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*Original Article*

# Efficacy of Green Chemistry Techniques in Reducing Environmental Impact of Pharmaceutical Manufacturing

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## ABSTRACT

Background: Pharmaceutical preparation and manufacturing activities generate substantial solvent-driven waste and consume considerable energy, particularly in settings where controlled environments, sterilization, and repeated cleaning cycles are routine. Green chemistry offers source-reduction strategies that may lessen these burdens, yet causal evidence from real-world hospital pharmacy production settings remains limited. Objective: To evaluate the efficacy of a structured green chemistry bundle in reducing waste generation and energy consumption during routine pharmaceutical preparation in a tertiary-care hospital setting. Methods: A pragmatic parallel-group randomized controlled trial was conducted in Faisalabad, Pakistan, using 120 eligible production runs as the unit of randomization, with 60 runs allocated to standard practice and 60 to a predefined green chemistry bundle. The intervention incorporated solvent substitution and minimization, streamlined work-up and cleaning steps, and energy-efficiency measures within validated operational constraints. Primary outcomes were total waste per run and energy use per run, while secondary outcomes included a PMI-aligned material-efficiency indicator and routine quality markers. Results: The intervention reduced total waste from 23.88 to 19.23 kg/run (mean difference -4.64; 95% CI -6.34 to -2.94; $p<0.001$) and energy use from 94.39 to 80.09 kWh/run (mean difference -14.31; 95% CI -19.61 to -9.00; $p<0.001$). The PMI-aligned indicator also improved from 136.6 to 118.2 (mean difference -18.35; 95% CI -28.86 to -7.85; $p<0.001$). Quality failures and rework did not increase. Conclusion: A structured green chemistry bundle can reduce solvent-dominated waste, lower energy demand, and improve material-efficiency performance in hospital pharmaceutical preparation without measurable deterioration in routine quality outcomes. Keywords: green chemistry, pharmaceutical manufacturing, hospital compounding, waste minimization, solvent selection, process mass intensity, energy efficiency, randomized controlled trial, hospital pharmacy, Pakistan.

## INTRODUCTION

Pharmaceutical manufacturing is among the most material- and energy-intensive domains within the chemical and healthcare sectors because the preparation of drug products commonly requires multistep processing, repeated solvent use, stringent purification, controlled environmental conditions, and high-quality assurance thresholds. These operational realities contribute to substantial waste generation, high utility demand, and broader environmental burdens that include hazardous releases, greenhouse-gas

emissions, and resource depletion. In pharmaceutical systems, solvent consumption is particularly important because solvents often account for a large share of total material throughput and waste, especially when repeated washing, extraction, purification, and cleaning cycles are embedded in routine workflows. Consequently, improving the environmental performance of pharmaceutical production requires interventions that target waste generation and energy demand at their source rather than relying only on downstream disposal measures (1-4).

Green chemistry provides a practical framework for achieving this objective by redesigning products and processes to minimize hazard, reduce waste, improve material efficiency, and lower energy consumption. The field has evolved from conceptual principles into applied operational strategies supported by solvent selection guides, green metrics, and process redesign methods that allow sustainability to be assessed alongside cost, quality, and productivity. Within pharmaceutical practice, the most influential green approaches have included solvent substitution, solvent minimization, reduction in unnecessary work-up steps, adoption of more efficient transformations, and optimization of heating, cooling, and other utility-intensive operations. Quantitative tools such as the E-factor and process mass intensity have further enabled manufacturers to translate sustainability into measurable performance indicators, thereby linking environmental improvement to operational efficiency and economic value (1,3,5-9).

Although much of the literature on green pharmaceutical production originates from industrial active pharmaceutical ingredient manufacturing, the same principles are highly relevant to hospital-based pharmaceutical preparation and compounding services. Tertiary-care hospital pharmacies routinely perform preparation, cleaning, sterilization, storage, and controlled-environment operations that consume electricity, generate solvent-containing and aqueous waste streams, and require repeated use of chemical auxiliaries. In low- and middle-income settings, these burdens may be amplified by infrastructure constraints, limited waste-treatment capacity, variable energy efficiency, and the need to balance sustainability with uninterrupted clinical service delivery. In Pakistan, where healthcare waste management and environmentally responsible disposal remain persistent concerns, hospital pharmacy operations represent an important yet understudied site for practical green intervention because even moderate improvements in solvent stewardship and energy use may yield meaningful environmental and operational benefits at scale (10-14).

Existing evidence strongly supports the theoretical and practical value of greener pharmaceutical processing, but much of this evidence is derived from case studies, retrospective audits, route-comparison exercises, lifecycle assessments, or industrial process demonstrations. These designs are useful for feasibility and benchmarking, yet they offer limited causal certainty because changes in waste or energy use may also reflect differences in staffing, equipment condition, workload, seasonal utility demand, or concurrent process modifications. This limitation is particularly important in hospital settings, where workflows are dynamic and sustainability measures must operate within validated quality and safety constraints. Despite growing interest in sustainable pharmacy practice, randomized evaluations of green chemistry interventions in real-world hospital production environments remain scarce, and causal evidence from such settings is still lacking (3,4,12,15-18).

Another important consideration is that environmental gains in pharmaceutical operations are rarely produced by a single isolated change. Solvent choice influences not only the mass and hazard profile of waste, but also cleaning burden, exposure control requirements, and downstream energy demand. Likewise, energy efficiency depends not only on equipment specifications, but also on scheduling, cycle design, idle runtime, and alignment between validated settings and actual operational needs. For this reason, bundled interventions that simultaneously address solvent practices, process steps, and energy-intensive workflow components may be more realistic and more effective than narrowly targeted modifications. However, the evidence base for such bundled strategies in routine tertiary-hospital

pharmacy settings remains limited, particularly in South Asian healthcare systems where local data are needed to support policy adoption and standard operating procedure reform (4,6,7,13,16,19).

The present study was therefore designed to evaluate the efficacy of a structured green chemistry bundle in reducing the environmental impact of pharmaceutical preparation under routine tertiary-hospital conditions in Faisalabad, Pakistan. Using production runs as the unit of randomization in a pragmatic parallel-group randomized controlled design, the study compared a predefined bundle of solvent substitution and minimization, process-efficiency adjustments, and energy-efficiency measures against standard practice. The primary objective was to determine whether the intervention could reduce total waste generation and energy consumption per production run without compromising routine quality performance. It was hypothesized that, compared with conventional procedures, the green chemistry bundle would produce lower waste mass, lower energy demand, and improved material-efficiency indicators under real-world hospital pharmacy conditions (1,3,5,8).

## MATERIALS AND METHODS

This study was conducted as a pragmatic, parallel-group randomized controlled trial to evaluate whether a structured bundle of green chemistry techniques could reduce the environmental impact of routine pharmaceutical preparation activities while preserving operational quality within a tertiary-care hospital pharmacy. A pragmatic design was selected because the purpose of the investigation was not merely to test theoretical process advantages under idealized laboratory conditions, but to determine whether the intervention remained effective when implemented within normal hospital workflow, existing staffing patterns, established documentation procedures, and validated quality requirements. The trial was carried out in Faisalabad, Pakistan, within hospital pharmacy services responsible for recurring preparation and compounding activities involving measurable material inputs, waste outputs, and utility demand. The study specifically focused on preparation processes in which solvents, cleaning agents, sterilization cycles, heating or cooling steps, ventilation-dependent controlled areas, and related auxiliary materials were part of routine operational practice.

The study unit was a single production run, defined as one standardized batch or preparation cycle of an eligible pharmaceutical process. Runs were considered eligible when they involved a repeatable workflow, generated measurable input and output records, and had non-trivial solvent, auxiliary chemical, or energy demand. This included workflows in which energy use was meaningfully influenced by mixing, drying, heating, refrigeration, sterilization, or controlled-environment operation. Runs were excluded when the process occurred too infrequently to support balanced allocation, when clinically mandated materials could not be modified within hospital policy constraints, or when emergency-only preparations could have been delayed or operationally compromised by protocolized intervention steps. Recruitment occurred at the level of eligible routine runs rather than at the patient level because the intervention targeted production processes and environmental performance rather than clinical outcomes in individual patients. All included runs were identified prospectively from the routine preparation schedule and screened against predefined eligibility criteria before allocation.

Production runs were assigned in a 1:1 ratio to either standard practice or the green chemistry bundle. Allocation was stratified by process category, particularly sterile-related versus non-sterile preparation workflows, to reduce baseline imbalance in waste intensity and utility demand across the two study arms. Blocked allocation within strata was used to preserve balance over the course of routine operations despite variation in pharmacy workload. Allocation concealment was maintained through a centralized assignment process managed independently from run execution, and the assigned condition was disclosed immediately before implementation to minimize anticipatory deviation from the allocated workflow. Full operator blinding was not feasible because staff could recognize differences in solvent use, workflow sequencing, or equipment settings; however, the main outcome measures were objective operational measures rather than subjective judgments. In addition, where routine product-quality

checks were performed by personnel separate from the preparation team, quality documentation was recorded without reference to intervention status in order to reduce detection bias.

Control runs were completed according to the hospital's routine standard operating procedures. These procedures reflected existing solvent choices, standard solvent volumes, usual work-up and cleaning routines, conventional sterilization practices, and typical equipment settings used for eligible processes. Intervention runs were performed using a predefined green chemistry bundle designed to target two principal environmental pathways: waste reduction and energy-efficiency improvement. The intervention included solvent substitution in favor of safer or lower-impact alternatives where technically acceptable, solvent volume minimization through optimized rinse sequences and elimination of unnecessary exchanges, preference for aqueous or aqueous-rich systems for suitable cleaning or preparation steps, streamlining of work-up and purification steps to reduce auxiliary material consumption, and use of more efficient process choices where these remained consistent with hospital policy and reproducibility requirements. The bundle also included energy-focused measures such as optimization of heating and cooling cycles, reduction of avoidable idle runtime, harmonization of equipment settings within validated ranges, and scheduling adjustments intended to consolidate energy-intensive tasks without disrupting patient service or contamination-control requirements. To promote fidelity, staff involved in intervention runs received short targeted training and checklist-based job aids so that implementation remained standardized across operators and across time.

Data were collected prospectively for each randomized run using routine batch documentation supplemented by structured study logs. For every run, the study team recorded the mass or volume of input materials, including solvents, reagents, excipients, and cleaning agents; the quantities of waste generated by stream, including solvent waste, aqueous waste, and solid or disposable waste; the duration of the run; any operational deviations; and routine quality-control outcomes. Waste was measured directly by weight whenever feasible, and calibrated volume-to-mass conversion procedures were applied only when direct weighing was impractical within operational constraints. Energy use was captured from equipment-level readings where such measurements were available and from predefined, validated cycle-based estimation logs where direct metering was not feasible. To support measurement reliability, weighing devices and relevant volumetric instruments were checked at predefined intervals, waste segregation procedures were standardized, containers and labels were harmonized across runs, and staff were trained in consistent recording procedures before study initiation. Source records remained traceable to the hospital documentation system to preserve auditability and data integrity.

The primary outcomes were total waste generated per production run, expressed in kilograms, and total energy consumption per run, expressed in kilowatt-hours. Waste was further categorized by stream so that the contribution of solvent, aqueous, and solid waste components could be examined descriptively. Because eligible runs varied in process characteristics and output scale, the analysis also incorporated a mass-intensity framework aligned with established green-manufacturing metrics. Secondary outcomes therefore included a process mass intensity–aligned indicator reflecting total material input per standardized output, as well as routine quality and operational markers such as pass or fail status in standard quality checks, rework frequency, and documented deviations. These variables were selected to ensure that environmental gains were interpreted alongside operational feasibility and quality preservation rather than in isolation from routine pharmaceutical service requirements (1-3,5).

Bias and confounding were addressed prospectively at both design and analysis stages. Stratified randomization was used to reduce imbalance in major process categories, while the use of production runs rather than retrospective audits reduced the risk of selection distortion associated with post hoc case identification. Objective operational outcomes were prioritized to limit observer bias. The intervention was constrained to validated process ranges to minimize performance drift attributable to unsafe or non-standard implementation. At the analysis stage, prespecified covariates with plausible influence on environmental outcomes, including process category, batch size, and operational conditions

likely to affect heating, cooling, or ventilation demand, were considered in adjusted models. Adherence to the intervention checklist was documented so that sensitivity analyses could explore whether the magnitude of benefit differed according to the extent of bundle implementation. This approach strengthened internal validity while preserving the pragmatic character of the trial.

The sample comprised 120 randomized production runs, with 60 allocated to each arm. This run count was selected as a pragmatic operational sample that allowed balanced representation of the principal process strata, supported stable comparison under real-world workflow conditions, and was feasible within the study period without disrupting routine service delivery. Because the intervention operated at the level of standardized production runs and relied on routinely captured operational measurements, this sample provided sufficient observational density for comparative analysis across the two groups while maintaining the practicality required in a hospital pharmacy environment. The final analytic dataset was assembled after verification of source records, review of run-level documentation, and consistency checks between input, waste, and energy logs.

Statistical analysis followed the intention-to-treat principle, meaning that each run was analyzed in the group to which it had been randomized regardless of minor implementation deviations. Continuous variables were summarized using means and standard deviations or medians and interquartile ranges according to distributional characteristics. Between-group comparisons were performed using parametric or non-parametric tests as appropriate for the underlying data structure. In addition to unadjusted comparisons, multivariable regression models were specified to account for prespecified covariates that could influence waste generation or energy consumption. Sensitivity analyses examined adherence-related variation in the intervention effect. Data completeness was reviewed before analysis using run-level source documents, and the analytic workflow prioritized verified operational measurements derived from routine records. Statistical analyses were conducted at the level of randomized runs, and all reporting focused on effect estimation and comparative interpretation in relation to the study objectives.

Ethical and governance procedures were followed in accordance with institutional operational norms for process-evaluation research. The study did not randomize patients or alter patient treatment allocation; instead, it evaluated validated process-level modifications within routine pharmaceutical preparation services. Quality assurance and patient safety requirements were treated as non-negotiable throughout the study, and any intervention component that risked breaching established quality standards was not implemented. All runs remained fully traceable through the hospital documentation system, and deviations were managed using routine corrective and preventive procedures. Staff participation in training and data-recording activities was conducted within workplace policy, and no personal identifiers were included in the analytic dataset. These safeguards supported ethical conduct, reproducibility, and integrity of the operational evidence generated by the trial.

## RESULTS

A total of 120 eligible production runs were randomized equally between the control arm and the green chemistry bundle arm, with 60 runs analyzed in each group. Randomization preserved broad comparability of process categories across study arms, including sterile-related and non-sterile workflows, supporting a balanced comparison of environmental performance under routine operational conditions. Across the full dataset, the intervention was associated with lower total waste generation, lower energy consumption, and better material-efficiency performance than standard practice, while routine quality outcomes remained high in both groups.

*Table 1. Summary of Primary and Secondary Continuous Outcomes by Study Arm*

| Outcome | Control (n=60) Mean ± SD | Green Bundle (n=60) Mean ± SD | Mean Difference (Green − Control) | 95% CI | p-value | Standardized Effect Size (Hedges g) | Relative Change vs Control |
|---|---|---|---|---|---|---|---|
| **Total waste (kg/run)** | 23.88 ± 5.36 | 19.23 ± 3.94 | -4.64 | -6.34 to -2.94 | <0.001 | -0.98 | -19.5% |
| **Energy use (kWh/run)** | 94.39 ± 16.06 | 80.09 ± 13.16 | -14.31 | -19.61 to -9.00 | <0.001 | -0.97 | -15.1% |
| **PMI-aligned indicator** | 136.6 ± 30.3 | 118.2 ± 27.8 | -18.35 | -28.86 to -7.85 | <0.001 | -0.63 | -13.5% |

The primary analysis showed a consistent advantage for the intervention arm across all continuous environmental outcomes. Total waste per production run decreased from 23.88 ± 5.36 kg in the control arm to 19.23 ± 3.94 kg in the green bundle arm, yielding a mean reduction of 4.64 kg/run (95% CI, -6.34 to -2.94; p<0.001), equivalent to a 19.5% relative reduction and a large standardized effect (Hedges g = -0.98). Energy use also declined materially, from 94.39 ± 16.06 kWh/run to 80.09 ± 13.16 kWh/run, corresponding to a mean difference of -14.31 kWh/run (95% CI, -19.61 to -9.00; p<0.001), a 15.1% relative reduction, and another large effect size (Hedges g = -0.97). The PMI-aligned indicator improved from 136.6 ± 30.3 in the control arm to 118.2 ± 27.8 in the intervention arm, with a mean difference of -18.35 (95% CI, -28.86 to -7.85; p<0.001), representing a 13.5% reduction and a moderate effect size (Hedges g = -0.63). Taken together, these results indicate that the environmental benefit of the green bundle was not limited to a single metric, but extended across waste generation, utility demand, and overall material throughput efficiency.

*Table 2. Distributional Summary of Continuous Outcomes*

| Outcome | Arm | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|---|
| **Total waste (kg/run)** | Control | 60 | 23.88 | 5.36 | 23.02 | 7.48 |
| | Green bundle | 60 | 19.23 | 3.94 | 19.04 | 4.07 |
| **Energy use (kWh/run)** | Control | 60 | 94.39 | 16.06 | 90.95 | 24.56 |
| | Green bundle | 60 | 80.09 | 13.16 | 77.67 | 23.20 |
| **PMI-aligned indicator** | Control | 60 | 136.6 | 30.3 | 136.2 | 43.65 |
| | Green bundle | 60 | 118.2 | 27.8 | 117.9 | 40.38 |

The distributional summaries reinforced the primary findings by showing that the observed differences were not driven solely by a small number of extreme runs. For total waste, the median decreased from 23.02 kg/run in the control arm to 19.04 kg/run in the intervention arm, while the interquartile range narrowed from 7.48 to 4.07, suggesting both lower waste generation and reduced variability under the green bundle. A similar pattern was observed for energy use, where the median declined from 90.95 to 77.67 kWh/run. The PMI-aligned indicator also shifted downward at both the mean and median levels, indicating that material-efficiency gains were broadly distributed across intervention runs rather than confined to isolated process instances.

*Table 3. Waste Stream Composition by Study Arm*

| Waste Stream (kg/run) | Control Mean | Green Bundle Mean | Absolute Difference (Green − Control) | Relative Change vs Control |
|---|---|---|---|---|
| **Solvent waste** | 13.12 | 9.43 | -3.69 | -28.1% |
| **Aqueous waste** | 7.16 | 6.30 | -0.86 | -12.0% |
| **Solid/disposables** | 3.60 | 3.50 | -0.10 | -2.8% |
| **Total** | 23.88 | 19.23 | -4.64 | -19.5% |

Disaggregation of total waste showed that the overall reduction was driven predominantly by the solvent fraction. Mean solvent waste fell from 13.12 kg/run in the control arm to 9.43 kg/run in the intervention arm, an absolute reduction of 3.69 kg/run and a relative decrease of 28.1%. In contrast, aqueous waste declined more modestly by 0.86 kg/run, equivalent to a 12.0% reduction, while solid/disposable waste changed only minimally, decreasing by 0.10 kg/run or 2.8%. Numerically, solvent waste accounted for approximately 79.5% of the overall reduction in total waste (3.69 of 4.64 kg/run), supporting the interpretation that solvent substitution and minimization were the dominant contributors to environmental benefit in this trial.

*Table 4. Routine Quality and Operational Events*

| Outcome | Control n/N (%) | Green Bundle n/N (%) | Effect Estimate | 95% CI | p-value |
|---|---|---|---|---|---|
| **Quality failures (any)** | 3/60 (5.0%) | 1/60 (1.7%) | RR 0.33 | 0.04 to 3.11 | 0.619 |
| **Rework required (any)** | 5/60 (8.3%) | 5/60 (8.3%) | RR 1.00 | 0.31 to 3.28 | 1.000 |

Routine quality outcomes remained favorable in both study arms. Quality failures were uncommon overall, occurring in 5.0% of control runs and 1.7% of intervention runs, but this difference was statistically imprecise and not significant (risk ratio 0.33, 95% CI 0.04 to 3.11; p=0.619). Rework frequency was identical in both groups at 8.3%, yielding no detectable between-group difference (risk ratio 1.00, 95% CI 0.31 to 3.28; p=1.000). These findings indicate that the environmental gains associated with the green chemistry bundle were not accompanied by a measurable deterioration in routine quality assurance outcomes under the conditions evaluated.

*Table 5. Comparative Effect Gradient Across Environmental Efficiency Outcomes*

| Outcome | Mean Difference (Green − Control) | 95% CI | p-value | Relative Change vs Control |
|---|---|---|---|---|
| **Total waste (kg/run)** | -4.64 | -6.34 to -2.94 | <0.001 | -19.5% |
| **Energy use (kWh/run)** | -14.31 | -19.61 to -9.00 | <0.001 | -15.1% |
| **PMI-aligned indicator** | -18.35 | -28.86 to -7.85 | <0.001 | -13.5% |

When the three key environmental outcomes were compared together, total waste showed the largest proportional reduction at 19.5%, followed by energy use at 15.1% and the PMI-aligned indicator at 13.5%. Although the absolute scales differ across these metrics, all three confidence intervals remained fully below the null value, indicating consistent directional benefit for the green chemistry bundle. This cross-outcome pattern suggests that the intervention improved not only waste handling performance, but also the deeper operational drivers of environmental impact, including material throughput and utility demand.

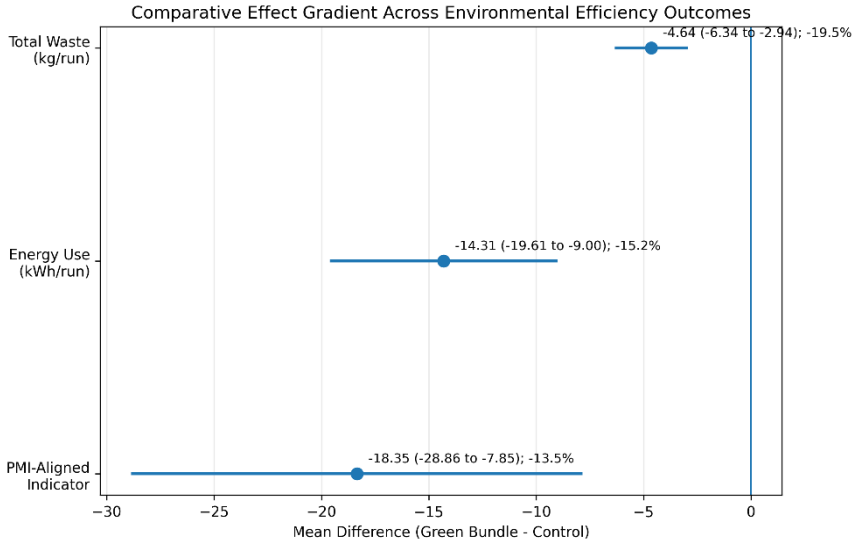


*Figure 1 Comparative Effect Gradient Across Environmental Efficiency Outcomes*

The intervention demonstrated a consistent improvement across all three major environmental endpoints, with total waste reduced by 4.64 kg/run (95% CI, -6.34 to -2.94), energy use reduced by 14.31 kWh/run (95% CI, -19.61 to -9.00), and the PMI-aligned indicator reduced by 18.35 units (95% CI, -28.86 to -7.85). Relative reductions were greatest for total waste at 19.5%, followed by energy use at 15.1% and PMI at 13.5%, indicating that the green chemistry bundle produced its strongest gradient of benefit in waste prevention while maintaining parallel gains in energy efficiency and overall material-use efficiency. None of the confidence intervals approached the null line, reinforcing the statistical robustness and directional consistency of the intervention effect across environmental performance domains.

## DISCUSSION

The findings of this pragmatic randomized controlled trial indicate that a structured green chemistry bundle can reduce the environmental impact of routine pharmaceutical preparation in a tertiary-hospital setting without measurable compromise in routine quality outcomes. Compared with standard practice, the intervention arm demonstrated lower total waste generation, lower energy consumption, and improved PMI-aligned performance, suggesting that the intervention influenced both visible waste streams and the underlying material-efficiency profile of the production process. The reduction in total waste was substantial and directionally consistent with the broader green chemistry literature, which has long identified pharmaceutical workflows as disproportionately waste-intensive because of repeated solvent use, auxiliary materials, and purification-related losses (20,21). In the present study, the magnitude and coherence of effect across multiple environmental endpoints strengthen the interpretation that the observed benefit was not an isolated metric artifact but reflected a system-level improvement in operational efficiency.

The waste-stream breakdown provides an important mechanistic insight into how the intervention likely achieved its effect. Most of the overall reduction in total waste was attributable to a decline in solvent waste, whereas aqueous and solid/disposable fractions changed modestly. This pattern is highly plausible because solvent use is frequently the dominant contributor to waste mass and environmental burden in pharmaceutical processing, particularly where washing, extraction, and cleaning operations are common (22,23). The intervention's emphasis on solvent substitution and solvent minimization therefore appears to have targeted the highest-yield environmental leverage point within hospital pharmacy production. This is consistent with solvent-selection frameworks that encourage replacement of problematic solvents with safer alternatives and reduction of avoidable solvent volume without sacrificing technical suitability or process reliability (24,25). In practical terms, the findings suggest that even in hospital-based preparation settings, where the scale is smaller than industrial API manufacturing, solvent stewardship remains one of the most effective routes to near-term environmental improvement.

The improvement in the PMI-aligned indicator further supports the interpretation that the green bundle did not merely redistribute waste between categories, but actually improved material throughput efficiency per standardized output. This distinction is important because waste reduction alone can sometimes reflect downstream segregation changes rather than genuine upstream prevention. By contrast, a lower PMI-aligned value indicates that fewer total input materials were required relative to productive output, which is more consistent with true process optimization. In pharmaceutical manufacturing, PMI has become one of the most useful practical sustainability metrics because it captures the broader material burden of a process rather than focusing only on reaction yield or a single disposal stream (21,26). Within the present study, the lower PMI-aligned values in the intervention arm are consistent with the combined effects of lower solvent volumes, streamlined work-up steps, and more efficient use of cleaning-related inputs.

The reduction in energy use is also a meaningful finding because energy-intensive operations are a major but sometimes underappreciated contributor to the environmental footprint of pharmaceutical services. In hospital pharmacies, energy demand is influenced not only by active processing steps but also by sterilization, drying, refrigeration, controlled-area ventilation, and avoidable idle runtime. The observed reduction in energy consumption is therefore compatible with the intervention's operational design, which included optimization of heating and cooling cycles, harmonization of equipment settings within validated limits, and scheduling adjustments intended to reduce repeated start-stop inefficiencies. Prior literature has emphasized that the "design for energy efficiency" principle in green chemistry should not be confined to reaction chemistry alone, but should extend to the full operational environment in which pharmaceutical preparation occurs (27). The present findings support that view and indicate that energy-efficiency strategies can be implemented in hospital pharmacy practice without

disrupting routine production performance when they are integrated into validated operational workflows.

An important strength of this study is that the intervention was evaluated under routine tertiary-hospital conditions rather than in an idealized laboratory scenario. This improves the applied relevance of the findings because hospital pharmacy services operate within fixed staffing structures, real-time clinical demand, established quality systems, and constrained infrastructure. In that context, the absence of a detectable increase in rework or routine quality failure is particularly important. Sustainability interventions are unlikely to be adopted in hospital practice if they threaten reproducibility, sterility assurance, or service continuity. The present trial suggests that greener process choices can remain compatible with operational reliability when they are implemented within validated ranges and supported by standardized checklists and staff enablement. This aligns with broader experience in green pharmaceutical practice, where sustainability programs are more successful when framed as structured operational refinement rather than as ad hoc deviation from established procedures (23,24).

The study also has methodological relevance because randomized evaluations remain uncommon in sustainability-oriented manufacturing research, especially in healthcare settings. Many published reports in this field rely on retrospective comparisons, modeling exercises, lifecycle assessments, or case-based route optimization. Although these approaches are informative, they are vulnerable to confounding by concurrent changes in workload, equipment condition, staff behavior, and process-mix variation. By randomizing production runs and analyzing objective environmental outcomes, the present study improved causal interpretability relative to most observational designs. Nevertheless, several limitations should be considered. First, the intervention was implemented as a bundle, which improves practical relevance but limits the ability to isolate the independent contribution of each component. It is therefore not possible to determine precisely how much of the observed effect resulted from solvent substitution, solvent minimization, work-up simplification, or energy-focused scheduling changes alone. Second, the study was conducted at a single tertiary-care site, so the magnitude of effect may differ in other institutions with different baseline solvent practices, equipment efficiency, waste infrastructure, or process mix. Third, full blinding of operators was not feasible, and some behavioral contamination between trial arms may have occurred if staff carried newly learned efficiency habits into control runs. Such contamination would most likely bias the results toward the null rather than exaggerate the intervention effect, but it remains a consideration when interpreting the observed differences.

Another limitation relates to measurement granularity. Although the study used direct weighing where feasible and predefined energy-capture procedures, some operational measurements were derived from validated estimation logs rather than universal equipment-level metering. This is a realistic compromise in a busy hospital environment, but more comprehensive instrument-based monitoring could strengthen precision in future studies. In addition, the environmental endpoints were necessarily focused on waste mass, energy use, and a PMI-aligned indicator. These are meaningful and operationally tractable measures, but they do not fully capture toxicity-weighted solvent impacts, upstream supply-chain burdens, or greenhouse-gas consequences linked to local electricity mix. Future work would therefore benefit from integrating lifecycle-oriented indicators and conducting component-level or subgroup analyses, particularly across sterile and non-sterile workflow categories, where utility profiles and operational constraints may differ substantially (27,28).

Despite these limitations, the study provides practical evidence that greener pharmaceutical preparation is achievable in a tertiary-hospital context through targeted, low-disruption changes in solvent practice, material handling, and energy-intensive workflow design. The findings are most immediately relevant to institutions seeking operational sustainability measures that can be embedded within standard operating procedures rather than pursued as separate environmental initiatives. In resource-constrained settings such as Pakistan, where healthcare systems must balance quality, safety, cost, and infrastructure limitations, interventions that reduce waste and utility demand simultaneously may offer particular

value. The present trial therefore contributes locally actionable evidence and supports the broader case for integrating solvent stewardship, material-efficiency monitoring, and validated energy-optimization practices into routine hospital pharmacy governance.

## CONCLUSION

This pragmatic randomized controlled trial demonstrated that a structured green chemistry bundle can reduce total waste generation, lower energy consumption, and improve material-efficiency performance in routine pharmaceutical preparation within a tertiary-hospital setting, without evidence of deterioration in routine quality outcomes. The strongest effect was observed in solvent-derived waste, indicating that solvent stewardship is likely the principal operational driver of short-term environmental improvement in this context. Although confirmation in multi-site studies with more granular metering and broader lifecycle endpoints is warranted, the present findings support the integration of validated green chemistry practices into hospital pharmacy standard operating procedures as a feasible and quality-compatible pathway toward more sustainable pharmaceutical production.

## REFERENCES

1. Sheldon RA. The E factor: fifteen years on. Green Chem. 2007;9:1273-1283. doi:10.1039/B713736M.
2. Jiménez-González 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. Org Process Res Dev. 2011;15(4):912-917. doi:10.1021/op200097d.
3. Benison CH, Payne PR. Manufacturing mass intensity: 15 years of process mass intensity and development of the metric into plant cleaning and beyond. Curr Res Green Sustain Chem. 2022;5:100229. doi:10.1016/j.crgsc.2021.100229.
4. Kerr MS, Cole KP. Sustainability case studies on the use of continuous manufacturing in pharmaceutical production. Curr Res Green Sustain Chem. 2022;5:100279. doi:10.1016/j.crgsc.2022.100279.
5. Alfonsi K, Colberg J, Dunn PJ, et al. Green chemistry tools to influence a medicinal chemistry and research chemistry based organization. Green Chem. 2008;10:31-36. doi:10.1039/B711717E.
6. Henderson RK, Jiménez-González C, Constable DJC, et al. Expanding GSK's solvent selection guide—embedding sustainability into solvent selection. Green Chem. 2011;13:854-862. doi:10.1039/C0GC00918K.
7. Prat D, Hayler J, Wells A. A survey of solvent selection guides. Green Chem. 2014;16:4546-4551. doi:10.1039/C4GC01149J.
8. Prat D, Wells A, Hayler J, et al. CHEM21 solvent selection guide. Green Chem. 2016;18:288-296. doi:10.1039/C5GC01008J.
9. Byrne FP, Jin S, Paggiola G, et al. Tools and techniques for solvent selection: green solvent selection guides. Sustain Chem Process. 2016;4:7. doi:10.1186/s40508-016-0051-z.
10. Curzons AD, Constable DJC, Cunningham VL. Solvent selection guide: a methodology for solvent selection. Int J Life Cycle Assess. 1999;4:93-102. doi:10.1007/s100980050014.
11. Amelio A, Van Gerven T, et al. Guidelines based on life cycle assessment for solvent selection during the process design and scale-up. Green Chem. 2014;16:3045-3060. doi:10.1039/C3GC42513D.
12. 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 Technol Environ Policy. 2017;19:2467-2477. doi:10.1007/s10098-017-1444-8.

13. Aboagye EA, Chea JD, Yenkie KM, Slater CS, Savelski MJ. Systems level roadmap for solvent recovery and reuse in industries. iScience. 2021;24(10):103114. doi:10.1016/j.isci.2021.103114.

14. Leemans Martin L, Peschke T, Venturoni F, Mostarda S. Pharmaceutical industry perspectives on flow chemocatalysis and biocatalysis. Curr Opin Green Sustain Chem. 2020;25:100373. doi:10.1016/j.cogsc.2020.04.011.

15. De Santis P, Meyer LE, Kara S. The rise of continuous flow biocatalysis – fundamentals, very recent developments and future perspectives. React Chem Eng. 2020;5:2155-2184. doi:10.1039/D0RE00335B.

16. Colacino E, Isoni V, Crawford D, García F. Upscaling mechanochemistry: challenges and opportunities for sustainable industry. Trends Chem. 2021;3(5):335-339. doi:10.1016/j.trechm.2021.02.008.

17. Solares-Briones M, Coyote-Dotor G, Páez-Franco JC, et al. Mechanochemistry: a green approach in the preparation of pharmaceutical cocrystals. Pharmaceutics. 2021;13(6):790. doi:10.3390/pharmaceutics13060790.

18. García F, et al. Green metrics in mechanochemistry. Chem Soc Rev. 2023. doi:10.1039/D2CS00997H.

19. Leitão A, et al. Comparison of traditional and mechanochemical production processes for pharmaceutical-relevant targets using green metrics. RSC Sustain. 2024. doi:10.1039/D4SU00385C.

20. Nowak PM, et al. Comparison of greenness and whiteness of selected mechanochemical and solution-based reactions using a new RGBsynt model. Green Chem. 2025. doi:10.1039/D4GC05097E.

21. Weaver E, O'Hagan C, Lamprou DA. The sustainability of emerging technologies for use in pharmaceutical manufacturing. Expert Opin Drug Deliv. 2022;19(7):861-872. doi:10.1080/17425247.2022.2093857.

22. Kinner A, Nerke P, Siedentop R, et al. Recent advances in biocatalysis for drug synthesis. Biomedicines. 2022;10(5):964. doi:10.3390/biomedicines10050964.

23. Broumidis E, Díaz-Kruik P, Paradisi F. Flow biocatalysis. Nat Rev Methods Primers. 2025. doi:10.1038/s43586-025-00428-5.

24. Oldenkamp R, Hamers T, Wilkinson J, Slootweg J, Posthuma L. Regulatory risk assessment of pharmaceuticals in the environment: current practice and future priorities. Environ Toxicol Chem. 2024;43(3):611-622. doi:10.1002/etc.5535.

25. Chen Z, et al. Life cycle assessment of pharmaceuticals: the ciprofloxacin hydrochloride case. Int J Life Cycle Assess. 2021;26. doi:10.1007/s11367-020-01841-6.

26. Ashfaq M, Khan KN, Rehman MSU, et al. Ecological risk assessment of pharmaceuticals in the receiving environment of pharmaceutical wastewater in Pakistan. Ecotoxicol Environ Saf. 2017;136:31-39. doi:10.1016/j.ecoenv.2016.10.029.

27. Zeeshan M, et al. Impact of hospital waste on environment and public health: a case study in Pakistan. J Pak Med Assoc. 2018;68(5). doi:10.26719/2018.24.5.443.

28. Ali M, Wang W, Chaudhry N, Geng Y. Hospital waste management in developing countries: a case study of Pakistan. Waste Manag Res. 2016;34(2). doi:10.1177/0734242X15616474.

29. Bibi M, et al. Eco-friendly synthesis and environmental assessment of diclofenac. Chemistry Africa. 2023. doi:10.1007/s13201-023-01954-x.

30. Alrabiah H, Ahmed V, Bahroun Z. A systematic review of waste management practices in the healthcare sector. Cleaner Waste Systems. 2025;12:100400. doi:10.1016/j.clwas.2025.100400.

31. Trost BM. The atom economy—a search for synthetic efficiency. Science. 1991;254(5037):1471-1477. doi:10.1126/science.254.5037.1471.