance of the analyzed pharmaceutical processes using green chemistry metrics,

(2) to identify solvent consumption hotspots across production stages, and

(3) to assess the potential environmental and economic benefits of improved solvent recovery scenarios.
The results are presented through quantitative indicators, comparative tables, and analytical discussion to provide a comprehensive understanding of solvent-related sustainability performance within the studied manufacturing system.

Baseline Solvent Consumption and Waste Generation

The first step of the analysis involved quantifying solvent consumption and solvent waste across the main solvent-intensive stages of the production process. The analysis was normalized per batch corresponding to 100 kg of finished product.
Table 2 summarizes the solvent usage, recovery efficiency, and waste solvent generation across the studied process stages.

Table 2. Baseline solvent consumption, recovery efficiency, and waste generation per process stage

Process Stage	Solvent Used (kg)	Recovery (%)	Waste Solvent (kg)
Reaction	420	60	168
Crystallization	520	50	260
Purification	310	55	139
Overall Process	**1,250**	**55 (avg.)**	**567**

As shown in Table 2, crystallization is the most solvent-intensive stage, accounting for approximately 42% of total solvent consumption and nearly 46% of total solvent waste generated per batch.
Despite comparable production volumes, the crystallization stage exhibits the lowest recovery efficiency (50%), resulting in disproportionately high solvent losses. This identifies crystallization as a potential environmental hotspot requiring targeted intervention.
To further examine the relative contribution of each stage to overall solvent waste generation, a Pareto analysis was conducted.

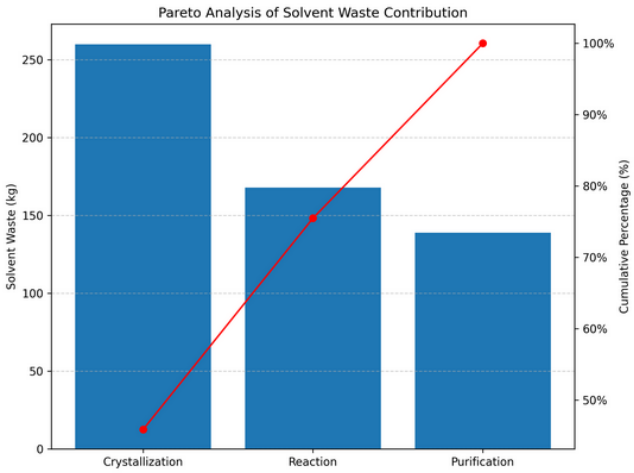

Figure 2. Pareto analysis of solvent waste contribution by production stage

Figure 2 clearly illustrates that crystallization and reaction stages together account for more than 75% of total solvent waste. According to the Pareto principle, improvement efforts focused on these two stages would yield the greatest environmental impact.

Environmental Performance Metrics

Based on the collected operational data, three green chemistry indicators were calculated: Process Mass Intensity (PMI), E-factor, and Solvent Intensity (SI). These metrics were used to evaluate the environmental performance of each production stage.
Table 3 presents the calculated indicator values across the analyzed process stages.

Table 3. Environmental performance indicators

Process Stage	PMI	E-factor	Solvent Intensity (kg/kg product)
Reaction	6.8	1.7	4.2
Crystallization	8.3	2.6	5.2
Purification	5.9	1.4	3.1
Overall Process	**7.0**	**2.0**	**4.2**

The results indicate that the crystallization stage exhibits the highest PMI and E-factor values among the analyzed process steps, highlighting its role as the primary environmental hotspot within the production system.

Figure 3 illustrates the comparative E-factor values across the production stages.

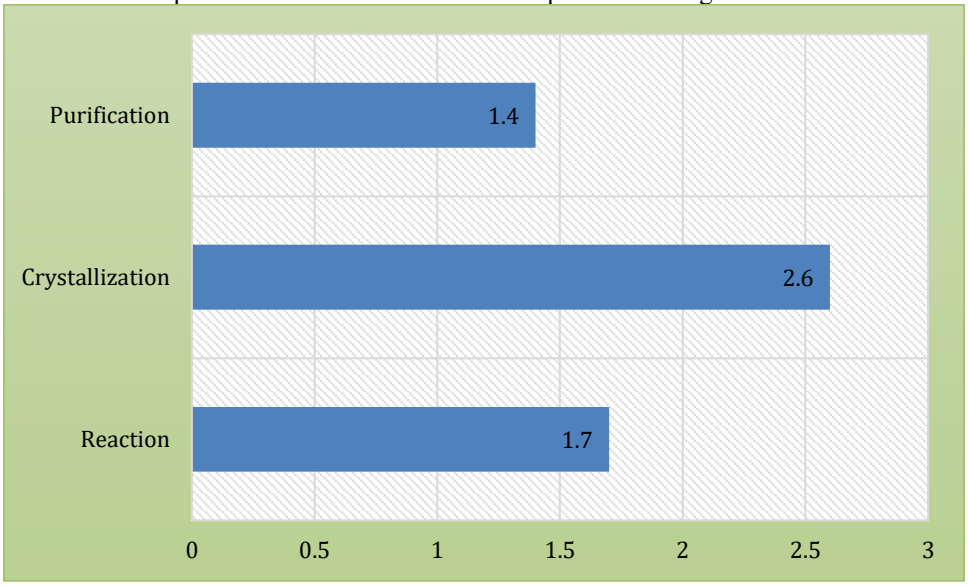

Figure 3. Comparison of E-factor values across production stages

As shown in Figure 3, the E-factor of the crystallization stage (2.6) is substantially higher than that of the reaction (1.7) and purification (1.4) stages, indicating a disproportionately large contribution to overall waste generation.
From a process perspective, this behavior can be attributed to several mechanisms commonly observed in pharmaceutical crystallization systems. First, solvent entrainment within the crystal slurry can lead to solvent losses during filtration and drying operations. Second, mother liquor streams often contain unrecovered solvent fractions that are difficult to recycle without additional separation processes. Third, washing steps required to meet pharmaceutical purity specifications frequently require additional solvent volumes, further increasing solvent intensity.
Similar patterns have been reported in previous studies of pharmaceutical manufacturing, where crystallization and downstream purification operations often dominate solvent consumption and waste generation. These findings suggest that crystallization represents a critical intervention point for improving the environmental performance of pharmaceutical production systems.
From an industrial perspective, targeted process optimization—such as improved solid–liquid separation, enhanced solvent recovery systems, or optimized solvent selection—could significantly reduce both material intensity and environmental impact.

Sensitivity Analysis

To evaluate the robustness of environmental performance, a sensitivity analysis was conducted focusing on two key parameters:

• solvent recovery efficiency
• solvent consumption per batch

The analysis assessed how variations in these parameters influence PMI and E-factor values.
Table 4 presents the sensitivity results for different recovery efficiency scenarios.

Table 4. Sensitivity of environmental metrics to solvent recovery efficiency

Recovery Rate	PMI	E-factor
55% (baseline)	7.0	2.0
65%	6.1	1.6
75%	5.4	1.2

The results demonstrate that improvements in solvent recovery have a strong nonlinear impact on environmental performance.
For instance, increasing recovery efficiency from 55% to 75% reduces the E-factor by approximately 40%. This indicates that solvent recycling infrastructure represents one of the most effective intervention points for reducing waste generation in pharmaceutical production.
Figure 4 illustrates the relationship between recovery efficiency and E-factor reduction.

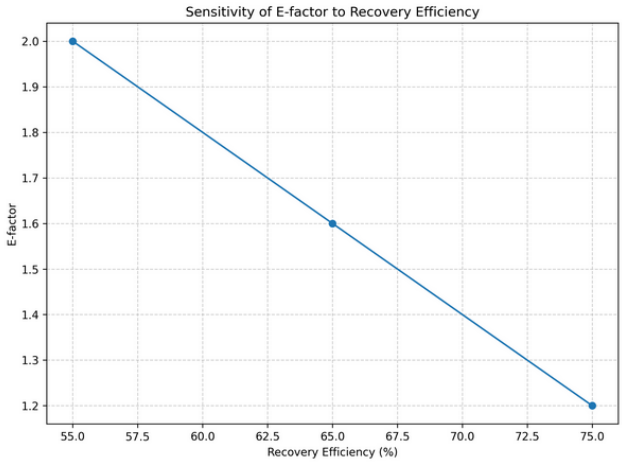

Figure 4. Impact of recovery efficiency on E-factor

The results indicate that improvements in solvent recovery efficiency lead to a significant reduction in both PMI and E-factor. As illustrated in Figure 4, increasing the recovery rate from 55% to 75% results in a substantial decrease in the E-factor, highlighting the strong sensitivity of environmental performance to solvent recovery efficiency. This relationship exhibits a nonlinear behavior. The nonlinear behavior arises because increased recovery simultaneously reduces both fresh solvent demand and waste generation. Consequently, relatively small improvements in recovery efficiency can generate disproportionately large reductions in process waste and overall material intensity.

Economic Implications of Solvent Management

In addition to environmental indicators, the economic implications of solvent management were evaluated by incorporating solvent procurement, recovery operation, and waste treatment costs. These cost components represent the primary economic factors associated with solvent use in pharmaceutical production systems.
Table 5 summarizes the solvent-related operational costs per production batch.

Table 5. Solvent-related cost structure per batch

Cost Category	Cost (USD)	Percentage of Total Cost (%)
Solvent procurement	4,850	60.6%
Solvent recovery operation	1,200	15.0%
Waste treatment	1,950	24.4%
Total solvent-related cost	**8,000**	**100%**

As shown in Table 5, solvent procurement represents the largest cost component, accounting for approximately 60.6% of the total solvent-related expenditure. Waste treatment constitutes the second largest share (24.4%), while recovery operations account for 15.0% of the total cost. These results indicate that solvent consumption not only affects environmental performance but also has a significant influence on operational expenditures.

Importantly, improvements in solvent recovery efficiency have the potential to simultaneously reduce two major cost drivers: the need for fresh solvent procurement and the costs associated with waste treatment. Increased recovery rates decrease solvent losses, thereby lowering both material input requirements and waste management burdens.

From a managerial perspective, these findings suggest that investments in enhanced solvent recovery technologies—such as improved distillation systems or closed-loop solvent recycling—can generate both environmental and economic benefits. Consequently, strategic solvent management should be considered not only a sustainability initiative but also a key component of cost optimization in pharmaceutical manufacturing.

Integrated Discussion

The integrated analysis of environmental and economic indicators provides several important insights into solvent management in pharmaceutical manufacturing.

First, the results confirm that solvent consumption is the primary driver of material intensity in the studied production process. As solvents represent the largest share of material inputs, improvements in solvent recovery and utilization efficiency can significantly influence both PMI and E-factor values.

Second, the analysis identifies crystallization as the principal environmental hotspot. The high solvent intensity and E-factor observed in this stage suggest that solvent losses during filtration, washing, and

mother-liquor handling play a critical role in overall waste generation. Consequently, targeted interventions in the crystallization stage—such as improved solvent recovery systems or optimized solvent selection—offer the greatest potential for environmental improvement.

Third, the integration of environmental metrics with economic cost data demonstrates a strong alignment between sustainability performance and operational efficiency. Improvements in solvent recovery simultaneously reduce raw solvent procurement and waste treatment costs.

Overall, the results indicate that green chemistry metrics can serve as practical decision-support tools for optimizing solvent management and improving sustainability performance in pharmaceutical manufacturing.

Overall, the results demonstrate that translating green chemistry indicators into operational and economic terms enables evidence-based managerial decision-making. The case study of ZDTA shows that data-driven solvent management can simultaneously enhance environmental performance, reduce costs, and strengthen process sustainability in pharmaceutical manufacturing.

V. Conclusions and Implications

This study investigated strategic solvent management in pharmaceutical manufacturing through an in-depth industrial case analysis at Zavieh Darouyi Teb Ariana (ZDTA). By integrating green chemistry metrics—namely Process Mass Intensity (PMI), E-factor, and Solvent Intensity (SI)—with operational and economic data, the study provided a comprehensive evaluation of solvent performance across reaction, crystallization, and purification stages.

The results identified crystallization as the primary environmental hotspot, exhibiting the highest PMI (8.3) and E-factor (2.6) values among the analyzed stages. Pareto analysis further confirmed that crystallization and reaction collectively account for the majority of solvent waste generation. Sensitivity analysis demonstrated a pronounced nonlinear relationship between solvent recovery efficiency and environmental performance; increasing recovery from 55% to 75% resulted in a substantial reduction in E-factor and overall material intensity. This nonlinear behavior arises because enhanced recovery simultaneously reduces both fresh solvent demand and waste generation. Economic evaluation further revealed that solvent procurement represents over 60% of solvent-related operational costs, emphasizing the financial significance of solvent efficiency improvements.

Collectively, these findings demonstrate that solvent management constitutes a high-leverage intervention point for simultaneously improving environmental sustainability and operational cost efficiency in pharmaceutical production systems.

Theoretical Contributions

This research contributes to the literature in three principal ways.

First, it bridges the gap between green chemistry metrics and managerial decision-making by operationalizing PMI and E-factor within a real industrial context rather than treating them solely as laboratory-scale indicators. By embedding these metrics into plant-level operational analysis, the study enhances their strategic applicability.

Second, the study advances sustainability research in pharmaceutical manufacturing by integrating environmental and economic dimensions into a unified analytical framework. While prior research often evaluates solvent selection tools or environmental metrics independently, this study demonstrates how process-level quantitative indicators can directly inform capital investment and operational optimization decisions.

Third, the study provides empirical evidence from a plant-level case in a developing manufacturing context, contributing to the limited body of real-world industrial sustainability assessments in pharmaceutical production. This empirical grounding strengthens the practical relevance of green chemistry evaluation frameworks.

Managerial and Industrial Implications

From a managerial perspective, the findings underscore the strategic importance of solvent recovery systems. Because increased recovery simultaneously reduces fresh solvent demand and waste treatment requirements, investments in enhanced recovery infrastructure—such as advanced distillation systems, closed-loop recycling configurations, or process intensification strategies—can generate compounded environmental and economic returns.

The identification of crystallization as a solvent hotspot suggests that targeted optimization of solid–liquid separation efficiency, mother liquor recycling, and solvent selection criteria should be prioritized within continuous improvement programs. Furthermore, integrating green chemistry indicators into routine performance monitoring dashboards can facilitate data-driven decision-making and long-term sustainability planning.

Strategic solvent management should therefore be positioned not merely as a regulatory compliance activity but as a core operational excellence strategy capable of enhancing competitiveness and resource efficiency in pharmaceutical manufacturing.

Limitations and Future Research

Despite its contributions, this study has several limitations. The analysis is based on a single industrial case, which may limit the generalizability of the findings across diverse pharmaceutical production systems. Moreover, the evaluation relied primarily on mass-based indicators and direct operational costs; a comprehensive life cycle assessment (LCA) incorporating upstream solvent production, energy consumption, and emissions would provide a more holistic environmental profile.

Future research could extend this framework to multi-plant comparative studies, integrate digital process monitoring and Industry 4.0 tools, or apply advanced optimization and artificial intelligence techniques to dynamic solvent management. Expanding the analytical scope to include carbon intensity, regulatory risk exposure, and supply chain impacts would further strengthen the strategic relevance of solvent sustainability assessments.

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