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Solvent Selection for Circular Designs – Bridging Process Needs and Sustainability Goals

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Abstract: Pharmaceutical industries play a crucial role in enhancing global health outcomes; however, like many other sectors, they also encounter significant environmental challenges. The extraction of raw materials and the manufacture of active pharmaceutical ingredients (APIs) result in considerable waste production, substantial resource consumption, and environmental pollution. Transitioning from traditional linear economic models to circular processes presents an opportunity for more sustainable pharmaceutical operations that benefit both communities and the environment. The circular economy framework – grounded in resource efficiency, waste minimization, and material regeneration – offers a path towards comprehensive sustainability in pharmaceutical practices. This is particularly relevant in the area of solvent usage, which accounts for over half the input mass and associated waste in most processes. This article examines the application of circular economy principles to solvent selection within process design, highlighting its significance as a central component of sustainable pharmaceutical development.

Keywords: Circular economy · Distillation · LCA · Solvent selection · Sustainable process development

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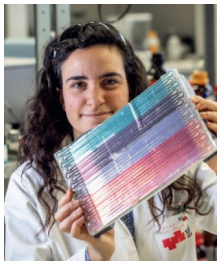

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1. Introduction

The pharmaceutical industry is an integral part of modern society, responsible for producing drugs and therapeutics that address critical health challenges worldwide. At the same time, its operations rely on resource-intensive manufacturing processes that have substantial environmental impacts. Historical regulations and business models in pharmaceutical manufacturing favor linear processes: raw materials are extracted, processed into products, and discarded as waste after use. This approach has resulted in resource depletion, ecosystem degradation, and mounting pressure on waste management infrastructures. Solvent use specifically constitutes about 80% of all mass input in most pharmaceutical manufacturing, of which most ends up as waste.[1] In transitioning from linear manufacturing processes to circular ones, the industry can ensure that manufacturing resources are retained in continuous loops, minimizing waste, maximizing resource usage, leading to more sustainable processes, affording better health outcomes for both, the patients and the planet.

Solvent selection is no longer optional but needed in addressing pressing environmental challenges, current and future regulatory demands, as well as market expectations. To do so, concerning materials and solvents are being replaced with bio-based, biodegradable, safer, and less polluting alternatives. Sustainable solvent selection is a critical cornerstone, leading to overall better outcomes for industries and the societies they are part of. However, to achieve sustainable manufacturing processes, one must not solely design around input materials, we need to start to design out waste streams too (Fig. 1).

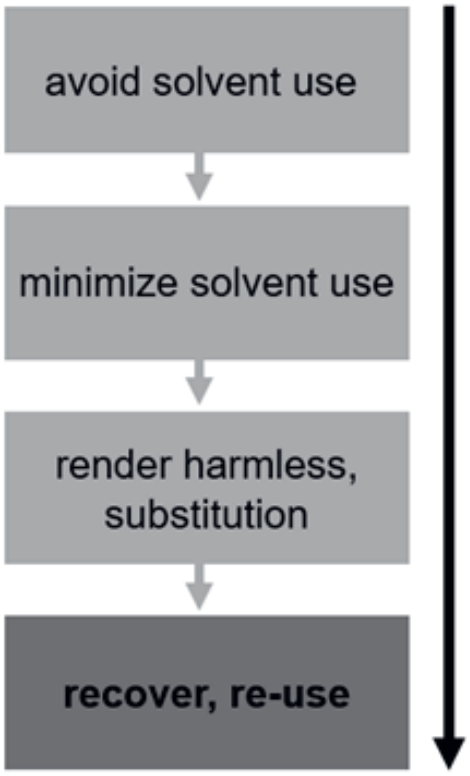

Fig. 1. Inherent process sustainability.

The philosophy of inherent sustainability requires actions at all stages. Making changes at later stages, trying to recover and re-use waste streams after the fact is traditionally associated with higher costs and technical challenges (Fig. 2). Product costs and environmental footprints are often determined early in the design phases through decisions on synthesis route and the selection of input materials. To mitigate this as much as possible, make it simple to recover and re-use potential waste streams, chemists must consider process outputs in their design.

Next to important criteria such as cost, regulations, or supply chain, the core principle behind most past solvent selection guides from GSK,[2] Sanofi,[3] Pfizer,[4] and others,[5] are Environment, Health, and Safety (EHS) frameworks, in which life cycle assessment (LCA) data has started to find hold. Environmental (E) impact criteria usually consider the solvent's lifecycle from production to disposal, or its biodegradability. Occupational health (H) criteria are focused on the toxicological profile of the solvent, exposure limits, and necessary protective measures, while for safety (S), the focus is primarily on physical properties that could pose direct risks during the handling, storage, and usage of the solvent such as flash point, auto-ignition temperature, explosive limits, or the boiling point, mostly focusing on solvent selection, or solvent substitution (Fig. 1). To complete the picture towards sustainable API manufacturing, we additionally must consider solvent recycling, recovery, and re-use.

2. Discussion

The question of how to measure the sustainability of solvents has been a matter of debate for quite a while. Current literature often defines a 'green' solvent as a solvent that combines a minimum environmental impact during its manufacture with a low risk to the environment, health, and safety per kg of solvent. Therefore, a bio-based solvent is not necessarily 'greener', safer, and less toxic compared to a fossil-based analogue. The 'green' solvent, whether it is bio-based or fossil-based, is the solvent that makes a product, or a process with the least environmental impact over its entire life cycle, while being relatively safe. This leads to another important conclusion that the greenness of any given solvent is application-specific because a certain solvent can be green for one application and not for another. Essentially, no solvent can be inherently green; but it can be considered as green in comparison to an alternative. While these ideas are a first step in the right direction, we must move beyond surface-level solutions and embrace a holistic perspective that encompasses environmental, social, and economic dimensions, considering the entire lifecycle, including production, recycling, or disposal, of all materials, thinking about sustainability in its entirety. The purpose of this manuscript is therefore to present an idea, an approach that might contribute to the advancement of sustainable solvent selection and promote circular chemical processes, as the design of chemical processes, the design of most actions in general, should aim to move towards closed material loops while maintaining social and ecological objectives for sustainable progress.

Integrating such sustainability considerations throughout entire development processes is essential. Nevertheless, the prioritization of certain aspects differs based on development stages and available resources. Due to attrition risks in early development programs within the pharmaceutical industry, process development resources are often limited to later stages. Unfortunately, decisions made during these early stages, such as the synthesis route, key starting materials, and the therefore often limited solvent selection, can significantly impact the sustainability of the final manufacturing processes, as certain materials and solvents cannot be changed easily. But fortunately, incorporating sustainability considerations into these decisions from the beginning requires less and less additional resources, using metric-based approaches, tools,[6] and assessments to focus upon inefficiencies

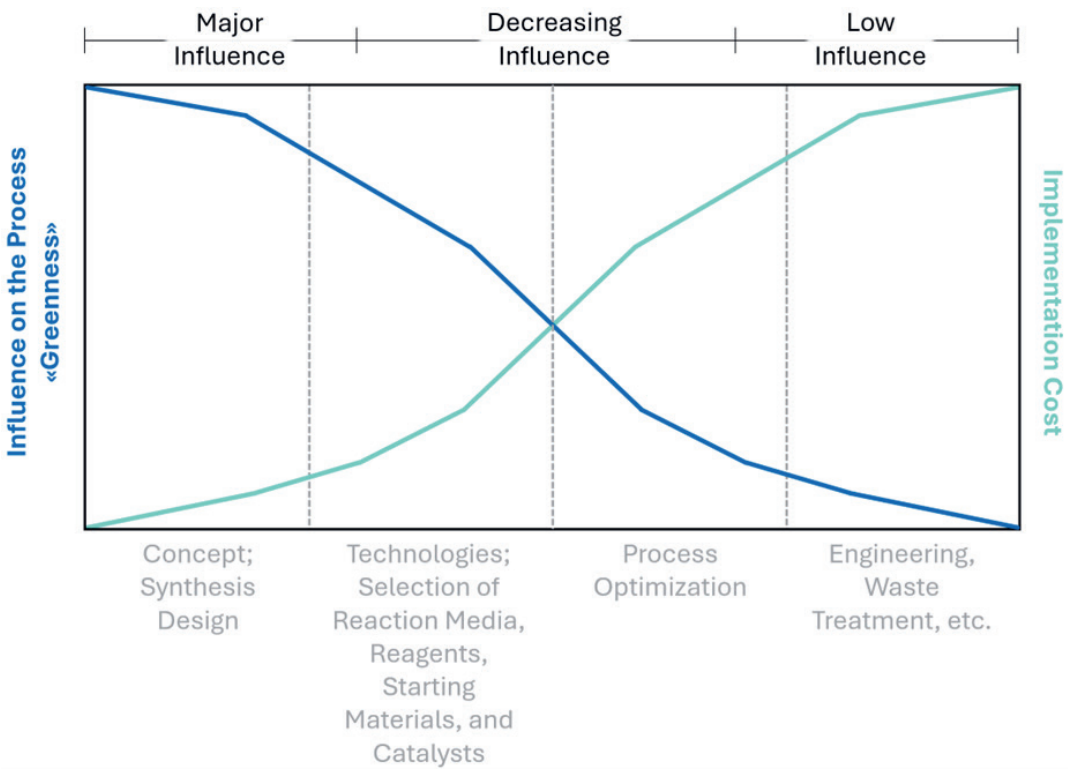

Fig. 2. Stages of sustainable process design.

(*e.g.* environmental hotspots) and envision development opportunities. With regard to solvent selection, it is notable that often more than half of all solvent inputs in typical small molecule API manufacturing processes are utilized during work-up or purification stages, as well as during reactor cleaning procedures. These solvents often end up as mixtures and are generally more ame-

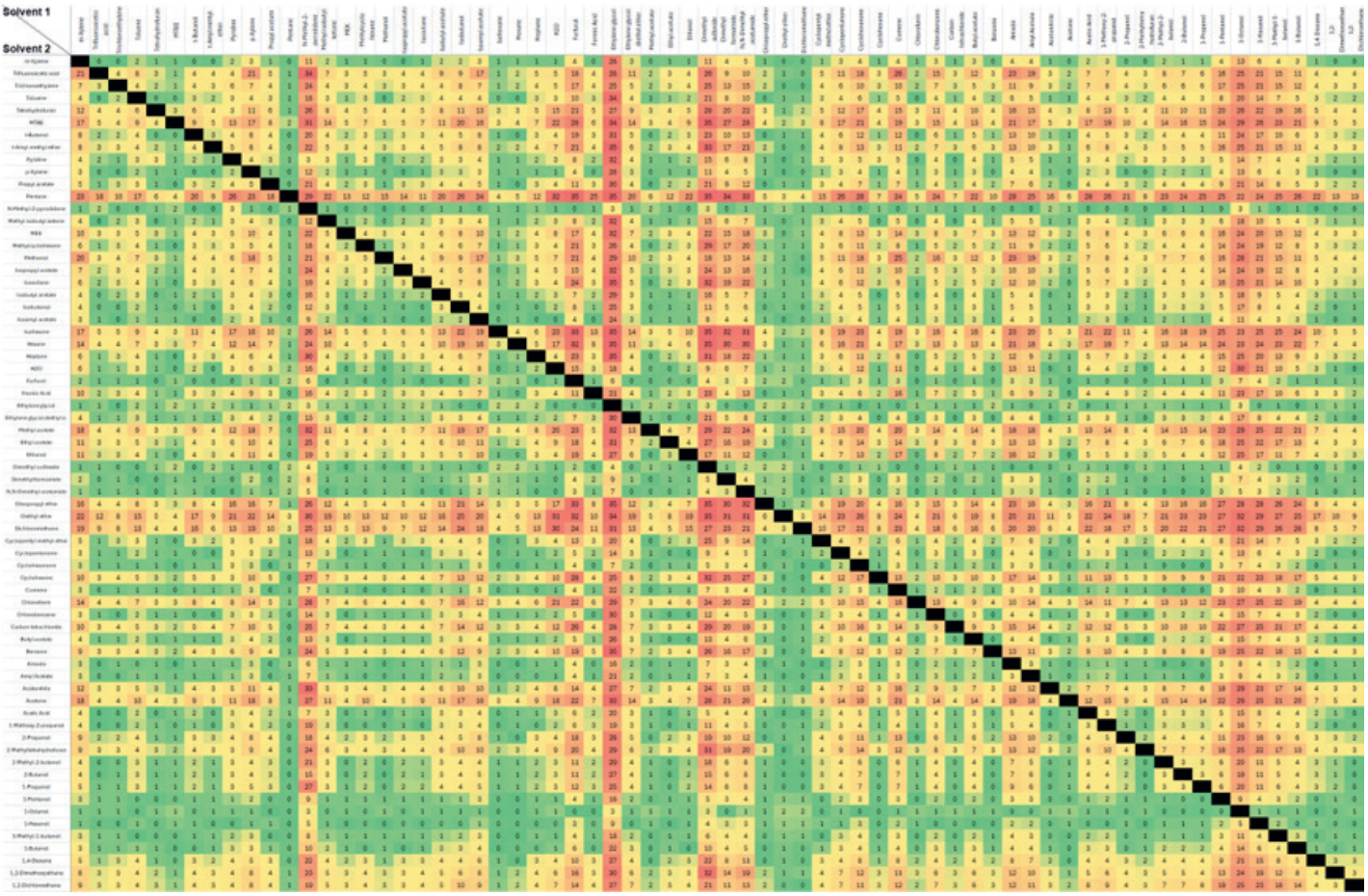

Fig. 3. Heat map of the process-independent calculated SSR 'solvent swap ratio' at 100 mbar pressure for 68 relevant solvents; number of theoretical solvent swaps [$V_{swap\ solvent,\ solvent\ 2}/V_{original\ solvent,\ solvent\ 1}$] required to achieve solvent purities of 99 %v.

nable to substitution than others selected to be used directly in the reaction steps. Therefore, our proposed approach focuses on these solvents, the ones used after the reaction has taken place, the ones easier to be substituted, yet the ones often neglected during process development, especially in academic settings.

To improve the selection of solvents, we propose to combine conventional environmental indicators from life cycle inventories like climate change, resource depletion, or the ozone depletion potential[8] with an indicator quantifying separability of solvent mixtures. The indicator we propose is similar to the recently introduced concept of the separation feasibility indicator (SFI).[7] However, instead of quantifying the number of theoretical stages required for separation, we utilized numerical simulations to derive a more practical and actionable metric: the simulated swap solvent ratio (SSR). This ratio, defined as [$V_{swap\ solvent}$ / $V_{original\ solvent}$], describes the replacement of 1 L of solvent A with solvent B, expressed as the volume of solvent B required to achieve a purity of 99 %v of solvent B in the distillation residue.

The classification of solvent combinations based on the SSR enables the design of resource-efficient manufacturing processes, specifically by evaluating a solvent's ease of separability from binary solvent mixtures. This directly impacts overall solvent consumption and contributes to process optimization. By using the SSR approach during early-phase process development, researchers can establish 'first-time-right' procedures with minimal effort. The methodology leverages pre-calculated SSR data displayed in matrix form, reducing trial-and-error experimentation in subsequent waste valorization steps. Consequently, this approach saves both time and resources while ensuring the environmental sustainability of solvent selection and usage. Fig. 3 presents simulated SSR values for 68 commonly used solvents.

The color coding reflects the solvent swap ratio required to achieve 99 %v in both solvents. Darker colors indicate higher solvent SSR ratios, signifying more challenging separations due to the increased amount of swap solvent needed.A representation that allows users to quickly identify solvent pairs that demand higher energy and resource inputs, as well as those that offer potential savings in distillative separation processes. It is important to note that these assessments are strongly influenced by operational parameters, such as temperature and pressure conditions, or the needed output qualities of the desired solvents, meaning that separability rankings may change drastically when process conditions are adjusted, something that is critical to adapting SSR-based tools to real-world development scenarios.

Since solvent mass intensities alone are not a direct indicator for environmental impacts, integrating SSR with additional environmental indicators is essential to provide a more comprehensive framework to assess solvent usage and its associated environmental footprint. Such an integration has the potential to supplement and guide current methods used to reduce the environmental footprint of solvent usage using different approaches: like 1) the direct reduction of solvent amounts through innovative process development and optimization; 2) substitution of current solvents with alternatives that exhibit a lower environmental footprint; 3) replacement of solvents with identical ones from renewable bio-based rather than fossil-based sources; 4) incineration of non-separable solvents in combination with heat recovery systems to harness energy while minimizing waste; or 5) recycling, recovery, or re-use of separable solvents – demonstrated through the calculations made to obtain SSR data in Fig. 3 – represent actionable pathways to reduce virgin solvent consumption and minimize hazardous disposal issues (Fig. 4). The latter approach, solvent regeneration, and re-use, not only reduces environmental burdens

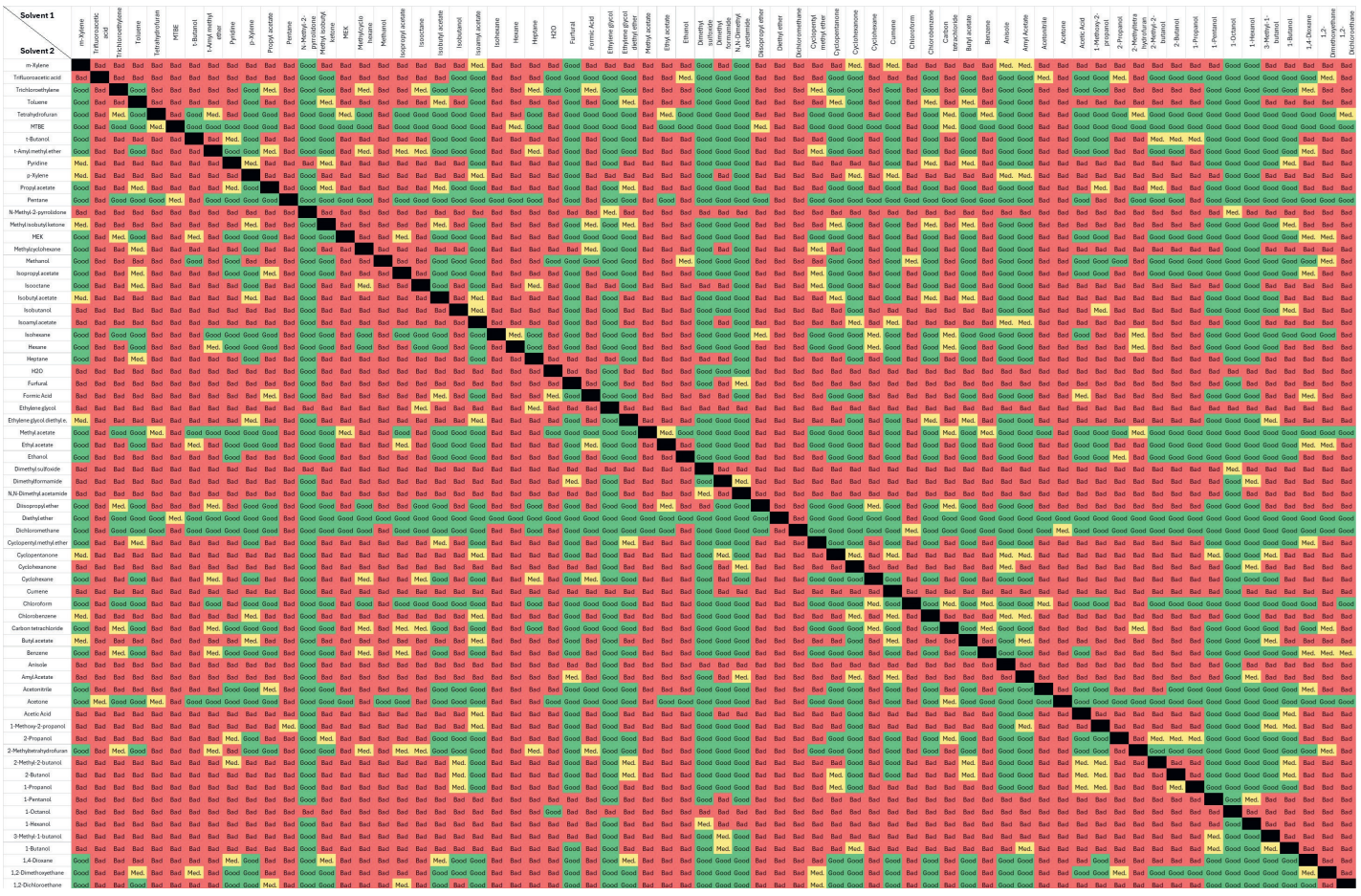

Fig. 4. Simplified heat map of recyclability of solvent 1 from solvent 2 at 100 mbar, using SSR data.

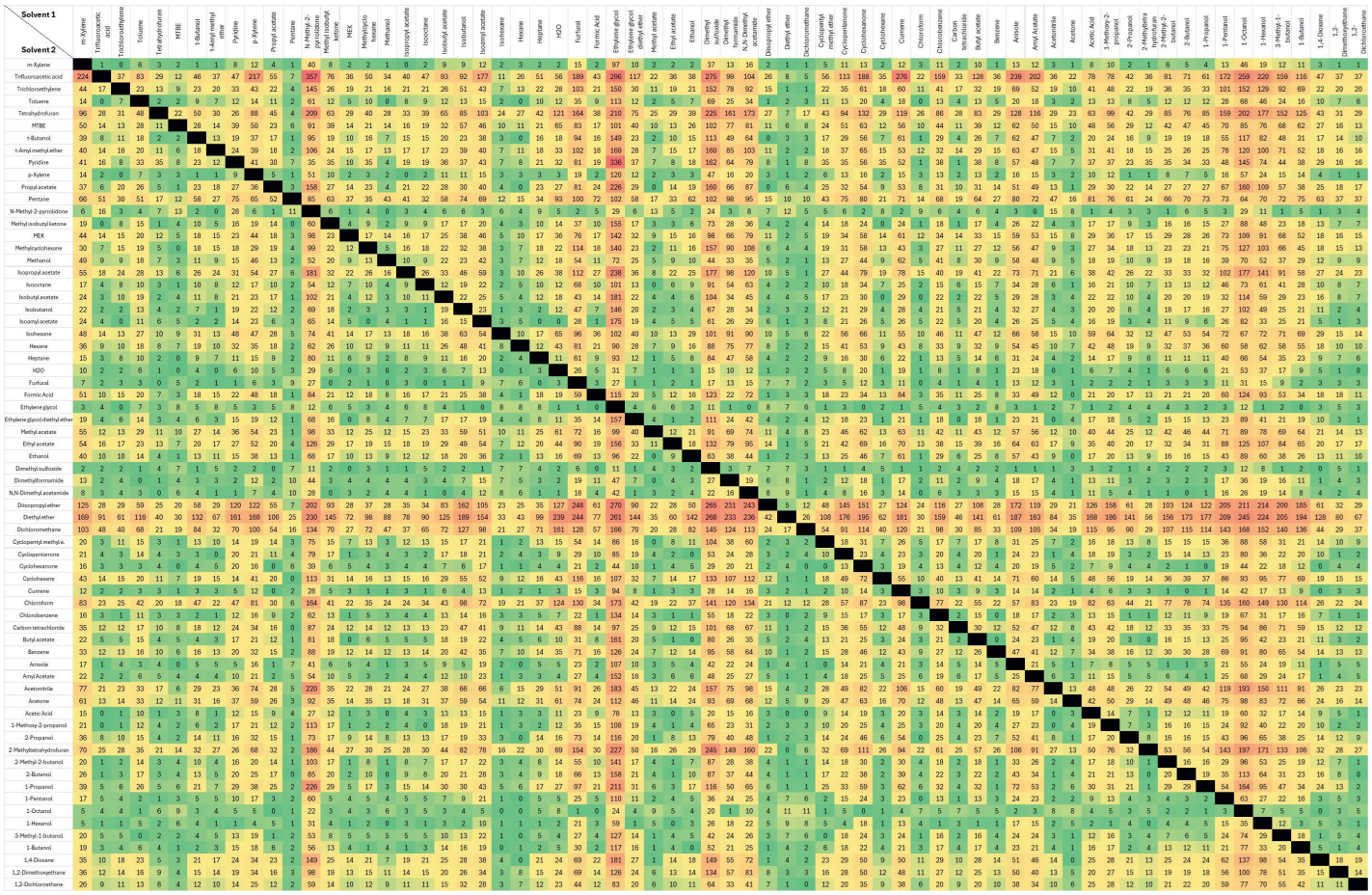

Fig. 5. Relative CO_2-burden of binary solvent mixtures; SSR x (CO_2-footprint of solvet 1 + solvent 2).

but also aligns with international sustainability frameworks such as the EU Circular Economy Action Plan,[9] REACH directives, and Environmental Protection Agency (EPA) waste regulations. Through these frameworks, industries are encouraged to shift toward circular processes, minimizing waste generation and enhancing resource efficiency. The ability to recover and reuse solvents exemplifies key principles of circular economy models, wherein materials are continually looped back into production cycles to reduce reliance on virgin inputs and diminish the environmental impacts of disposal. By adopting such practices, pharmaceutical and chemical industries can simultaneously prevent regulatory non-compliance while positioning themselves as leaders in environmental stewardship and sustainability, something that ensures that the chosen path aligns not only with regulatory requirements but also with broader corporate sustainability goals, such as reducing greenhouse gas emissions, energy consumption, resource depletion, and waste generation.

The application of SSR-based solvent characterization goes beyond simply reducing separation complexity and resource consumption. It helps chemists to strategically align their process designs with broader environmental goals, such as reducing energy utilization, cutting greenhouse gas emissions, and minimizing waste generation. By identifying solvent combinations that not only optimize separability but also align with life cycle sustainability indicators (*e.g.* carbon footprint, human toxicity), it can be possible to systematically minimize environmental trade-offs across an entire production process.

But to begin from the start, the SSR provides a quantitative measure of practicality and efficiency of removing or recovering solvents from mixtures of solvents, originating from the reaction itself or later operations, evaluating properties that dictate separation challenges. For example, solvents with close boiling points to the solvent desired to be recovered require greater energetic inputs, generate higher engineering challenges, resulting in higher operational costs. Solvents with low volatility or high affinity for water can also pose difficulties, necessitating additional separation steps or specialized equipment. Comparatively, an ideal solvent – according to the SSR – exhibits distinct phase behaviors, enabling simpler and more resource-efficient distillative separation to be used. Thus, the concept of SSR has the potential of becoming a predictive tool that supports solvent choice optimization in early-stage process design. However, while the SSR addresses the practicalities of solvent separation, it does not inherently account for the environmental characteristics of solvent candidates – an essential consideration in sustainable development practices. And herein lies a critical area for synergy: coupling the SSR with environmental indicators can produce a holistic solvent selection framework that aligns solvent mass efficiency with ecological thinking. Environmental indicators typically consider factors such as climate change, ozone depletion potential, and cumulative energy demand during selected stages of solvent life cycles. For instance, solvents derived from fossil-based feedstocks can exhibit low SSR values (*e.g.* favorable separation characteristics) at the same time as scoring poorly on environmental metrics due to bioaccumulation risks, resource depletion, and other factors like toxic emissions generated in their supply chain. Conversely, solvents derived from renewable biobased materials might generally improve certain environmental scores but often exhibit less favorable SSRs due to challenges in separation or recovery operations as the high boiling points or high viscosities pose challenges. Thus, balancing these two perspectives – SSR and environmental indicators – illustrates the necessity of multi-criteria decision-making frameworks, where both mass-based performance and sustainability are optimized

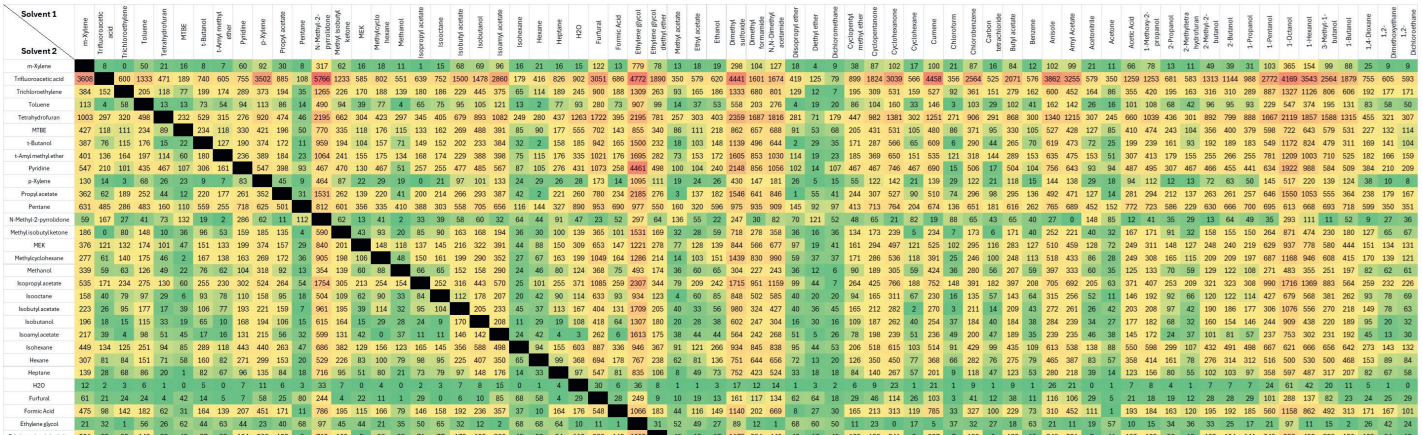

Fig. 6. Relative environmental burden of binary solvent mixtures; SSR x (ES indicators solvent 1 + solvent 2).

within solvent selection. Integrating comprehensive environmental metrics into the concept of SSR, therefore facilitates a deeper understanding of trade-offs in solvent findings.

By multiplying the data from Fig. 3 – specifically, the number of solvent swaps required to achieve 99 %v purity of both solvents in a distillative separation scenario, used here as a complexity indicator for solvent separations – with environmental metrics such as the CO_2-production footprint for each solvent in a binary mixture, relative values are obtained providing insights on the CO_2-burden associated with individual mixtures (Fig. 5).

This approach can be extended to include additional environmental sustainability (ES) indicators found in life cycle inventories for individual solvents, contributing to a more comprehensive assessment of the overall environmental burdens associated with potential solvent mixtures (Fig. 6). To streamline decision-making and reduce the number of matrices produced, multiple ES indicators for each solvent can be normalized and weighted to yield a single numerical score representing each solvent's environmental impact.[8]

However, reducing multiple environmental indicators into a single score inherently introduces a trade-off between simplicity and detail. By condensing distinct environmental dimensions into one numerical score, the relative importance of each indicator becomes dependent on the normalization and weighting factors applied, which are often subject to subjectivity or reflect the specific priorities of an organizations, regulatory framework, or region. For instance, certain users could prioritize greenhouse gas emissions (climate change) above other environmental impacts, while others may place greater emphasis on factors such as water use, resource depletion, or human toxicity potential. While this simplification facilitates quick comparisons across different solvent mixtures and scenarios, it is crucial to remain aware of the underlying assumptions driving the aggregation process. Transparency regarding such assumptions can help mitigate unintended biases and ensure the validity of assessments.

Looking at the specific composition of the normalization and weighting factors as described in the environmental footprint (EF) method and used in this manuscript,[10-12] it can be seen that the carbon footprint (climate change) tends to have a predominant influence on the total environmental impact. Including a broad range of indicators nevertheless ensures important to provide a comprehensive perspective and minimize the risk of burden shifting – that is, the inadvertent neglect or exacerbation of other environmental impacts despite improvements in certain areas. For instance, a solvent mixture that minimizes carbon footprint may induce higher levels of toxicity, water stress, or resource depletion elsewhere in its life cycle. Therefore, including a diverse set of indicators ensures a more holistic perspective and supports informed decision-making that better aligns with overarching sustainability goals.

An important point that must be emphasized again at this stage is that solvent selection, particularly for reaction environments, should not inadvertently compromise reaction kinetics or selectivity. Solvents play a critical role in determining the thermodynamic and kinetic properties of chemical reactions, influencing reaction rates, equilibrium constants, product yields, and even the formation of undesired by-products. Solvent parameters such as polarity, viscosity, dielectric constant, or hydrogen-bonding capabilities can significantly affect the solvation of reactants, transition states, and intermediates, as well as influencing the stereochemical and regioselective outcomes. These intricate interactions between solvent properties and reaction mechanisms highlight the fact that solvent selection cannot be solely guided by environmental considerations or sustainability efficiency metrics. While

Fig. 7. Solvent selection process using combined SSR and environmental metrics; example mixtures of THF (reaction solvent) and potential esters used in a work-up scenario.

the combination of the SSR and environmental indicators is invaluable for solvent selection in downstream processes – such as extraction, separation, and purification – it may not be suitable for choosing solvents directly involved in the chemical reaction itself, as they do not account for the mechanistic complexities inherent in reaction environments. A poorly selected solvent driven solely by sustainability metrics might thereby lead to adverse effects on multiple process metrics. To ensure a balanced approach, solvent choice for reaction environments should be guided primarily by reaction-specific criteria, while downstream solvent considerations should benefit more from SSR rankings and environmental indicators, a scenario that is illustrated in Fig. 7. THF from an example reaction is assumed to be treated with one of the selected esters. An examination of Fig. 7a–c demonstrates that recovering any specific ester from this mixture is likely to be challenging, whereas THF appears to be more readily recoverable. If cost and supply chain constraints are disregarded and the process accommodates all esters, isobutyl acetate emerges as the preferred option (Fig. 7d, e). However, if the process is restricted to isopropyl acetate or ethyl acetate, the selection becomes less straightforward. While a THF mixture with ethyl acetate generally presents a lower environmental impact, Fig. 7c indicates that THF can be recycled or recovered more efficiently from an isopropyl acetate mixture, a consideration that reduces the environmental footprint, making isopropyl acetate the more sustainable alternative.

The integration of the SSR with environmental metrics offers a powerful advancement in solvent selection frameworks, allowing them to address not only process efficiency but also broader concerns regarding hazardous waste management and environmental persistence. Industrial solvents, particularly halogenated ones such as chloroform or dichloromethane, have long been a cornerstone of chemical processes due to their favorable physical and chemical properties. However, their use comes with significant and far-reaching risks. These solvents exhibit characteristics such as high persistence in the environment, acute and chronic toxicity, and the potential for bioaccumulation in ecosystems, all of which contribute detrimentally to environmental degradation and human health risks. Moreover, disposal practices, including incineration, do not fully mitigate these hazards, as harmful halogens such as hydrochloric acid and potentially toxic dioxins can be liberated during combustion, exacerbating local air and groundwater pollution.

From the standpoint of sustainable solvent selection and responsible chemical manufacturing, reducing or completely restricting the use of all kinds of environmentally harmful solvents is an urgent priority. This aligns with both ethical imperatives and global regulatory initiatives designed to phase out substances of very high concern (SVHCs) as defined under frameworks such as REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) and EPA hazardous chemical classifications. While some halogenated solvents may appear favorable when considered solely through an SSR lens due to their ease of separability, their overarching environmental burdens demand a paradigm shift in solvent selection practices. The proposed integration of SSR and environmental midpoint indicators provides precisely such a mechanism, ensuring that sustainability and environmental safety do not take a back seat to pure process efficiency.

Any solvent selection framework that combines SSR with broader life cycle and hazard metrics should prioritize environmentally benign alternatives, even in cases where these options may entail somewhat higher energy demands for separation. For instance, solvents derived from renewable, bio-based feedstocks or those designed to be inherently biodegradable and less toxic offer long-term environmental benefits that often outweigh the short-term gains achieved through energy-efficient separations. Such an approach shifts industrial practices from reactive, cor-

rective measures – such as end-of-pipe waste treatment or pollution mitigation – to preventive strategies that inherently avoid the use of materials with high environmental and human health risks.

This shift to preventive, sustainable solvent systems further aligns with the principles of green chemistry, which emphasize pollution prevention, the use of safer chemicals and processes, and maximized resource efficiency. By embedding this ethos into solvent selection frameworks, industries can ensure that their practices align not only with regulatory requirements but also with sustainable development goals (SDGs) focused on combating climate change (SDG 13), protecting life below water (SDG 14), and promoting responsible consumption and production (SDG 12).[13] Adopting such an integrative solvent selection strategy does more than mitigate negative impacts; it can drive innovation.

3. Summary and Conclusions

In conclusion, the integration of environmental sustainability strategies into the development and manufacturing of APIs is essential for the long-term viability of the pharmaceutical and chemical industries in a resource-constrained world. It is imperative to empower scientists within pharmaceutical companies to adopt sustainable tools and technologies that can future proof their processes. To achieve this, collaboration between scientists and regulators is of great importance. Policies should encourage best practices such as the recycling, recovery, or re-use of different types of solvents within the pharmaceutical industry or other industrial settings, reducing pollution and resource depletion. Collaborative initiatives between academia, industry, regulators, and research institutions foster the development of novel, eco-friendly solutions, potentially leading to more efficient and effective manufacturing processes. To move towards transformative improvements in API manufacturing sustainability, investment in technological innovation outside of standard product development timelines, metrics, tools, and capabilities must be developed, standardized, and shared.

Working towards the described goals, the approach presented aims at supporting solvent selection during chemical process development at an early stage, highlighting environmental hotspots leading to inefficient solvent usage. The solvent swap ratio (SSR) in combination with additional environmental indicators demonstrates that the commonly held assumption more sustainable solvents afford more sustainable processes is not always correct; selecting solvents affording separable mixtures can lead to more positive outcomes. Addressing any potential trade-offs will require continual refinement of solvent impact models, ensuring that key environmental indicators are represented to reflect the complex priorities of stakeholders, including governmental agencies, or industries. Overall, these combined efforts contribute to advancing sustainability in industrial chemical processes, demonstrating how innovative solvent management practices can align with global environmental objectives while fostering operational resilience and compliance.

An additional aspect to consider is the use of alternative technologies for circular solvent management, such as membrane separation or adsorption techniques. Evaluations conducted within the boundaries of these methods may yield different results. Nevertheless, due to the current predominance that distillative solvent recovery technologies, this analysis has been limited to distillation as the sole recovery method.

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