Green Chemistry & Technology Letters
eISSN: 2455-3611, Vol 7, No 1, 2021, pp 18-27
https://doi.org/10.18510/gctl.2021.713

GREEN SYNTHESIS, GREEN CHEMISTRY, AND ENVIRONMENTAL SUSTAINABILITY: AN OVERVIEW ON RECENT AND FUTURE PERSPECTIVES GREEN CHEMISTRY IN PHARMACEUTICALS

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Article History: Received on 13th May, Revised on 09th July, Published on 14th July 2021

Abstract

Purpose: The chemistry society has activated to expand new chemistry that is less destructive to the environment and human health. This approach has extensive interest and designates as green chemistry, environmentally friendly chemistry, clean chemistry, and atom economy.

Methodology: There is advancement toward involved chemistry with the facts and do not prevent the properties of the target compound or the efficacy of solvents or reagents. The use of chemistry in a way that maximizes benefits while reducing adverse effects has come to be green chemistry.

Main findings: Reduce the use and formation of harmful products or by-products. Presently maximum pollution to the environment is caused by some chemical industries. So, need to design and develop synthetic methods in such a way that the waste products are lowest and have no effect on the environment and their handy disposal.

Applications of the work: Green chemistry plays a vital role in pharmaceuticals for developing new drugs which are less toxic, more effective with low side effects.

The novelty of the work: The industries performing manufacturing using green synthesis methods to carry out their productions have positive impacts on environmental sustainability. This review is looking ahead at longer-term challenges and prospects in research, industrial applications, and education.

Keywords: *Green chemistry, green synthesis, clean chemistry, environmental sustainability, atom economy.*

INTRODUCTION

Green Chemistry (GC) or Sustainable Chemistry (SC) is an approach that refers to the synthesis of chemical compounds that eliminate or reduce the use and formation of harmful substances. The chemistry that exploits its profit while reducing its undesirable impacts has come to be called GC or SC. The "green," reaction should have three green sections: solvent, reagent/catalyst, and energy expenditure. As a new branch of chemistry with ecological advances and involves reducing or eliminating the use of harmful chemicals in synthesis and reduced harmful intermediates and products. The GC is an approach to dealing with risk reduction and prevention of pollution by tackling the basic hazards of compounds. For example, benzene as a solvent must be evaded because it is carcinogenic. If possible, it is outstanding to performed reactions in the aqueous phase. Synthesis methods should be designed as the maximum extent of reactants is consumed into final products and should not produce any toxic by-products or wastes (Adam et al., 2020; de Marco et al., 2019; O'Brien et al., 2009).

The GC is based on twelve principles that can be used to form products, reactions, and methods that are safer for the environment as well as humans. The GC developed in all areas of chemistry, such as organic, biochemical, inorganic, physical, toxicological, polymeric, environmental, etc. GC is an oath for chemists, to preserve natural resources and the environment which reasonably analyzes the techniques and materials used in development. If no hazardous materials are used or produced, then the risk is zero and there is no need to concern about eliminating harmful compounds from the environment. GC is also about reducing raw materials, waste, risks, energy, environmental impact, and expenditure (Cerminara et al., 2020; de Marco et al., 2019; Singh & Wakode. 2018; Kim et al., 20153-6).

Sustainability and environmental issues are rapidly emerging as the most essential topics for manufacture and product development (Sezen & Çankaya 2013). The executions of GC are some of the efforts that can be prepared to recover the quality of the environment. The forthcoming challenges in resource, economic, environmental, and sustainability require more skilled, organized technologies related to chemicals and manufacturing. GC has overcome these challenges by opening various scope to maximize the favored substances and decrease by-products, equipment used in the formation of greener chemicals that are inherently, ecologically, and environmentally (Sharma et al., 2011). Research associated with GC has focused to reduce or eliminate the use or production of toxic substances for the environment and health. The GC also aims to replace non-renewable raw materials with renewable materials to reduce the dangers that impact negatively on health and the environment (Saini & Singh 2002).

BASIC PRINCIPLES OF GREEN CHEMISTRY

The principles of green chemistry (GC) address the reduction or removal of harmful substances from the synthesis. Thus, the use of toxic substances to human health and the environment is reduced or eliminated. When designing a GC process, it is impractical to convene the necessities of all principles of the method at the same time, but its efforts to apply various principles as hopeful during definite stages of synthesis (Singh & Wakode 2018; Ivankovic & Talic 2017; Escobedo et al., 2016; Manmohan et al., 2012; Valavanidis et al., 2009).

- Designing safer chemicals
- Design of degradation
- Prevention of waste or by-products
- Use of biotechnology alternatives.
- Least energy necessity for any synthesis
- Prevention or minimization of toxic substances.
- Whenever possible evade the use of protecting the group.
- Needless derivatization should be evaded whenever achievable.
- Selecting the most appropriate solvents, reagents, and catalysts.
- Use of innovative techniques to be recognized industrial methods.
- Most incorporation of the reactants and reagents into the final products.
- Chemical compounds should be designed to save effectiveness of utility while decreasing toxicity.
- Energy necessities should be recognized for their environmental and economic impacts should be minimized.
- Raw material should be renewable rather than depleting, whenever scientifically and cost-effectively feasible.
- Chemical compounds should be designed as they do not persist in the environment and break down into harmless degradation compounds.
- Analytical procedures need to be developed to permit real-time, procedure examining and control previous to the development of toxic compounds.
- Design manufacturing units to eliminate the chance of accidents during processes escalation of analytical practices to control toxic compounds.
- Whenever feasible synthetic procedures should be designed to use and form a compound that causes little or no harm to human health and the environment.
- Substances used in chemical methods should be chosen to decrease the potential for chemical accidents, explosions, and fires.

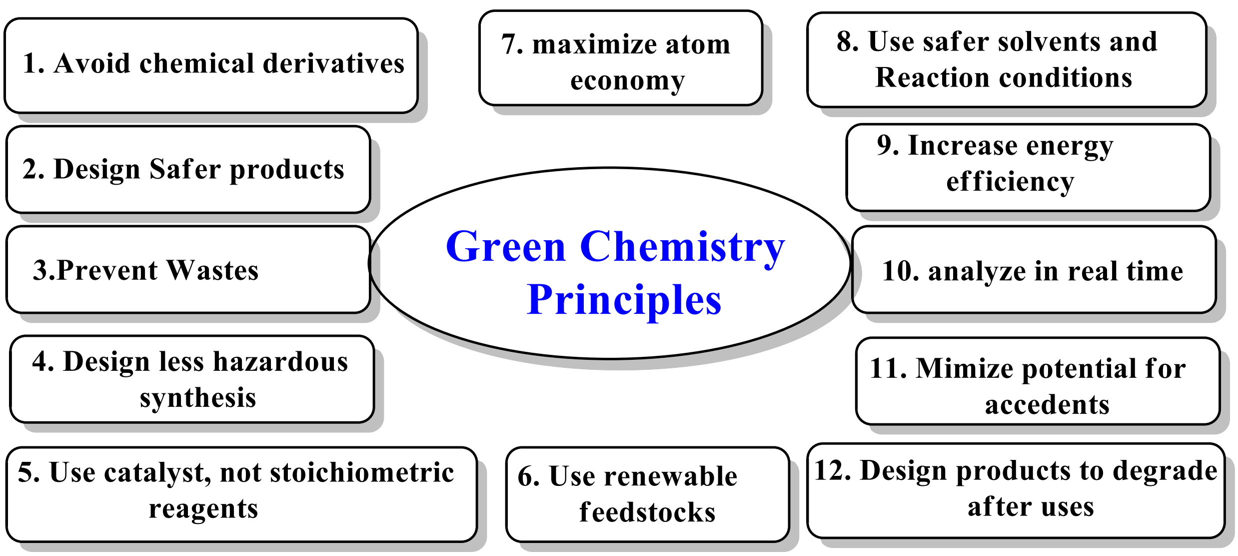

Fig. 1: Principles of Green Chemistry

PHARMACEUTICAL GREEN CHEMISTRY

Pharmaceutical companies are the most active part of chemical production. It is in the front position for big alterations towards "greener" feedstock, safer solvents, substitute methods, and creative ideas. All these modifications will improve the environmental credentials of the pharmaceutical companies, but at the same time will cut down costs and substances for the producing operations make a step in the right way of sustainability (Cichosz & Masek 2020; Lasker et al., 2019; Fanelli et al., 2017; Tucker 2006).

The use of GC principles in the pharmaceutical company can be viewed as both a responsibility and an important chance to improve our optimistic impact on the global population.

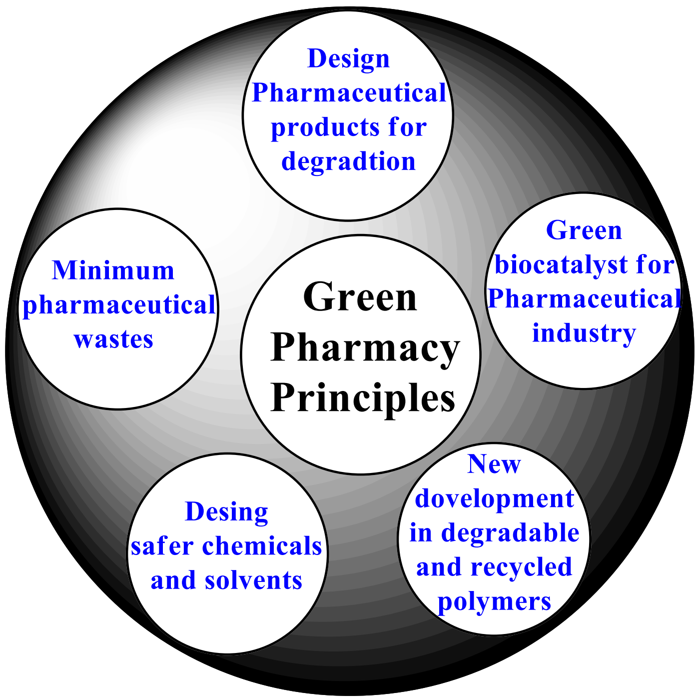

Fig. 2: Green chemistry in a pharmaceutical company

Chemists assist the drug company in its regular efforts to develop drugs and medicines with less risky side effects, using techniques that produce less toxic waste or by-products. The chemical discovery of drugs for profitable use is very much dissimilar from conventional manufacturing. Some companies, environmental specialists, medicinal chemists, chemical engineers all work together to advance drug development. The pharmaceutical company for years was accepted more and more "green" techniques and operations. The research departments of some drug companies made various advances for novel techniques, improved bio-catalysis reactions, fewer solvents, and less waste formation. Several years require pharmaceutical companies to interpret green principles into considerable aims for environmental research, progress, and production. Among drug manufacturers introduced accurate safety and health system to protect their workers and environmental criteria for their products. Safety, effectiveness, consistency, and economy are the four pillars of modifying and their support is measured as a competitive advantage, improved environmental credentials, and economical profit.

GREEN SYNTHESIS

Green synthesis (GS) is commonly used as a term to describe synthesizing products that do not harm the environment during any part of the synthetic procedure (Acharya et al., 2014). The GS is proven to a very vital idea for the reduction of industrial waste and emission. Inexpensive benefits and competitive results can be attained from avoided waste, and GS aims to permit the use of wealth efficiently and also can improve the activity of the ecological (Paul et al., 2014). Green technology is also called the use of one or more of the disciplines of environmental, GC, environmental examining, and electronic devices to test, model, and the natural environment and resources protection, and aims to protect the negative impacts of human concern (Dornfeld 2013). There are two perspectives of GS; first, in the slight perspective, GS related to the synthesis of the green products, such as those used in the system of energy renewable and clean skill of equipment; while in the broad sense, it refers to the greening of synthesis with decreasing the waste and saving resources. The use of GS practices in the synthesis method can be influenced by external factors, like policy environment, corporate awareness, and stakeholder act. The execution of GS in a firm also has a value of economic, social, and ecological effects (Pang & Zhang 2019). The environmental synthesis practices such as reducing raw material use, recycling solid wastes, redesigning substances can make be more ecologically sustainable (Rusinko 2007). The term relates to GS is a study that reflects a new synthesis pattern that uses different green techniques to be more ecologically capable, with the development of products or systems that use less substance and energy, replacing input materials (non-toxic to toxic, renewable to non-renewable), reduce needless production and change output to input or recycling (Deif 2011). The GS can reduce the product life cycle and this can reduce the cost of the manufacturing. Due to the ecological tasks, the company aims to seek to reuse, reproduce and recycle used products to decrease the negative impact on the environment, particularly producers of electric consumer products. Therefore, the reverse synthesis problem, which is directly related to all stages of product development, is a critical problem for all levels of the computer and electricity industry. The best possible inventory system was developed to know the value of related factors in policy and to find the control of cost products in semi-green supply chains (Lee et al., 2021).

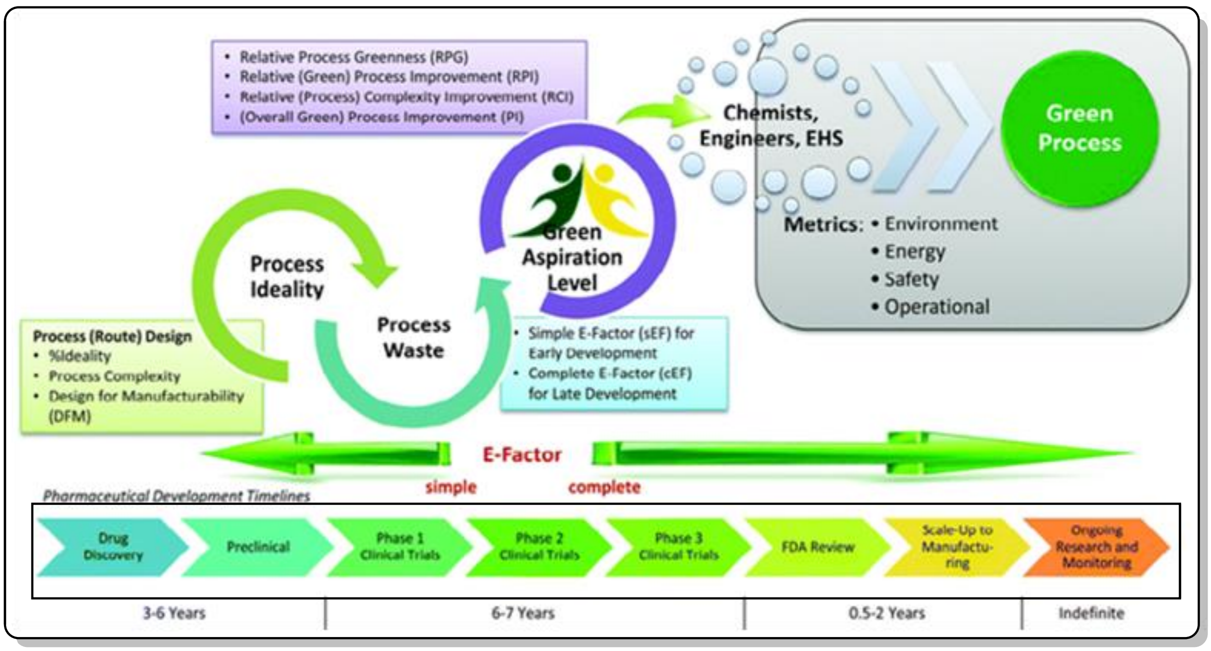

Fig. 3: Pharmaceutical company: the green aspiration level concept

GREEN CHEMISTRY AND ENVIRONMENTAL SUSTAINABILITY

Green chemistry (GC) is a technique used to defeat environmental problems both in terms of chemicals formed, methods, or reaction stages. This technique is based on decreasing the use and synthesis of toxic chemicals in procedures (Crawford et al., 2017). The chemical risks area is a part of the GC concept include a variety of threats to human health and the environment, physical hazards, consists of toxicity, exhaustion of natural resources, and global climate change (Kharissova et al., 2019). The GC targets to study the use of various chemical principles in the design or synthesis of chemicals in reducing the use or making of toxic compounds that can interfere with the health and conserve the environment (Schulte et al., 2013). The GC is a crucial part of an inclusive plan to guard human health and the environment. The GC is linked to matters in reducing waste at the source, the use of catalysts, safe reagents, increased economic efficiency, use of renewable materials, solvents that are safe and can be recycled (Shanghi 2003). The GC aims to improve the industry's environmental and the health of employees (Ubuoh 2016).

The idea of sustainability was driven by environmental and disastrous events and worried about the pollution of chemical and resource exhaustion. Sustainability has based on the triple-bottom-line theory of three fields- social, economic, and environmental. This theory highlighted that in carrying out development, it must ensure addition and balance between the economy, society, and the environment (Anastas & Warner 1998). Sustainability is the design of human and industrial systems by ensuring that the use of natural resources and the human cycle does not result in a reduction in the value of life and reduces inequality of the environment (Ragazzi & Ghidini 2017). The act of environmental sustainability can be in the form of reducing solid/liquid waste, emissions, resources, and use of toxic materials, the incidence of environmental accidents, and also improving human health (http://alliedacademies.com/euro-green-chemistry, 2017). Sustainable progress was agreed as growth to meet current needs without compromising the right to meet the requirements of the lives of upcoming generations. There are two key ideas, namely (i) the first is the idea of "needs", to continue human life, and (ii) the idea of limits arising from the technical and social association conditions of the ability of the environment to meet current and upcoming needs which will come (Geyer & Jackson 2004).

The environmental profit of GC is noteworthy; the execution of GS has an important positive impact on the environment. The acceptance of GS can result in decreased waste, fewer resources, and energy use, less pollution. It is very essential to assess GS methods and products, like recognize possible sources of contamination or pollution. These pollutants cause danger in the environment to our future, like greenhouse effects, harmful emissions formed by substance processing, and waste disposal (Nukman et al., 2017). In the chemical industries, design for sustainability is more than sustained development of green chemical methods, process escalation, and process redesign with broad research and development programs at all levels of chemistry. Sustainability has been extensively authorized as the overarching objective of ecological strategy (de Marco et al., 2019).

PHARMACEUTICAL APPLICATIONS

Pharmaceutical companies can get better environmental performance by using the information associated with green chemistry (GC). The GC is engaged in developing novel drug release methods which are less poisonous and more useful, proficient and could help millions of patients (Santi et al., 2021; Al-Hakkani et al., 2021; Banik et al., 2021; Arora et al., 2021; Draye et al., 2020; Gao et al., 2020; Patel et al., 2020; Dwivedi et al., 2019; Castilla et al., 2018; Jahangirian et al., 2018; Jahangirian et al., 2017; Jaiswal et al., 2017; Sindhu et al., 2017; Shah et al., 2015; Smita & Falfuni. 2012; Wolfson et al., 2007; Ingrid et al., 2006; Yogesh et al., 2001; Anastas et al., 2000), Examples:-

1. Phosphoramidite; a solid phase which is a mix of antisense oligonucleotides has been changed to entrain the ideas of GC by removal the usage and generation of hazardous materials and recycling the main substances like protecting groups amenities and solid support, thus advance the cost-efficiency and atom economy.

2. The synthesis of Naproxen with a chiral metal catalyst containing 2,2'-bis[diphenylphosphino]-1,1'-binaphthyl ligand with an excellent quantity of product.

3. Green solvents like water can substitute several hazardous solvents and are found very proficient in various organic reactions out of which include the synthesis of benzothiazoles, and benzothiazoline, etc. Glycerol, on the other hand, was reported as an important green solvent. Glycerol may join the benefits of water with low toxicity, low price, huge accessibility, and renewability. The high polarity of glycerol allows for the reduction of various carbonyl compounds with sodium borohydride.

4. Supercritical carbon dioxide ($ScCO_2$) is a main commercial and industrial solvent due to its role in chemical extraction in addition to its low toxicity and ecological impact. The $ScCO_2$ is a fluid state of CO_2 where it is detained at or above its critical temperature (31.10 ^{0}C) and critical pressure (72.9 atm) increasing to fill its container like a gas but with a density like that of liquid. The $ScCO_2$ works correspondingly with other challenging chemicals without toxic effects with the advantage of the water. The hydrogenation, epoxidation, radical reactions, palladium-mediated C-C bond development, ring-closing metathesis, polymerization, and various other reactions can be performed with $ScCO_2$ as a reaction medium. The use of $ScCO_2$ forms micro and nanoscale particles for pharmaceutical uses.

5. Traditional organic synthesis aspects stoichiometric quantities of reagents, leading to huge extents of waste or by-products, the right catalyst technologies increase product value, which reducing waste streams and enhancing cycle times. Recent advancement in catalysis has lined the approach for various precious applications, particularly in the synthesis of active pharmaceutical ingredients (APIs) and intermediates. Two types of catalysts are biocatalysis and chemo-catalysis.

6. In the synthesis of anthraquinone for the dyestuffs company like aluminIum chloride ($AlCl_3$) is the key catalyst in the initial step, acylation of benzene. It is a Friedel-craft type reaction in which the used catalyst is useless along with wastes. Fresh catalyst is required for the subsequent batch of reactants. The $AlCl_3$ complexes strongly bind with the products i.e., Cl^- forming [$AlCl^-$] and cannot be cheaply recycled, resulting in large amounts of corrosive wastes. A new catalyst with superior ecological credentials is now being tried out. Compounds such as the highly acidic triflate (trifluoromethane sulfonate), dysprosium (iii) offer the option of breaking away from the sacrificial catalyst by permitting the catalyst to be recycled.

7. Pharmaceutical company discovers and produces the drugs for uses as medicines. The pharmaceutical company is measured now as the most dynamic sector of the chemical company. The anti-inflammatory and analgesic drugs are produced in high amounts every year. Some important medicines are aspirin (acetylsalicylic acid), acetaminophen (Paracetamol), and Ibuprofen.

Paracetamol was synthesized from phenol in three steps. In the synthetic route, the solvent from step two was kept helping reduce atom economy. The first step involved electrophilic aromatic substitution on phenol with nitric acid to form 4-nitrophenol. An iron (catalyst) by hydrogenation in the second step produced p-aminophenol. Finally, Paracetamol was formed by acylation of the aminophenol. This method including the green step and minimized chemical waste. Ibuprofen belongs to non-steroidal and anti-inflammatory drugs (NSAIDs). This synthesis is a six-step method and given 60% of unwanted waste or by-products that must be disposed of or managed. Several of the wastes are formed and not being incorporated into the desired Ibuprofen but into unwanted by-products.

1. Another drug that requires less waste to produce is the chemotherapy drug, paclitaxel (Taxol). It was initially made by extracting chemicals from yew tree bark, a procedure that used a lot of solvent in addition to killing the tree. The drug is now made by growing tree cells in a fermentation vat.

2. The GC used in the manufacturing of a key intermediate of atorvastatin and the procedures take place in two steps: -

A. In the first step, bio-catalytic reduction of ethyl-4-chloro-3-oxobutanoate occurs with a mixture of keto-reductase and glucose for regeneration of the useful compound which is vital for the activity of enzyme forming a compound ethyl-4-chloro-3- hydroxybutyrate with high yield.

B. In the next step, a halohydrinde halogenase is used to hasten the substitution of the chloro with cyano group, and this reaction takes place at neutral pH and atmospheric temperatures in presence of a catalyst.

Invented clean, quick, and cheap methods for the synthesis of amines with a huge portion of drug molecules. Industries prepared amines in two-step methods at high cost, and it results in high amounts of by-products. On the other hand, concepts of GC do not form any waste product, and reaction is also a quick one-step method in presence of a catalyst. Steps for aspirin synthesis with microwave using catalysts like H_2SO_4, $MgBr_3.O(C_2H_5)_2$, $CaCO_3$, NaOAc, Et_3N, $AlCl_3$, and solvent-free methods have been designed.

FUTURE PERSPECTIVES OF GREEN CHEMISTRY

The future perspectives of green chemistry (GC) will be comprehensive more critically in various research fields. Manufactured goods and the environment should be considered together, and it should be considered that this earth needs a balance of nature. Every attempt to hurt this equilibrium will come across more severe effects. Due to this, we need greener strategies and ideas. Future Trends in GC comprises oxidation reagent and catalysis involved of toxic matters like heavy metals illustrated significant negative effect on human health and environment which can be altered by the use of safe substances, noncovalent derivatization, biometric multifunctional reagents, supramolecular chemistry is ongoing to develop reactions which can continue in the solid-state without solvents uses, combinatorial GC is the chemistry of being capable to produce various chemical compounds rapidly on a small scale using reaction matrices, increase of solventless reactions helps in the progress of product isolation, separation, and refining that will be less solvent and to maximize the benefits.

- Green Nano chemistry
- Combinatorial green chemistry
- Supramolecular chemistry
- Oxidation reagents and catalysts
- Biometric multifunctional reagents
- Non-covalent derivatization methods

In the pharmaceutical industry, GC is a movement to design safer chemicals and techniques. It reduced the negative impact of chemicals on human health and the environment and assists in getting sustainability in the CS. The desire of chemists to make products that are useful and inexpensive extended the scope of GC.

- Source reduction
- Solar cells
- Waste prevention
- Base metal catalysis
- Generating wealth from waste
- Minimization in hazardous products
- Include Sustainability early in the design process.
- Development of eco-friendly chemicals and materials
- Use of environmentally benign solvent systems.
- To generate industrial procedure that prevents hazard problems
- Analysis of the eco-toxicological and environmental effects of biomass processing.

DISCUSSION

Based on the literature review green synthesis (GS) and green chemistry (GC) have a role in improving the quality of the environment. Both GS and green GC have the aim to reduce the use of toxic chemicals that have an impact on the environment and human health. Besides provide profit to the environment, the use of GS and GC also plays a vital role in providing economic profits. It is probable in calculation some of the profits of economic created by the execution of GC in industrial processes, like less need for investment in waste storage, management, and compensation expenses for environmental harm. Without continual growth and progress, improvement, achievement, and success have no meaning. GC is designed for safer chemicals and processes. It reduces the negative impact of chemicals on the environment and helps in getting sustainability in chemical synthesis. The desire of chemists to make products that are useful and cheap expanded the scope of GC. The practice of GC not only leads to environmental profits but also economic and social values. The combination of these three profits is called the "triple bottom line" and gives strong support to expand sustainable materials and methods. The GC is not a solution to all the ecological problems; it is a basic approach to avoid pollution as it is better to prevent waste than to treat it after it is produced (Chen et al., 2020; Tobiszewski et al., 2015). The GS methods are selective and efficient and often associated with microwave and sonochemical activation techniques. The removal of harmful solvents and their substitute by greener solvents like ionic liquids, water, and supercritical liquids is also a vital issue. Solvent-free and solid-phase synthesis are also gaining growing interest. The progress and use of green catalysts are also demanding fields. Other aspects like enantio-selective methods, synthesis of chemicals from biomass and wastes, extraction of natural compounds, green analytical methods, green biotechnology, and the sustainability problems relevant to ecological-friendly chemistry are received (Crua et al., 2019; Wojnarowicz, et al., 2020).

The alternative method for the synthesis of Ibuprofen is a classic example of GC ideas and can influence the better synthetic methods, not only from the economic point of view but also the more effective technical and scientific methods. In the future, researchers believe that GC is going to transform the pharmaceutical industry and drug manufacturing. GC can deliver both environmental and economic benefits and the company is keen to adopt most of its principles. Though GC idea has been accepted by the scientific community, technical GC progress by education and investment to achieve the proper attention.

CONCLUSION

Chemistry has invented vast useful belongings from drugs, and it not only gives the necessary product but also other harmful and unwanted waste. It is a challenge for the industries to synthesize non-harmful products. Green chemistry (GC) gives a huge stage to overcome these harmful substances. It opens a versatile and broad research scope for the development of more competent reaction methods to reduce waste and highly desired product yield. But GC alone cannot reduce these impacts. Principles of GC assist to pave a method towards a greener world. Massive efforts are still carried out for the design of an excellent method that started with pollution-free raw material and without by-products and no requirement of solvents for purification, isolation, and storage. The pharmaceutical company has made a key role to both the life expectancy and the quality of life of the human, but these assistances must be made without harm to the environment. The GC executed help to the pharmaceuticals to get its environmental goal. So, the task is on the producer to build up and work sustainable methods, like, decreasing waste, improving method effectiveness by using less raw materials, recycling and re-using of solvents, and developing cleaner, greener, and energy-efficient methods. The GS and GC aim to reduce environmental troubles. The use of GS and GC has an optimistic impact on the environment and human health. So the execution of GS and GC needs to be executed by diverse companies in carrying out their trade activities. In this review, we have tried to confine some of the main successes in moving to greener pharmaceutical companies to improve their performances. Though, many challenges and prospects remain excellent.

ACKNOWLEDGMENTS

The authors are grateful to Glocal School of Pharmacy, Glocal University, Saharanpur, Uttar Pradesh, India to provide support and facilities to carried to the work.

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