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Review Article

The use of green chemistry in the reduction of pollution in pharmaceutical plants

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ABSTRACT

The expanding chemical production, particularly from the pharmaceutical industry, has led to the generation of significant wastes and pollutants, prompting the need for a comparative assessment of efficiency across various chemical manufacturing sectors. Green chemistry has emerged as a holistic approach, aiming to minimize the adverse impacts on human health and the environment by devising innovative chemical processes that tackle pollution at its source. The application of green chemistry principles within the pharmaceutical industry has focused on the development of eco-friendly solvents, catalysts, and manufacturing processes while acknowledging the challenges posed by the complexity of pharmaceutical molecules and stringent regulatory requirements. This paper emphasizes the significance of green chemistry practices, such as microwave-assisted organic synthesis and UV/H_2O_2 treatment for the removal of pharmaceuticals from liquid waste, highlighting their contributions to reducing waste and energy expenses. Moreover, the implementation of Quality by Design (QbD) principles in pharmaceutical development has resulted in improved product performance and reduced product variability, ensuring the highest standards of safety and quality. With a specific emphasis on solvent recovery and reduction, the paper underscores the critical role of these strategies in curbing emissions and fostering sustainable practices within the pharmaceutical industry.

Keywords: Green chemistry, Pollution, Pharmaceutical plants, Implementation, Microwave synthesis

Introduction

Chemical production often leads to the generation of substantial waste by-products and pollutants, including contaminated solvents, depleted reagents, and air pollutants, with the pharmaceutical industry being a notable contributor. To facilitate a comparative analysis of the efficiency levels across various chemical manufacturing sectors, **Table 1** presents the quantities of waste and by-products produced by pharmaceutical companies.

Table 1. Comparison of chemical industry sectors by quantity of byproduct per kilogram of product [1]

Industry sector	Product tonnage	Kg byproducts/kg product
Oil refining	10^6 -10^8	0.1
Bulk chemicals	10^4-10^6	<1-5
Fine chemicals	10^2-10^4	5-50
pharmaceuticals	10-10^3	25-100

Chemists have utilized their knowledge and expertise to create a large number of novel materials that surpass the capabilities of natural products. These innovations include high-tech polymers, liquid crystals, designer drugs, genetic materials, and novel energy sources. The overarching objective has been to develop chemicals and chemical processes that mitigate adverse effects on

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both human health and the environment. Green chemistry represents a paradigm shift, not in the sense of merely cleaning up pollution but in devising entirely new chemical processes that curtail pollution at its source [2].

The core goal of green chemistry extends beyond simply reducing or eliminating the use of hazardous solvents during chemical processes. It encompasses a holistic approach that also addresses various factors influencing chemical procedures and reactions. This includes the development of safer procedures and products. This approach places a strong emphasis on seeking eco-friendly alternatives to procedures and solvents that pose environmental hazards. Moreover, the chemical industry has witnessed significant expansion in recent years, resulting in a corresponding surge in waste production and pollution. In 1998, the foundational principles of green chemistry were established [3]. These principles guide the practice of green chemistry and include:

1. Waste Prevention: Prioritize waste reduction over waste cleanup.
2. Atom Economy: Synthetic methods should be designed to optimize the utilization of all materials involved in the process, ensuring their maximum incorporation into the final product.
3. Less Dangerous Chemical Synthesis: Restructure chemical processes to reduce toxicity and hazards through the use of less harmful products and reactions.
4. Develop Safer Chemicals and Products: Design products using efficient chemical processes while minimizing their adverse effects.
5. Safer Solvents and Auxiliaries: Promote the use of environmentally safe solvents and minimize the use of auxiliaries that generate additional waste.
6. Energy Efficiency: Minimize the economic and environmental impact of chemical processes by favoring conditions with lower energy requirements.
7. Renewable Feedstocks: Promote the use of renewable raw materials and reduce dependency on consumable resources.
8. Avoid or Reduce Derivatives: Minimize the use of derivatives, which generate extra waste due to additional reagent steps.
9. Catalysis: Catalytic reagents which are selective, are superior to stoichiometric reagents.
10. Biodegradation: Design chemical products to naturally degrade harmlessly after use.
11. Real-Time Analysis to Prevent Pollution: Monitor procedures and chemical reactions in real time to control and prevent the formation of harmful waste.
12. Accident Prevention: Plan for solvents and chemical substances in advance to reduce the risk of accidents, including explosions and leaks.

Application of green chemistry

The pharmaceutical industry has been actively applying green chemistry principles to reduce its ecological footprint [4]. One of the critical areas of focus within this endeavor is the development and utilization of green solvents [5]. Solvents play a pivotal role in green chemistry because they are used in significant quantities, and many of them are volatile organic compounds (VOCs) that pose substantial risks in terms of waste generation, air pollution, and potential health hazards [6]. Green solvents, such as water, glycerol, supercritical carbon dioxide (ScCO2), and superheated water, exhibit properties similar to traditional organic solvents while adhering to environmentally friendly principles. They have proven to be ideal and cost-effective alternatives for chromatography and various separation techniques, offering a safer and more sustainable alternative to hazardous solvents [7]. Glycerol, for instance, combines the benefits of water (low toxicity, affordability, abundant supply, and renewability) with those of ionic liquids (high boiling point, low vapor pressure) [8, 9]. Supercritical carbon dioxide (ScCO2) stands out as a versatile green solvent that can replace traditional hazardous chemicals in a wide range of reactions, including hydrogenation, epoxidation, radical reactions, Palladium-mediated C-C bond formation, ring-closing metathesis, biotransformation, and polymerization. Additionally, it has been demonstrated that ScCO2 can be employed as a solvent to load substances such as Ibuprofen into mesoporous silica, resulting in materials with a high Ibuprofen content.

Creating a sustainable production process involves minimizing waste by efficiently utilizing resources, preferably renewable ones, and avoiding toxic and hazardous reagents and solvents [10, 11]. This objective is driven by the application of green metrics like the E-factor, which measures waste generation. A practical approach to achieve significant waste reduction is replacing outdated processes that use stoichiometric reagents with more environmentally friendly catalytic alternatives [12, 13].

The E-factor, developed by Roger Sheldon, is widely used to compare the efficiency of pharmaceutical manufacturing to that of petroleum [12, 14]. However, due to the various product complexities among industries, this comparison has limits. Petroleum facilities are built for large-scale production of simple chemicals, whereas pharmaceutical scientists have to develop very complicated compounds with limited engineering adaptability [15, 16]. The complexities of pharmaceutical compounds, combined with restricted regulations and the need to accelerate the time to market due to patent considerations, place a heavy burden on pharmaceutical researchers to enhance efficiency. Industry laws also require significant efforts and costs for implementing and justifying late-stage process innovations, emphasizing the value of established techniques for mitigating regulatory risks and reducing deadlines [17, 18].

Green catalysts

Green catalysts, also known as eco-friendly or sustainable catalysts, are crucial in modern organic synthesis, particularly in the pharmaceutical industry [19]. They offer environmentally friendly methods for drug synthesis by minimizing or eliminating the use of hazardous materials. This shift not only reduces the environmental impact of drug production but also enhances

reaction efficiency and selectivity, resulting in higher yields and fewer undesirable byproducts [20, 21]. The two main categories of green catalysts are biocatalysis and chemocatalysis. Chemocatalysis strategically employs catalysts in the synthesis of organic compounds, allowing for precise control over chemical transformations. This approach facilitates milder reactions that generate fewer byproducts and require less energy [22]. Biocatalysis, on the other hand, utilizes enzymes as catalysts and operates under benign conditions, significantly reducing solvent usage and avoiding hazardous materials. Enzymes such as lipases, proteases, and cytochrome P450s have gained prominence due to their high selectivity and efficiency [23]. Moreover, the use of aqueous media in biocatalysis addresses environmental concerns, although challenges remain when dealing with hydrophobic substrates. Recent innovations focus on developing resource-efficient biocatalytic processes, including enzyme engineering and cofactor regeneration [24, 25].

Another significant class of green catalysts is organocatalysts, which facilitate the synthesis of active pharmaceutical ingredients (APIs) through sustainable methods [26]. For example, organocatalysts are essential in aldol reactions, critical for forming covalent bonds, and their capacity for supporting asymmetric transformations enables the synthesis of chiral molecules with high enantioselectivity [27, 28]. This reduces the environmental impact of drug synthesis while promoting the use of renewable starting materials. Transitioning from stoichiometric to catalytic approaches enhances overall efficiency by lowering energy requirements, improving selectivity, and minimizing waste. For instance, catalytic hydrogenations, such as Noyori hydrogenation, replace stoichiometric reagents, reducing waste generation [12, 29, 30].

The integration of environmentally friendly metals like iron, copper, silver, and gold in drug synthesis offers appealing alternatives to toxic metals like mercury and palladium. These metals not only possess low toxicity but also feature advantages in recovery and recycling, contributing to sustainable practices [30, 31]. Ultimately, as the pharmaceutical industry embraces green catalysts, it fosters a transition towards environmentally conscious drug development, promoting sustainability and reducing the ecological footprint of pharmaceutical manufacturing [32].

Microwave

Microwave-Assisted Organic Synthesis has emerged as a recent and highly regarded advancement, surpassing traditional heating methods in the realm of organic chemistry [33]. This innovative technique represents a leading-edge approach within the field [34], offering a spectrum of advantages that include cleanliness, simplicity, efficiency, speed, and cost-effectiveness in the synthesis of various organic compounds. It has introduced a new dimension to organic synthesis, characterized by significantly accelerated reaction times, improved yields, and enhanced product quality [35]. Crucially, microwave-assisted synthesis aligns with the principles of green chemistry, as it embodies an environmentally friendly approach that is increasingly being adopted in laboratory settings. Its potential impact extends to various domains, including combinatorial chemistry, screening, medicinal chemistry, and drug development [36]. In contrast, conventional organic synthesis methods often require longer heating times, tedious apparatus setups, increased process costs, and excessive use of solvents and reagents, contributing to environmental pollution [37].

The growth of green chemistry is pivotal in mitigating the production of byproducts, reducing waste, and cutting down on energy expenses [38]. Microwave irradiation's unique ability to directly interact with reaction molecules and rapidly elevate temperatures has been used to enhance numerous organic synthesis processes [39]. This heating mechanism in microwave ovens is based on the interaction between charged particles within the reaction material and the electromagnetic wavelengths of the specific frequencies [40]. Heat generation through electromagnetic irradiation occurs either by conduction or collision. As the wave energy oscillates between positive and negative polarity with each cycle, it induces rapid molecular orientation and reorientation, leading to heating through collisions [41]. In cases where charged particles are free to move within a material, such as electrons in a carbon sample, electromagnetic fields induce currents that move in sync with the field [42]. Conversely, when charged particles are bound within material regions, the electric field component prompts them to shift until opposing forces balance the electric force [43].

The environmentally friendly green chemistry in pharmaceuticals

Emerging pollutants, such as pharmaceuticals, have garnered significant attention within the scientific community [16, 17]. Although these compounds are not currently part of routine monitoring programs, their inclusion may be warranted in the future, contingent upon an assessment of their environmental impact. Pharmaceuticals are extensively employed for human and veterinary purposes, as well as in animal husbandry [17]. Once their intended purpose in target organisms is fulfilled, they are excreted via feces or urine, existing either as parent compounds or metabolites. Subsequently, these compounds can find their way into the aquatic environment through treated or untreated wastewater discharge [18]. Addressing this challenge involves a multi-stage wastewater treatment process. In the initial phases, physical unit procedures are employed to eliminate organic waste, large solid particles, and specific suspended solids. Subsequent treatment stages utilize biological unit processes to eliminate suspended particles and biodegradable organic waste, often augmented with chemical additions for enhanced efficacy. Among the prevalent options for further treatment, conventional activated sludge systems take precedence. Within these systems, microbial oxidation of organic molecules occurs, facilitating diverse pollutant removal mechanisms, including biological breakdown, sorption to suspended particles, and integration into microbial agglomerates [19].

Solvent recovery

Solvent recovery is an effective waste reduction method widely used in various industries. It offers an alternative to solvent replacement, minimizing waste generation during the production process. This approach is particularly advantageous as it requires minimal alterations to existing operations, similar to end-of-pipe pollution control. Additionally, the wide availability of solvent recovery equipment, especially suited for small-scale and batch operations, makes in-process recovery economically preferable to raw materials substitution. Commercially available solvent recovery equipment includes techniques such as carbon adsorption, distillation and condensation, and solvent dissolving in another material, each presenting specific advantages and challenges [41, 44, 45].

Using UV and H_2O_2 to remove pharmaceuticals from liquid waste (wastewater)

The combination of ultraviolet (UV) radiation and hydrogen peroxide (H_2O_2) is a promising approach for removing pharmaceutical contaminants from wastewater. This method works by generating hydroxyl radicals (•OH), highly reactive molecules that break down complex pharmaceuticals into less harmful substances. By pairing UV light with H_2O_2, the energy needed to degrade pharmaceuticals is significantly reduced, making this process both energy-efficient and effective in addressing pharmaceutical pollution [46, 47].

This approach is part of advanced oxidation processes (AOPs), which are designed to oxidize and degrade persistent pollutants. AOPs, including UV-H_2O_2, offer a cleaner and sustainable solution as they leave no harmful residues and minimize the use of toxic chemicals. Continued advancements in AOP technologies are focused on improving their efficiency and scalability for broader wastewater treatment applications, contributing to cleaner water systems and reducing the environmental impact of pharmaceutical waste [48, 49].

Quality by design

Quality by Design (QbD) represents a rigorous and scientifically grounded approach that goes beyond merely testing a product at the end of its development process [50]. Instead, it focuses on instilling quality into a product right from its initial design stages. The primary objective of QbD is to engineer a robust manufacturing process that facilitates the creation of a product with predetermined specifications and characteristics. By doing so, it effectively reduces product variability and defects, thereby minimizing the likelihood of recalls and rejections [51]. Quality serves as the cornerstone that underpins the entire concept of Quality by Design. Quality can be defined as the "standard or suitability for the intended use," encompassing crucial aspects such as identification, potency, and purity. Quality by Design, therefore, can be best described as a systematic approach to product development that commences with a well-defined objective. This approach places paramount importance on achieving a comprehensive understanding of both the product and the manufacturing process, with a strong emphasis on process control. It is firmly grounded in the principles of science and quality risk management, ensuring that products not only meet their intended purposes but also consistently uphold the highest standards of safety and quality [52, 53].

Applications of quality by design

Quality by Design (QbD) has gained significant prominence in the pharmaceutical industry due to its diverse range of applications. It has proven instrumental in the determination of purity, as exemplified in the development of a capillary electrophoresis method for the chiral purity determination of dexmedetomidine [54]. Additionally, QbD has played a critical role in the optimization of various processes and formulations. For instance, it has facilitated the development of functionalized particles with modified-release properties [55], while also streamlining the process and formulation parameters of different compounds, including rizatriptan-loaded chitosan nanoparticles and venlafaxine loaded nanostructured lipid carrier [56-58].

In terms of method development, QbD approaches have demonstrated efficacy in the field of HPLC and LC-MS, enabling the simultaneous quantification of specific compounds, such as telmisartan and HCTZ impurities [59]. Furthermore, it has contributed to the development of green micellar HPLC methods for the simultaneous determination of atorvastatin and amlodipine [60]. QbD has also made significant contributions to the development of novel drug delivery systems, facilitating the creation of oral lyophilizes containing meloxicam nanocrystals and metronidazole-loaded chitosan nanoparticles [61, 62].

Moreover, in the realm of stability studies, QbD has been employed to develop stability-indicating assay methods for various drugs, including linezolid in newly developed gelatin nanoparticles, ticagrelor and its impurities, and linagliptin drug products [63, 64]. These applications collectively emphasize the versatility and significance of the Quality by Design approach, underscoring its crucial role in enhancing different aspects of pharmaceutical research and development, ultimately contributing to the advancement of the field and the improvement of drug development processes.

Application of green chemistry to pharmaceuticals

When examining the application of green chemistry in the pharmaceutical industry, it becomes evident that the implementation of a solvent recovery or reduction system within manufacturing processes can play a vital role in significantly curbing the associated emissions. Surprisingly, the crucial role of solvents and their usage in the production of complex drug

products is often underestimated, as highlighted in a report by GlaxoSmithKline (GSK) [11]. Despite their limited involvement in the actual chemical reactions, solvents dominate both the mass and energy requirements in pharmaceutical manufacturing, accounting for approximately 80-90% of the reaction mass and roughly 60% of the energy consumed during the production of active pharmaceutical ingredients (APIs) [65].

These solvents serve various functions, including facilitating the necessary reactions for API synthesis and aiding in the purification processes and washing steps required to refine the final API product. However, the prevalent industry practice of incinerating solvent waste during disposal further amplifies environmental concerns [66]. In light of this, conducting a life cycle analysis of pharmaceutical solvent use and recovery highlights two significant environmental incentives. Firstly, by increasing the proportion of recycled solvents, there is a corresponding reduction in the demand for virgin solvents, thereby fostering a more sustainable approach [67]. This is particularly crucial given that nearly 83% of waste in this context is attributed to the top ten solvents frequently utilized in the pharmaceutical sector. Understanding these dynamics underscores the importance of integrating solvent recovery and reduction strategies within the pharmaceutical industry to mitigate environmental impact and promote sustainable practices.

Conclusion

Through the systematic integration of green chemistry principles, the pharmaceutical industry has demonstrated a commitment to sustainable and environmentally conscious practices. The implementation of environmentally friendly solvents, catalysts, and manufacturing processes, coupled with innovative techniques such as microwave-assisted organic synthesis and UV/H_2O_2 treatment for wastewater management, has significantly contributed to the reduction of waste and energy consumption. The adoption of Quality by Design (QbD) principles has facilitated the enhancement of product quality and the streamlining of manufacturing processes, ensuring the consistent delivery of safe and reliable pharmaceutical products. Additionally, the strategic incorporation of solvent recovery and reduction strategies has played a crucial role in curbing emissions and promoting a more sustainable approach to chemical production. As the pharmaceutical industry continues to evolve, the principles and applications of green chemistry serve as a cornerstone for fostering a more environmentally sustainable future, emphasizing the industry's dedication to responsible and ethical chemical manufacturing practices.

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