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Green Chemistry Approaches in Pharmaceutical Synthesis: A Comprehensive Review

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ABSTRACT

Green chemistry has become a new paradigm for modern pharmaceutical synthesis through designing chemical processes that are environmentally friendly and economically sustainable. Traditional methods of pharmaceuticals manufacturing have used hazardous materials such as toxic solvents and high energy to produce medications which in turn create significant environmental pollution and health risks. By implementing principles of green chemistry into pharmaceutical synthesis, waste reduction can be achieved through safer reaction conditions and efficient resource utilization. Therefore, this review will provide an overview of green chemistry approaches in pharmaceutical synthesis including fundamental principles, green synthetic methodologies, catalyst strategies, industrial applications, green solvent use, Biocatalysisand future prospects. Adopting green chemistry is crucial for the long-term sustainability of drug production and ensuring the protection of our **environment.**

Keywords: Green chemistry; Pharmaceutical synthesis; Catalysis; Biocatalysis; Sustainable manufacturing

INTRODUCTION

The expansion of the pharmaceutical sector has enhanced global healthcare through the creation and manufacture of drugs. At the same time, however, it has created significant problems from an environmental and economic standpoint. Typically, conventional pharmaceuticals synthesis involves the use of high-energy consumption, large amounts of hazardous chemicals and the generation of large volumes of waste products resulting in significant costs associated with the production of medicines.[1,2]

Paul Anastas and John Warner came up with the idea of green chemistry to solve these problems by encouraging the creation of chemical processes that are safe for the environment. It focuses on cutting down or getting rid of dangerous chemicals in the design, production, and use of chemical products.[3]

Because of strict environmental laws and a growing awareness of sustainability, green chemistry principles are becoming more and more important in pharmaceutical synthesis. The pharmaceutical industry is being pushed to find ways to make drugs that are cheaper and better for the environment without lowering their quality or effectiveness. Green chemistry gives us a way to reach these goals by making every step of drug development more sustainable. The industry is being pushed to find ways to make drugs that are both cheaper and better for the environment without hurting their quality or effectiveness. Green chemistry gives us a way to reach these goals by making sustainability a part of every step of drug development, from choosing raw materials to making the final product.[5]

One of the main reasons to use green chemistry in the pharmaceutical industry is the high environmental factor (E-factor) that comes with making drugs. Pharmaceutical processes usually make a lot more waste per unit of product than bulk chemicals do. This is mostly because drug molecules are very complicated and solvents and reagents are used a lot. Using green chemistry techniques can help cut down on waste, make better use of atoms, and make the whole process more efficient.[6]

Another important thing about green chemistry is that it helps the economy. It may cost money to start using green technologies, but in the long run, they are better for the economy because they use less material, less energy, and cost less to throw away. Green processes also often lead to better product quality and yield, which makes the business more profitable.[7,8]

PRINCIPLES OF GREEN CHEMISTRY

There are twelve basic rules that guide green chemistry. These rules help people design chemical processes that are good for the environment. Paul Anastas and John Warner came up with these principles to cut down on or get rid of the use and production of dangerous chemicals while making chemical synthesis more efficient and sustainable.

Waste Prevention

The idea behind waste prevention is that it's better to stop waste from happening in the first place than to clean it up or treat it after it happens. In pharmaceutical synthesis, a lot of waste is made because of multi-step reactions and purification processes.

Waste can be reduced at the source by making synthetic pathways that are more efficient, have fewer steps, and are more selective. This not only helps the environment, but it also saves money on waste disposal and treatment. Preventive strategies include using catalytic processes, optimizing reaction conditions, and not using reagents that aren't needed.[9,10]

Atom Economy

Atom economy refers to the efficient utilization of all atoms present in the reactants to form the desired product. A reaction with high atom economy ensures that most of the reactants are incorporated into the final product, thereby minimizing the formation of by-products.

In pharmaceutical synthesis, improving atom economy is crucial for reducing waste and increasing process efficiency. Reactions such as addition and rearrangement typically exhibit higher atom economy compared to substitution or elimination reactions. Designing synthetic routes that maximize atom economy is a key objective in green chemistry.[11,12]

Less Hazardous Chemical Synthesis

This principle requires designing new methods that utilize safe chemicals whose residues are harmless to both man and the environment. Most of the chemicals used in conventional processes are very dangerous in their handling and processing, as well as in their residue disposal. Green chemistry seeks to substitute dangerous chemicals with safe ones, as well as optimize reaction conditions such that minimal dangerous by-products are formed.[13-15]

Designing Safer Chemicals

In designing new products, one needs to be cautious of their functional properties and the associated risks to health. In the case of pharmaceutical products, one must consider safety of drugs that not only offer therapeutic benefits but also have low impacts on patients and the environment. Safer chemicals should offer functional properties without harming the users or causing any form of pollution to the environment.[16]

Safer Solvents and Auxiliaries

Solvents have been widely used in the production of drugs because of their ability to act as catalysts in the reaction processes involved. Traditional solvents are, however, highly pollutive due to their volatility, toxicity, and inability to undergo biodegradation. Green chemistry encourages the use of water, ethanol, and supercritical carbon dioxide as environmentally-friendly alternatives in place of other traditional solvents.[17]

Design for Energy Efficiency

Energy consumption forms an integral part of the environmental impact of the chemical process. The principle of energy efficiency involves conducting the reactions under normal temperature and pressure conditions to minimize energy requirement. There are several ways of optimizing energy consumption including the adoption of processes such as microwave-assisted synthesis and flow chemistry.[18]

Utilize Renewable Feedstocks

The use of renewable feedstocks is a critical principle when considering the sustainability of chemical production. Renewable feedstocks include plant-based raw materials and biomass as alternatives to non-renewable resources such as fossil fuels. The application of renewable feedstocks within the context of pharmaceutical syntheses can lead to decreased dependency on finite sources of energy and contribute towards sustainability. New technological advances in fields like biotechnology and green chemistry are driving the creation of new chemical processes using renewable sources.[19]

Minimize Derivatives

Use of protecting groups and derivatives generally creates more complex syntheses and produces more waste products. This principle encourages reduction or elimination of derivatization and protection stages from syntheses. Creating shorter syntheses, reducing reagents, and simplifying processes leads to increased efficiency and lower costs.[20,21]

Use Catalysis

Catalysis is one of the most important concepts in green chemistry because it helps increase efficiency and selectivity of reactions while requiring less severe conditions compared to uncatalyzed reactions. Catalysts decrease the requirement for excess reagents, making chemical processes safer and greener. Catalytic processes are commonly employed in pharmaceutical syntheses in order to maximize yield and limit formation of by-products. Most catalysts can be reused, making them an attractive option over stoichiometric reagents in many cases.[22,23]

Design for Degradation

Designing chemical products to be capable of breaking down into safe by-products after use will prevent their harmful buildup in the environment. For example, pharmaceutical drugs that end up in ecosystems either through misuse or excretion must be designed to be environmentally safe by decomposing into harmless products.[24,25]

Real-Time Analysis for Pollution Prevention

Utilization of real-time analysis methods provides the possibility of detecting any hazardous materials in the process early and avoiding formation of dangerous intermediates or products. Advancements in analytical tools give chemists better insight and allow for fine process adjustment to produce desired chemicals without unwanted by-products and wastage.[26]

Inherently Safer Chemistry for Accident Prevention

It states that design and engineering of chemical processes need to incorporate all measures required to prevent accidents. These include choosing appropriate chemicals and conditions, ensuring process safety and minimizing risks such as explosion, fire or toxic gas release. Pharmaceutical manufacture poses great safety risks due to the presence of dangerous chemicals.[27]

GREEN CHEMISTRY METRICS

Metrics of green chemistry represent vital tools necessary for providing quantitative analysis of environmental performance and sustainability of chemical processes. Within the context of pharmaceutical synthesis, such metrics enable scientists to compare classical methods of chemical reactions with those proposed by green chemistry and to determine the areas for improvement.[28]

Atom Economy

Atom economy describes how efficiently an atom from reactants is converted into a final product. An ideal chemical reaction will incorporate all of its atoms into the product without any waste production or formation of other compounds. Reactions that include additions and rearrangement have a very high atom economy, while substitution and elimination reactions produce significant amounts of waste.[29]

$$\text{Atom Economy} = \frac{\text{Molecular weight of desired product}}{\text{Total molecular weight of all reactants}} \text{ x } 100$$

Environmental Factor (E-Factor)

E-Factorrefers to an index that estimates the ratio between waste produced and the total amount of final product. An ideal process would have E-Factor equal to zero. Typically, E-Factors observed in the pharmaceutical sector are much larger compared to bulk chemical production because of the complexity of reactions involved. Solvents are often used extensively, making it difficult to achieve low E-Factor.

$$\text{E-factor} = \frac{\text{Total waste generated}}{\text{Total product obtained}}$$

Process Mass Intensity (PMI)

Another metric used to measure process efficiency is called Process Mass Intensity (PMI). This metric measures the total mass of materials consumed by a process to produce the unit mass of a final product.[30]

$$\text{PMI} = \frac{\text{Total mass of raw materials used}}{\text{Mass of product obtained}}$$

Reaction Mass Efficiency (RME)

Reaction Mass Efficiency (RME) takes into account both atom economy and yield.

$$\text{RME} = \frac{\text{Mass of desired product}}{\text{Mass of all reactants}} \text{ x } 100$$

Whereas atom economy is a theoretical indicator, RME takes into account practical experimental conditions such as losses in processing and incomplete reactions, making it a more practical measure of efficiency in realworld applications.[31]

Carbon Efficiency

Carbon efficiency is a term which indicates the extent to which the carbon atom of a reactant is used in the product. This becomes more important in organic synthesis as the most of the reactants used consist of hydrocarbons. The higher the carbon efficiency the better the use of raw materials, and the less the wastage of carbon, making the process both economically and environmentally sustainable.[32]

Energy Efficiency Metrics

The rate at which energy is used is a determinant of the greenness of a chemical process. Measures of the energy efficiency of a process quantify the energy used to perform a reaction. Mild condition processes for room temperature and pressure are defined as more energy saving. Microwave assisted synthesis and flow chemistry have contributed greatly to energy saving in pharmaceutical synthesis.[33,34]

Life Cycle Assessment (LCA)

The values of the entire life cycle LCA is defined as the evaluation of the environmental impacts of a product or process from cradle to grave.In the context of pharmaceutical synthesis, LCA has been employed to pinpoint key steps of process - identified as detrimental, as it were - and outlined directions of what can be done to turn this damage to the absolute minimum. It considers the factors as energy and resource consumption, emissions, waste etc. hence is directly relevant to development in sustainable way.[35]

Eco-Scale

The Eco-Scale is a semi-quantitative way of assessing the greenness of a chemical reaction. It uses a system to award penalty points depending on factors like yield, safety, cost and environmental impact.A larger Eco-Scale is indicative of a greener process. The Eco-Scale score can be used to compare the two routes side by side and choose the greener process.[37]

CONVENTIONAL VS GREEN PHARMACEUTICAL SYNTHESIS

In the past, the demands placed on pharmaceutical synthesis have been very specific; those of high yield, purity and large scale. Although these principles remain relevant, the direction of traditional synthetic approaches have often tended to neglect issues of environment and sustainability. This has resulted, historically, in traditional pharmaceutical manufacture exhibiting concerns over high waste outputs, energy requirements and the use of toxic reagents. Green pharmaceutical synthesis attempts to rival this by introduction of drug synthesis using environmentally benign principles at all aspects of chemical manufacture

Sr. No.	Aspect	Conventional Synthesis	Green Synthesis
1.	Waste generation	High	Low
2.	Solvent use	Hazardous solvents	Green solvents
3.	Energy consumption	High	Low
4.	Reaction steps	Multiple	Reduced
5.	Environmental impact	Significant	Minimal
6.	Safety	Lower	Higher

Table 1: Comparison between Conventional Synthesis and Green Synthesis

GREEN SYNTHETIC METHODOLOGIES

Green synthetic methodologies is the application of the principles of green chemistry, into pharmaceutical synthesis. Green methodologies uses novel synthetic techniques with the view to mitigating production across a number of parameters such as waste reduction, avoidance of toxic reagents, reduction of energy consumption and improving overall process sustainability, through various innovations.

Green Solvents

Solvents are an integral part of the vast majority of chemical reactions and are vital in the synthesis of pharmaceuticals. They are, however, a significant source of chemical wastes and pollution. Conventional organic solvents, like chlorinated hydrocarbons and aromatic compounds, are often toxic, volatile and non-biodegradable. Green chemistry ensures that solvents are environmentally friendly. They also have health advantages for human life.[39]

Water as a Green Solvent

Water, as the most environmentally benign solvent, is nontoxic, non-flammable, and readily available in abundance. It possesses special physicochemnical characteristics that extend its applicability towards a broad spectrum of chemical reactions. In pharmaceutical synthesis, the use of aqueous reactions reduces the reliance on dangerous organic solvents. Water also promotes some reactions by hydrogen bonding and hydrophobic effects.[40]

Ethanol and Bio-Based Solvents

Ethanol is also a popular green solvent because of its biodegradable and low toxicity nature. It is most efficiently derived from renewable sources like biomass, instead of the common, petroleum. Other bio-solvents such as ethyl lactate and glycerol are increasingly employed in synthesis of green pharmaceuticals.[41]

Supercritical Fluids

Supercritical carbon dioxide (CO) is arguably the most widely used of the popular "green" solvents. It possesses the high infusibility characteristic of gases while maintaining the ability to produce strong solvating power found in liquids. Supercritical CO is nontoxic, non-flammable and the most easily eliminated from the final product and therefore suited for extraction and purification in the production of pharmaceuticals.[42]

Ionic Liquids and Deep Eutectic Solvents

Ionic liquids consist of salts that are liquids at relatively low temperature. Ionic liquids have ultra low vapor pressure which causes reduction of air pollution and lost of solvent. Another group of GREEN solvent are deep eutectic solvents (DES). These solvents are composed of two or more compounds, which form a eutectic mixture. These solvents are biodegradable, inexpensive and environmentally friendly.[43]

Solvent-Free Synthesis

The use of solvent free synthesis is an important green method that does not utilize any type of solvent. reactants are reacted together directly in the solvent free methods.This method offers several advantages:

- Noticeable decrease in the production of waste
- Enable simplified product isolation and purification;
- Reduced impact on the environment

Solvent free reactions have been already used in solid state reactions, being successfully applied in the preparation of some pharmaceutical intermediates.[44]

Microwave-Assisted Synthesis

Microwave-assisted synthesis. This is a new method of physicochemical synthesis in which microwave radiation is used to activate and accelerate chemical reactions. Microwave irradiation induces direct interaction with the molecules, resulting in a quick and even heating.

This technique offers several benefits:

- Enhanced reaction yield
- Reduce energy use
- Better reproducibility

Microwave assisted synthesis finds wide application in pharmaceutical research for rapid synthesis of drug candidates and intermediates.[45]

Ultrasound-Assisted Synthesis (Sonochemistry)

It is the use of high frequency (above 20kHz) sound to accelerate a reaction. The use of ultrasound induces micro-bubbles which is the process known as cavitation.Appears to be the byproduct of cavitation, which induces high localized temperatures and pressures, thus increasing reaction rate and enhancing mass transfer.

Advantages of ultrasound-assisted synthesis include:

Improved reaction efficiency
Reduced reaction time
Lower energy requirements
Improved product yield

This method is particularly useful for reactions that are otherwise slow or require harsh conditions.[46]

Photochemical Reactions

Photochemistry is the use of light energy to initiate a chemical reaction. The use of photochemical reactions in green chemistry is appealing since they generally do not require elevated temperature or reagents. Reactions driven by light could have high selectivity and energy efficiency. Harnessing the sunlight or energy saving lighting is even more environmentally friendly. Application of Photochemistry in Pharmaceutical Synthesis is widely increasing especially for assembling complex molecules.[47]

Continuous Flow Chemistry

Continuous flow chemistry is an established and refined methodology that involves the use of chemical reactions in a flowing stream instead of using batch reactors. Monitoring parameters can be precisely manipulated such as reaction temperature, pressure and time.

Key advantages include:
Safer when carrying out more dangerous reactions.
Increased scalability for industrial production.
Less waste created
Improved heat and mass transfer

Flow chemistry is very useful in pharmaceutical production since a consistent product quality and scaled-up production are of importance.

Mechanochemistry

Mechanochemistry is the application of mechanical force, for instance through grinding or milling, for inducing chemical reactions in any phase. It frequently involves no solvents and less energy. Mechanochemistry is getting recognition as a green route to synthesize pharmaceutical compounds despite its use either in solution or solidstate reactions.[48]

Electrochemical Synthesis

Electrochemical such techniques utilize electrical energy to produce chemical reactions. It can eliminate the most dangerous chemicals from many reactions by substituting for conventional redox reactions.

Electrochemical synthesis offers:

- High selectivity
- Less waste
- Energy savings
- Selection of compost friendly ingredients

CATALYSIS IN GREEN CHEMISTRY

One of the cornerstone ideas of green chemistry is catalysis this technique can be used to improve the efficiency, selectivity, and "greenness" of a chemical process.In comparison to reagents, catalysts are not the materials that are outright used in the reaction,but rather they are the materials that enable the reaction to proceed in the desired manner.[49,50]

Homogeneous Catalysis

Homogeneous catalysis is where the catalyst and reactants are both in the same phase, usually in solution. It allows for an even distribution of reactants and catalysts, resulting in high rates and selectivity.

In organic synthesis, homogeneous catalysts are mainly employed for over-mentioned reasons. As they give fine control over the overall pathway, they are very suitable for reactions demanding high levels of stereo-selectivity. They are ideal for example for asymmetric synthesis. But one of the problems using homogeneous catalysis is the separation of catalyst from the reaction mixture. It limits their ability to be recovered and then reused. However, researchers are continually working on improving the separation methods and recyclable homogeneous catalysts.[51]

Heterogeneous Catalysis

Heterogeneous catalysis is defined as those where the catalyst is in a different phase to the reactants. Most common form is solid catalysts which react with liquid or gaseous reactants, thus enabling catalysts to be separated easily.Heterogeneous catalysts have long been used in industrial processes because of the ready availability, stability, reusability and ease of handling. Such catalysts are particularly suitable for manufacturing of drugs on the large scale.

Key benefits include:

- Simple separation and recovery
- Recycle of catalyst
- Lower final product contamination
- Enhanced process sustainability

Biocatalysis

One of the most important benefits of biocatalysis, is the high stereoselectivity which can be obtained using enzymes. This is particularly important in the synthesis of 'chiral' pharmaceutical drugs, where the enzyme can be used to produce one enantiomer exclusively.The use of toxic chemicals is minimized and waste generation is decreased. Other improvements in enzyme engineering and biochemistry have allowed the facilitation of more reactions and therefore increasing the importance of biocatalysis in pharmaceutical synthesis.[52]

Nano catalysis

Nano-catalysis is a new area of science involving catalytic activity of nano-sized particles. It is a combination of nanotechnology and catalysis. They have high activity and selectivity because of their high surface area to volume ratio.Nano-catalysts can be tailored to have certain characteristics, increased stability and reusability being features that can be exploited. They are very useful when the reaction has high demands on efficiency and accuracy. Nano catalysis is promising in pharmaceutical synthesis for enhanced catalytic efficiency and greener processes.[53]

Photocatalysis

Photocatalysis includes the utilization of light-activated catalysts for powering chemical reactions. This method has the advantage to use renewable energy sources such as the Sun.Photocatalysis can be used for oxidation and reduction reactions where it is often highly advantageous as it is carried out under mild conditions and uses less dangerous reagent.[54]

Electrocatalysis

Electrocatalytic processes involve the application of a potential during a reaction in order to speed up the rate of a chemical transformation. Electrocatalysis gives an often used but difficult to understand shortcut to the kinetic study and a means of gaining insight into reaction intermediates.Electrocatalysis is the use of electrical energy to promote a chemical reaction in the presence of a catalyst. This approach has the potential to substitute for the common use of redox reagents, a move which would substantially lessen the generation of chemicals waste.[55]

APPLICATIONS IN PHARMACEUTICAL INDUSTRY

Green chemistry methods are already used extensively in the preparation of active pharmaceutical ingredients, in process development and in high volume industrial manufacture, lending evidence to the practicality and commercial viability of sustainable methods.[56]

Green Synthesis of Active Pharmaceutical Ingredients (APIs)

The manufacturing of APIs is certainly among the most significant and costly operations in processing the drugs. From the traditional point of view, the manufacturing has been included several consecutive reactions, dangerous reagents and huge number of solvents.

Green chemistry approaches focus on:

- Enhancing atom efficiency
- Substituting toxic and hazardous reagents with safe chemicals
- Minimising solvent consumption.[57]

Case Study: Ibuprofen

The synthesis of ibuprofen with less harmful reagents is probably one of the most often cited cases of the application of green chemistry to synthesize pharmaceuticals.

Conventional Process

The initial methods of ibuprofen synthesis, were developed during the 1960's. This was a six-step synthesis which used isobutylbenzene as the starting material. This involved the use of stoichiometric reagents, for example aluminum chloride and produced high amounts of waste, in the form of inorganic salts and by-products.

The process had several drawbacks:

- Poor atom economy;
- High E-factor
- Waste generated in large quantities
- Use of toxic chemicals.

Green Process

One of the biggest innovations was the development of a new catalytic process by the Boots-Hoechst-CelaneseCompany. This new improved process drastically shortened the synthesis to three steps and employed catalytic rather than stoichiometric reactions.

Key improvements included:

- Use of catalytic hydrogenation

- Replacement of dangerous reagents.
- Improved atom economy.[58]

Application in Antibiotics and Antiviral Drug Synthesis

While many antibiotics and antivirals are not yet being prepared using green chemistry the complex nature and multiple steps involved in their preparation make this an ideal area for process improvement. Biocatalysis has been especially useful here. Enzymatic reactions allow for selective modifications, avoiding the use of dangerous reagents and helping to cut waste.[59]

Application in Oncology Drug Development for Cancer

The synthesis of anticancer drugs is challenged by the structural complexity of many of these compounds. Green chemistry offers new approaches for making synthetic synthons and minimising their impact on the environment.

Strategies include:

- Improvement in efficiency through the use of catalytic reactions
- Substitution of hazardous reagents with less hazardous ones.60

Process Optimization and Scale-Up

One of the main concerns of pharmaceutical manufacturing is the challenge of moving from laboratory procedures to industrial practice. Green chemistry is very important to such processes because:

- They enable better manipulation of conditions, improved reproducibility and lower waste emissions. Flows have the added advantage of improving safety as well by limiting the transport of dangerous chemicals.
- When different sized particles are mixed in one process the efficiency increases. This is because a smaller number of process steps are required. The efficiency is also increased because processes are less complex.[61]

FUTURE PERSPECTIVES

The outlook for green chemistry in pharmaceutical synthesis is very positive, given the ongoing progress of science and technology, coupled with global efforts towards sustainability. As concerns about the environment deepen and worse case scenarios are legislated against more harshly, green chemistry will become indispensable rather than merely desirable.

A major direction for the future will be the increased application of renewable resources as feed stocks in chemical synthesis. Replacing fossil raw materials with those based on biomass driven compounds will be essential in reducing the overall pollution levels, while also supporting sustainable development in the long-term. Advances in biorefinery technologies should allow the more efficient conversion of renewable materials into high value pharmaceutical intermediates.

The widespread adoption of flow chemistry and continuous manufacturing techniques are predicted to revolutionise the future of pharmaceutical synthesis as they utilize tremendous advantages including greater control of process conditions, increased safety and scalability relative to batch production, as well as minimising waste generation and providing for more consistent products.Expect bio-catalysis to grow even more with emerging innovation within enzyme engineering and synthetic biology. The application of environmentally friendly methods for the synthesis of nanoparticles will lead to the development of 'greener' technologies. However, scaling of such innovations will not be easy and will require collaboration between different industries, academia and regulation to be successful.[62]

CONCLUSION

Green chemistry is changing the way we think about the synthesis of pharmaceuticals and is providing a more sustainable route to chemical synthesis. In this review we have investigated different green chemistry aspects such as its principles, quantitative measures, synthesis techniques, catalysis and applications at industrial level. Several green solvent, biocatalysis, microwave synthesis and flow chemistry techniques proved to be very promising.The fact that green chemistry can indeed be applied to industrial processes, exemplified by the synthesis of Ibuprofen, has shown that it is not only feasible but also cost effective. Its use in the production of drugs to treat complex diseases such as Cancer also proves its significance to the future of health care. Although there are many hurdles that still need to be overcome for realizing the promise of green chemistry, existing challenges such as high capital investment and technical limitations are being addressed through ongoing research and technological advancement.This paper has demonstrated that green chemistry is fundamental to a sustainable and economically feasible pharmaceutical manufacture. The future of the pharmaceuticals has green chemistry will certainly be bright and with the enhanced support for research and education, green chemistry should reach its full potential.

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