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Green Chemistry - New Approach in Drug Synthesis

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ABSTRACT

Green Chemistry approach is need of the hour in the field of chemistry. Considering the damage to environment, all Pharmaceutical and chemical industry develop interest in new synthetic processes using green chemistry. Most of the drugs are designed, developed and synthesized using various approaches of green chemistry. Microwave assisted synthesis, sonochemistry, solvent free reactions, reuse of catalyst are various approaches of green chemistry used in drug and chemical synthesis. These approaches will be promising in obtaining drug with good yield, less toxic to environment and cost effective.

Keywords: Green Chemistry, Microwave Assisted Synthesis, Solvent Free Reaction, Sonochemistry

I. INTRODUCTION

In early days, drug synthesis is based on the pollute-and-then-clean-up approach. Now a day's more ecofriendly approach of drug synthesis was adopted called Green chemistry. This concept was introduced in the early 1990s in a special program launched by the US Environmental Protection Agency (EPA). It was adopted by mass-media as the new approach of synthesis.[1, 3]

Green chemistry, also called **sustainable chemistry**, is an area of chemistry and chemical engineering focused on the designing of products and processes that minimize the use and generation of hazardous substances.[1,2]

Attention must be paid towards the issues related to safety, health and protection of the environment, due to reactants (starting materials, products and reagents), auxiliaries (mainly solvents) and waste; in order to evaluate the greenness of a particular process. Green Chemistry insists that our synthetic objectives are achieved while assuming additional considerations related to the unnecessary environmental burden created during operations.[4]

Pharmaceutical industry produce a higher ratio of waste per kilogram of product when compared to their peers, such as petrochemical, bulk, fine chemical, and polymer firms. The chemical industry uses two measures to quantify the waste generated by a process:

1) E-factor, which is defined as the unit of waste generated per unit of product (API);
2) PMI, which is defined as unit of raw material used per unit of product.

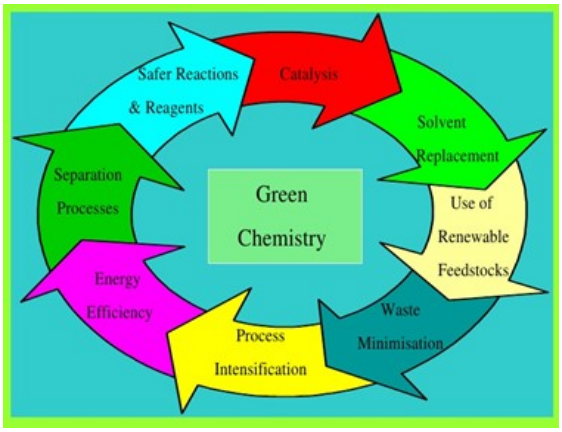
A lower value on both is desirable, and is the goal that the pharmaceutical industry is driving towards. Cost Savings, Consumer Awareness, Regulations, Development of innovative new products, Senior Management Commitment and increased R&D investment, are key factors for driving adoption of green chemistry by pharmaceutical industry. [5]

In some country to enhance the research and implementation of green chemistry various awards are also given.

- ✓ Australia's Green Chemistry Challenge Awards overseen by The Royal Australian Chemical Institute (RACI).
- ✓ The Canadian Green Chemistry Medal.
- ✓ In Italy, Green Chemistry activities center arrange an inter-university consortium known as INCA.
- ✓ In Japan, The Green & Sustainable Chemistry Network oversees the GSC awards program.
- ✓ In the United Kingdom, the Green Chemical Technology Awards are given by Crystal Faraday.
- ✓ In the US, the Presidential Green Chemistry Challenge Awards recognize individuals and businesses

12 Principles of Green Chemistry: [1, 2, 4,11]

1. **Pollution Prevention:** It is much better to prevent environment pollution rather than first pollute and then clean up.
2. **Atom Economy:** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemical Synthesis:** Wherever **it is possible**, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**: The design of chemicals with minimal toxicity reduce the potential risk to human health and the environment; decrease the costs of production and site remediation; and increasing team commitment to workplace health and safety.
5. **Safer Solvents and Auxiliaries:** Reduction or elimination of solvents is often possible while in some cases where solvent is needed, less hazardous solvents should be employed.
6. **Design for Energy Efficiency:** Energy requirements of chemical reactions should be minimized for environmental or economic impacts. If possible, the synthetic methods should be conducted at the ambient temperature and pressure.
7. **Use of Renewable Feedstocks:** Whenever technically and economically practicable, raw material or feedstock should be renewable rather than depleting it.
8. **Reduce Derivatives:** Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis :** Catalytic reagents are superior to stiochiometric reagent. They enhance the selectivity of reaction and extent of conversion to products by reducing temperature.
10. **Design for Degradation :** Chemical products should be designed so that, at the end of their function they break down into degradation products and do not persist in the environment.
11. **Real-time analysis for Pollution Prevention :** It is always important to monitor the progress of the reaction to know when the reaction is complete or to detect the generation of unwanted byproducts. Methods and technologies should be developed so that the prevention or minimization of generation of hazardous waste is achieved.
12. **Inherently Safer Chemistry for Accident Prevention:** Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.



Advantages of Green Chemistry: [7, 8]

Green chemistry has many advantages like

- Non toxic
- Environment Friendly
- Simple
- Sustainable
- Economical
- Safe
- Avoid Waste

Disadvantages Green Chemistry:

- High implementing costs.
- Lack of information
- Lack of awareness about alternative chemical or raw material inputs
- No known alternative process technology
- Uncertainty about performance impacts
- Lack of human resources and skills.

Green Chemistry Approaches:

1) Solvent Free Reactions: [6,7]

Reaction in absence of solvent is one of the method to reduce waste generation of chemicals from reagent. Hence designing of reaction with no use of hazardous and expensive solvents, e.g., "solvent-free" reactions, has gained special attention. Green Chemistry reaction should ideally, be conducted under solvent-free conditions with minimal or no side-product formation and with utmost atom-economy. A solvent-free or solid state reaction may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina or other matrices. Thermal process or irradiation with UV, microwave or ultrasound can be employed to bring about the reaction. Various heterocycles like jasminaldehyde, 4(3H)-quinazolinones, isobenzofuran, pyrazolones, N-substituted pyrroles, Sulphonamide, 6- amino uracil and pregabalin can be synthesized by using solid support. Various name reactions like Aldol condensation reaction, Pinacol-Pinacolone reaction, Pericyclic reaction, Bayer-Villiger Oxidation, Michael Addition are carried out in solvent free environment.

2) Microwave induced green synthesis: [3,9,12]

Microwave reactions involve selective absorption of electromagnetic waves by polar molecules, non-polar molecules being inert to microwaves. In microwave induced organic reactions, the reactions can be carried out in a solvent medium or on a solid support in which no solvent is used. It is one of the good green approach of synthesizing drugs. As it reduces time and also economic, this approach is widely used in synthesis. Only disadvantage is large scale production is not possible. Hence It is used in research, for enhancing the time required for synthesis.

Furans and benzofurans , Pyrroles, indoles , indolizines , Thiophenes , Imidazoles, pyrazoles and benzimidazoles, thiazoles, benzoxazoles , benzothiazoles , Triazoles , Pyridines, quinolines, isoquinolines, Benzopyrans and many more have been synthesized by using microwave. Over-the-counter analgesics such as aspirin, acetanilide, phenacetin, and acetaminophen are conveniently prepared in a microwave at 30% power for five minutes

3) Catalysis: [2,5]

A Green catalyst can play a very important role in chemical processes by replacing reagents, by enabling more efficient processes, by reducing the environmental impact of processes and by reducing the costs of the processes. Biocatalysis offers many attractive features such as mild temperatures, less solvents, biodegradable nature of the enzyme catalyst, high selectivity and functional group compatibilities, all of which favour green chemistry. One of these biocatalysts is Candida Antarctica Lipase, which catalyses alcoholysis, ammoniolysis, and perhydrolysis reactions. Clay-supported zinc chloride (clayzic), HMS-supported zinc triflate, Zeolites are popularly used catalyst.

4) Aqueous mediated synthesis:

Aqueous mediated reactions offer useful and more environmentally friendly alternatives to their harmful organic solvent versions and have received increasing interest in recent years. benzothiazoles/benzothiazolines, Thioesters, Fischer indole synthesis and Michael addition of nitroalkanes are few examples of Aqueous mediated reactions.

5) Ionic liquids: [2, 4]

A new process to separate problematic chemicals from ionic liquids was proposed by Dame et al. Ionic liquids occur in two main categories, namely simple salts (made of a single anion and cation) and binary ionic liquids (salts where equilibrium is involved). For example, [EtNH3][NO3] is a simple salt whereas mixtures of aluminum(III) chloride and 1,3-dialkylimidazolium chlorides (a binary ionic liquid system).

Synthesis of (S)-Naproxen in the ionic liquid BMIM-PF4 has been reported. The very common organic reaction, Friedel-Crafts alkylation proceeds smoothly and efficiently in chloroaluminate (III) ionic liquids.

6) Sonochemistry in Organic Synthesis, without Solvents

Sonochemistry is also considered a methodology of organic reactions without solvents. Their use has been described before and it is obvious that their applications in organic chemistry will be extended further. High yields, low energy requirements, low waste, no use of solvents are some of the fundamental advantages of these sonochemical techniques.

Some application of green Chemistry in Drug Synthesis:

Ibuprofen was synthesized by conventional method in 1960 and widely used. In 1990 new green chemistry

approach is used. It is synthesized in three steps using Nickel (Raney nickel) as catalyst which can be recycled and reused.

Adipic acid is a very important starting material for Nylon-6,6 and catehole (which is used in the pharmaceutical and pesticide industries). Other scientists promoted the biocatalytic method of synthetic adipic acid from D-glucose. It is achieved with genetically transgenic bacteria *Klebsiella pneumoniae*, a non-toxic strain of *Escherichia coli, (Enterobactiriaceae)*.[13]
Methods for synthesis of Aspirin with microwave irradiation using catalysts such as $AlCl_3$, H_2SO_4, H_3PO_4, $MgBr_2.OEt_2$, $CaCO_3$, NaOAc, Et_3N and solvent-free approach have been designed.[14]

Anastas et al has described synthesis of Naproxen with chiral metal catalyst containing BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) ligand with good yields.[15]

The green synthesis for a key intermediate of atorvastatin has been developed in two steps. First step involves the biocatalytic reduction of ethyl-4-chloroacetoacetate using a ketoreductase in combination with glucose and a NADP-dependent glucose dehydrogenase (GDH) for cofactor regeneration. The (S)ethyl-4-chloro-3-hydroxybutyrate product is obtained in very good yield. In the second step, a halohydrindehalogenase (HHDH) is employed to catalyze the replacement of the chloro substituent with cyano, by reaction with HCN at neutral pH and ambient temperatures. These natural enzymes were highly selective for the reactions. [16]

Tetrahydropyrimidinones was synthesized by Biginelli reaction using conventional heating. A. k. Bose et al has used modified version of Toda"s method of grinding solids together for solvent-free chemical reactions called Grindstone Chemistry to synthesize tetrahydopyridinones using p-toluenesulfonic acid as an acid catalyst. [3]

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