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CHEMISTRY GOES GREEN: A REVIEW ON CURRENT AND FUTURE PERSPECTIVES OF PHARMACEUTICAL GREEN CHEMISTRY

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ABSTRACT

Over the past few decades, the chemistry community has been mobilized to develop a new chemistry that is less hazardous to the environment as well as human health. This new approach has received extensive attention and nominated by many names including Green Chemistry, Environmentally Benign Chemistry, Clean Chemistry, Atom Economy and Benign by Design Chemistry. Below all of these different designations there is a movement toward pursuing chemistry with the knowledge that the consequences of chemistry do not stop with the properties of the target molecule or the efficacy of a particular reagent. The practice of chemistry in a manner that maximizes its benefits while eliminating or at least greatly reducing its adverse impacts has come to be known as green chemistry. It focuses on a process (whether carried out in industry or a chemical laboratory) that reduces the use and generation of hazardous substances or by-products. As on today, maximum pollution to the environment is caused by numerous chemical industries. Therefore, attempts have been made to design synthesis for manufacturing processes in such a way that the waste products are minimum, they have no effect on the environment and their disposal is convenient. In pharmaceutical industry, some drugs generate large amount of waste as byproducts during their synthesis which results the low yield in the final products. For carrying out reactions it is necessary that the starting materials, solvents and catalysts should be carefully chosen. Green chemistry play important role in pharmaceutical in developing innovatory drug delivery methods which are less toxic and more useful, effective with minimum side effects and could help millions of patients. In this review, we will also be looking ahead at the immediate and longer-term challenges and opportunities as I now see them in research and in industrial application and also in education and promotion.

KEYWORDS: Green chemistry, Atom Economy, Design Chemistry, Environmentally Benign Chemistry, Clean Chemistry.

INTRODUCTION

What is Green chemistry?[1-6]

Green or Sustainable Chemistry is a term that refers to the creation of chemical products and processes that reduce or eliminate the use and production of harmful substances. The practice of chemistry in a manner that maximizes its benefits while eliminating or at least greatly reducing its adverse impacts has come to be known as **green chemistry.** As a new branch of chemistry with ecological approaches it involves reducing or eliminating the use of harmful substances in chemical processes as well as reducing harmful and toxic intermediates and products. To be called "green," each reaction should have three green components: solvent, reagent /catalyst and energy consumption. Another aspect of the definition of Green Chemistry is found in the phrase “use and generation”.

“It is better to prevent waste than to treat or clean up waste after it is formed”

Finally, the definition of Green Chemistry includes the term “hazardous”. It is important to note that Green Chemistry is a way of dealing with risk reduction and pollution prevention by addressing the intrinsic hazards of the substances rather than those circumstances and conditions of their use that might increase their risk. For example, Benzene (C_6H_6) as a solvent must be avoided at any cost since it is carcinogenic in nature. If possible, it is best to carry out reactions in the aqueous phase. With this view in mind, synthesis methods should be designed in such a way that the starting materials are consumed to the maximum extent in the final product. The reaction should also not generate any toxic by-products.

Green chemistry is based on twelve principles that can be used to create or recreate molecules, materials, reactions and processes that are safer for human health and the environment, and the processes of green chemistry developed to date include mainly all areas of chemistry, including Organic, inorganic, biochemical, polymeric, toxicological, environmental, physical, technological, etc.

Green chemistry is a Hippocratic Oath for chemists, and in order to preserve natural resources and the environment, a new generation of scientists and technologists is being developed, which economically analyze the processes and materials used in production and development.

If no hazardous substances are used or produced, then the risk is zero and there is no need to worry about removing hazardous substances from the environment or limiting exposure to them or "Green chemistry is about reducing waste, raw materials, risks, energy, environmental impact and cost".

Basic Principles of Green Chemistry[7-11]

The principles of green chemistry speak about the reduction or removal of dangerous or harmful substances from the synthesis, production and application of chemical products and thus the use of substances dangerous to human health and the environment is reduced or eliminated. When designing a green chemistry process, it is impossible to meet the requirements of all principles of the process at the same time, but it attempts to apply as many principles as possible during certain stages of synthesis.

- Prevention of waste/ by-products
- Application of innovative technology to established industrial processes
- Maximum incorporation of the reactants (starting materials and reagents) into the final product
- Energy requirements should be recognized for their environmental and economic impacts and should be minimized
- Prevention or minimization of hazardous products
- Use of biotechnology alternatives
- Designing of safer chemicals
- Minimum energy requirement for any synthesis
- Selecting the appropriate starting Solvents
- Selecting the most appropriate solvent
- Whenever possible avoid the use of protecting group
- Whenever possible prefer use of catalysts
- Design of degradation
- Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products
- Analytical methodologies need to be further developed to allow for real time, in process monitoring and control prior to the formation of hazardous substances
- A raw material or feedstock should be renewable rather than depleting, whenever technically and economically practicable
- Design manufacturing plants so as to eliminate the possibility of accidents during operations Strengthening of analytical techniques to control hazardous compounds
- Whenever practicable synthetic methodologies should be designed to use and generate a substance that poses little or no toxicity to human health and the environment
- Chemical products should be designed to preserve efficiency of function while reducing toxicity
- Unnecessary derivatization (blocking group, protection, deportation, temporary modification of physical/chemical processes) should be avoided whenever possible
- Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

Fig. 1: Principles of Green Chemistry.

Concept of Pharmaceutical Green Chemistry[12-15]

The Pharmaceutical industry is the most dynamic part of the chemical industry. It is in the forefront for big changes towards "greener" feedstock, safer solvents, alternative processes and innovative ideas. All these changes will increase the environmental credentials of the pharmaceutical industry, but at the same time will cut down cost and materials for the manufacturing operations making a step in the right direction of sustainability.

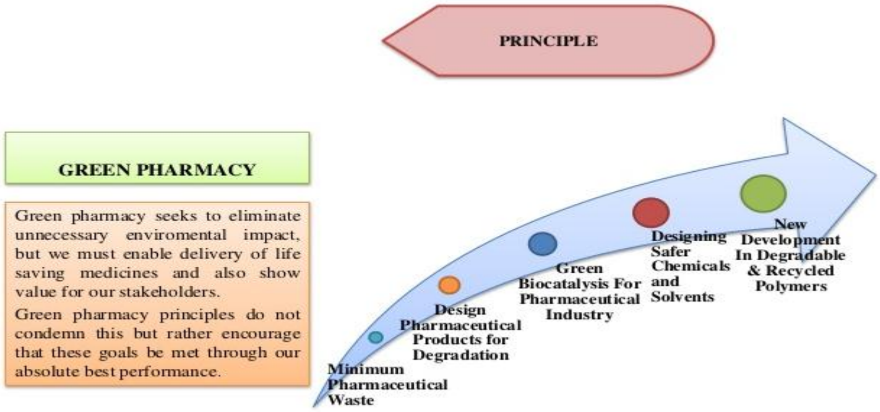

Fig. 2: Green chemistry in pharmaceutical industry.

The utilization of green chemistry principles in the pharmaceutical industry can be viewed as both an obligation and a significant opportunity to enhance our positive impact on the global community.

Pharmaceutical Chemists aid the drug industry in its ongoing efforts to develop medicines with less harmful side-effects, using processes that produce less toxic waste. The chemical production of drug molecules for commercial use is vastly different from conventional bulk manufacture of, for instance, commodity chemicals. More than half the mass constituting a process stream in the chemical manufacture of active pharmaceutical ingredients generally stems from the solvent(s) utilized; 80– 90% if water is included. This means that the potential for production improvements is huge. At some companies, environmental specialists, pharmaceutical development chemists, chemical engineers and medicinal chemists all work together to improve drug manufacturing.

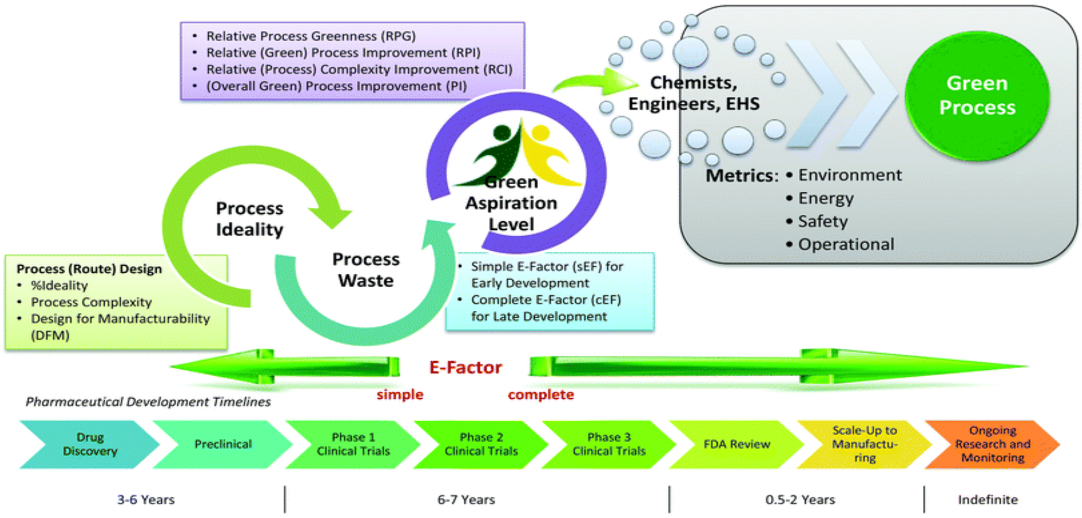

Fig. 3: Green chemistry in pharmaceutical industry: the green Aspiration Level concept.

The pharmaceutical industry for years was embracing more and more "green" processes and technology operations. The research departments of many big drug manufacturers in the developed countries made many advances for new methodologies, better biocatalysis reactions, less solvents and cuts in waste production. Researchers noticed that it took several years for pharmaceutical companies to translate green principles into measurable goals for environmental sound research, development and production.

Among industrial enterprises drug manufacturers introduced rigorous safety and health regulations to protect their workers and environmental criteria for their products. Safety, Efficiency, Reliability and Economy are the four pillars of change and their promotion is considered as a competitive advantage, better environmental credentials and economical benefits.

Pharmaceutical Applications of Green Chemistry[16-34]

Pharmaceutical companies have the capacity to improve the environmental performance by using the knowledge related to green chemistry. Green chemistry is engaged in developing innovative drug deliverance methods which are less toxic and more useful, efficient and could help millions of patients, Examples:-

1. Phosphoramidite: solid-phase which is blend of antisense oligonucleotides has been altered to entrain the concepts of green chemistry by discarding the usage and formation of toxic or hazardous materials and recycling the important materials like protecting groups amidites and solid support, thus upgrading the cost-efficiency and atom economy.
2. The formation of Naproxen with chiral metal catalyst containing 2,2'-bis[diphenylphosphino]-1,1'-binaphthyl ligand with fine quantity of product.
3. Green solvents such as water can replace many toxic and hazardous solvents and has been found very efficient in many organic reactions out of which include the synthesis of benzothiazoles/benzothiazoline, chromeno-isoxazole etc. Glycerol on the other hand, was recently reported as a valuable solvent (important) green solvent. Glycerol may combine the advantages of water with low toxicity, low price, large availability and renewability. The high polarity of glycerol allows for the simple reduction of different carbonyl compounds with sodium borohydride.
4. Super critical carbon dioxide $ScCO_2$ is becoming an important Commercial and industrial solvent due to its role in chemical extraction in addition to its low toxicity and environmental impact. Super critical carbon dioxide $ScCO_2$ is a fluid state of CO_2 where it is held at or above its critical temperature (304.25K, 31.10^{o}c, 87.98^{o}F) and critical pressure (72.9atm, 7.39mPa, 1,071psi) expanding to fill its container like gas but with density like that of liquid. It is reported that, super critical carbon dioxide $ScCO_{2s}$ work similarly with other problematic chemicals without hazardous effects with advantage of water. Reported that, hydrogenation, epoxidation, radical reactions, palladium-mediated C-C bond formation, ring closing metathesis, polymerization and many others reactions can be performed with $ScCO_2$ as a reaction medium. Processes that use $ScCO_2$ to produce micro and nano- scale particles, often for pharmaceutical uses, are under development.
5. Traditional organic synthesis features stiochiometric quantities of reagents, leading to large quantities of byproducts, which add to the burdens of wastage, the right catalyst technology enhances product value, which minimizing waste streams and improving cycle times. Recent advancement in catalysis has paved the way for many valuable applications, notably in the synthesis of APIs (Active pharmaceutical Ingredients) and intermediates. Two types of catalysts technologies: Chemocatalysis and Biocatalysis.
6. In the manufacture of Anthraquinone for the dyestuffs industry for example, aluminium chloride is the crucial catalyst in the initial step, the acylation of benzene. This is a type friedel- craft reaction in which the spent catalyst is discarded along with waste from the process. Fresh catalyst is required for the next batch of reactants. The problem is that the aluminium chloride complexes strongly with the products i.e. Cl^- forming [AlCl $^-$] and cannot be economically recycled, resulting in large quantities of corrosive waste. New catalyst with better environmental credentials is now being tried out. Compounds such as the highly acidic dysprosium (iii) triflate (triflouromethane sulfonate) offer the possibility of breaking away from the sacrificial catalyst by enabling the catalyst to be recycled.
7. Pharmaceutical industry discovers, develops, produces and markets drugs or pharmaceutical drugs for uses as medications. Pharmaceutical industry is considered now as the most dynamic sector of chemical industry for the 21st century. The analgesic and anti- inflammatory drugs are a category of medicines which are produced in vast amounts every year. Some of the most important are: Aspirin (acetylsalicylic acid), Acetaminophen (Tylenol, Paracetamol) and Ibuprofen.

Acetaminophen or Paracetamol is a well-known drug that is used to relieve headaches, fever and aches and pains in joint and muscles. It is also a main ingredient in many cold and flu medications and prescriptions. It is considered a safe and effective drug when used in the recommended dosages. It was synthesized from phenol in three steps. In this synthetic route the solvent from step two was kept to help minimize atom economy. The first step involved electrophilic aromatic substitution on phenol with nitric acid to create p- nitrophenol. An iron (as a catalyst) through hydrogenation in the second step produced p-aminophenol. Finally acetaminophen was synthesized by acylation of the aminophenol. This new method including the green step minimized chemical waste.

Ibuprofen belongs to non-steroidal and anti-inflammatory drugs with very high sales. It was synthesized in 1990 by the pharmaceutical company Boot (England) and sold under the commercial name Aspro, Panadol and Nurofen. This synthesis is a six-step process and results in 60% of unwanted waste chemical byproducts that must be disposed of or otherwise managed. Much of the waste that is generated is a result of many atoms of the reactants not being incorporated in to the desired products (Ibuprofen) but in to unwanted byproducts.

1. Another notable drug that requires less waste to produce is the chemotherapy drug, paclitaxel

(marketed as Taxol). It was originally made by extracting chemicals from yew tree bark, a process 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.

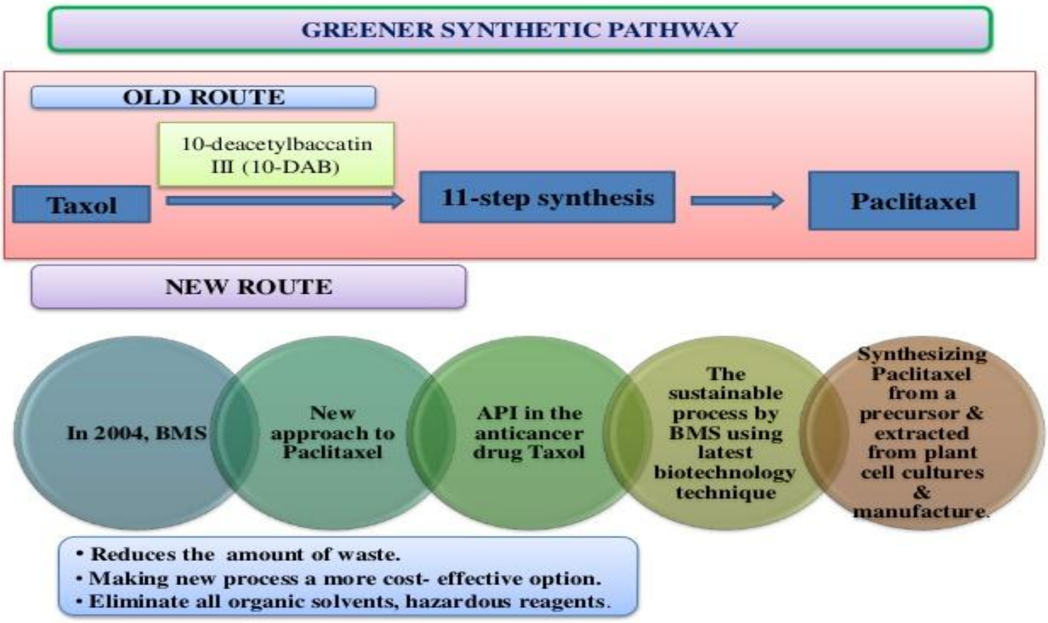

Fig. 4: Greener synthetic pathway of Paclitaxel.

2. The green chemistry used in the manufacturing of a key intermediate of atorvastatin and the processes take place in two steps :-

A. In first step, bio catalytic reduction of Ethyl-4-chloro-3- oxobutanoate occurs with combination of keto-reductase and glucose for regeneration of the useful substance which is essential for activity of enzyme forming a product [S]ethyl-4-chloro-3-hydroxybutyrate with high yield.

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

C. Few workers have invented clean, quick and inexpensive way for the preparation of amines with huge portion of drug molecules. Presently, industries manufacture amines in a two-step process at high cost and it results in grand amounts of by-products as a waste material. On the other hand, concepts of Green chemistry don't produce any waste product, and reaction is also a quick one- step process in presence of little amount of catalyst. Steps for Aspirin synthesis with microwave irradiation using catalysts such as H_2SO_4, $MgBr_3.OEt_2$, $AlCl_3$, $CaCO_3$, NaOAc, Et_3N and solvent free approach have been designed.

Future Perspectives of Pharmaceutical Green Chemistry

Future perspective of green chemistry will be extended more seriously in many research areas. Product and environment should be considered together and it should be remembered that this planet needs a balance of nature. Every attempt to heart this balance will come across more serious effects. That is why we need greener strategies and greener thinking.

Future Trends in Green Chemistry includes oxidation reagent and catalysis comprised of toxic substances such as heavy metals showing substantial negative effect on human health and environment which can be changed by the use of benign substances, Non covalent derivatization, Supramolecular chemistry research is currently on going to develop reactions which can proceed in the solid state without the use of solvents, Biometric multifunctional reagents, Combinatorial green chemistry is the chemistry of being able to make large numbers of chemical compounds rapidly on a small scale using reaction matrices, Proliferation of solvent less reactions helps in development of product isolation, separation and purification that will be solvent-less as well in order to maximize the benefits.

- Green Nanochemistry
- Supramolecular Chemistry
- Oxidation Reagents and Catalysts
- Biometric Multifunctional Reagents
- Combinatorial Green Chemistry
- Non Covalent Derivatization Techniques

In pharmaceutical Industry, Green Chemistry is a new trend to design safer chemicals and processes. It minimizes the negative impact of chemicals on the human health & environment and helps in achieving sustainability in the chemical production. The desire of chemists to make products that are effective and economical expanded the scope of Green Chemistry.

- ✓ Source Reduction
- ✓ Incorporate Sustainability early in the design process
- ✓ To Create Industrial Processes that avert hazard Problems
- ✓ Development of Eco-friendly chemicals and materials
- ✓ Analysis on the eco-toxicological and environmental effects of biomass processing
- ✓ Use of environmentally Benign Solvent systems
- ✓ Generating Wealth from Waste
- ✓ Waste Prevention
- ✓ Minimization in hazardous products
- ✓ Base metal catalysis
- ✓ Solar Cells

CONCLUSION

Chemistry has invented many beneficial things from drugs and it not only yields the required product but also the other harmful and undesirable waste. It is the challenge for the prospect industries is to synthesize non-harmful products. Green chemistry provides a big platform to overcome from these unwanted harmful substances. It opens a multifaceted and wide research scope for the invention of more efficient reaction process to minimize the waste and maximize the desired product yield. But green chemistry alone cannot reduce these impacts. Principles of green chemistry help to pave a way towards the greener world. By using the proper sample preparations one can obtain accurate and exact results of analysis. An enormous effort are still undertaken for the designing of a superlative process which initiated with pollution free raw material and obtaining no secondary product and does not require any solvents for purification, isolation and chemical conversion.

The pharmaceutical industry has made a major contribution to both the life expectancy and the quality of life of the human population, but it is clear that these contributions must be made without major detriment to the environment. Green chemistry is a tool, which when implemented right, can help the pharmaceutical industry to achieve its environmental goal. Therefore, the responsibilities is on the manufacturers to develop and operate sustainable processes, for example, by reducing waste, improving process efficiency by using less raw materials and recycling and re-using solvents whenever possible and lastly developing cleaner, greener, and more energy-efficient processes. The alternative pathway for the synthesis of Ibuprofen is a classic example of how Green Chemistry ideas can influence to the better industrial synthetic methods, not only from the point of economic efficiency, but also from the point of more effective scientific and technological methods.

In the future, Scientists believe that Green Chemistry is going to transform the pharmaceutical industry and drug manufacturing. Green Chemistry can deliver both environmental and economic benefit and the pharmaceutical industry is keen to adopt most of its principles. Although Green Chemistry philosophy has been generally accepted by the scientific community, technical Green Chemistry evolution through education and investment has yet to achieve the appropriate attention and effort.

In this review, we have tried to capture some of the major achievements in moving to a greener pharmaceutical industry an in general the performance to date has been good. However, there are many challenges and opportunities that remain out- standing. In our view the scope for innovation and improvement remains as wide as ever.

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