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Application of green chemistry in pharmaceutical industry

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Abstract
Green chemistry does not means Green as a color but an alternative to design of chemical products and processes that reduce, minimize or eliminate the use and generation of hazardous substances. Green chemistry is based on the fundamental or outstanding principles that when implemented right will maximize the incorporation of raw materials into the final products with environmentally-friendly substances and methodologies. The use of solvents and catalysts as greener technologies are emphasized. In pharmaceutical industry, some drugs generate large amount of waste as byproducts during their synthesis which results the low yield in the final products. In this review, the green alternative pathway of Acetaminophen (paracetamol) and Ibuprofen among other were reported.

Keywords: green chemistry, green solvents, green catalysts, pharmaceutical molecules, pharmaceutical industry

Introduction

The discovery of insulin and penicillin by Fredrick Bating and Alexander Fleming respectively in the 1992s indeed marked the beginning of modern pharmaceutical industry that has become a major contributor to the economy of many nations of the world. It was recently reported on 12 June 2017 by Pharmatime, that in the United States, the biopharmaceutical sector alone is said to have contributed significantly to the economic development of the country in diverse ways. For instance the sector has offered employment to nearly 850,000 workers while supporting over 3.4 million jobs and that is in 2014 alone. In India, china, Japan and host of other nations, the pharmaceutical industry has directly and indirectly contributed tremendously to their development. Apart from providing health benefits to the populations around the world, the impact of Research and Development in the discovery is being felt in the discovery and development of new medicines, creation of highly skilled jobs and stimulating high level innovations [Ngozi U. 2017] [15].

The issues of economy nose-diving has necessitated the need to make a paradigm shift from consuming economy to producing economy. For any nation to thrive as producing economy there is need for Green chemistry among the young chemists [Zainab S.A 2009] [31]. Chemicals are used in production of must goods made in the Nigeria, they are present in the commodities we import and every day we used a wide array of chemicals products from paint to cosmetics to pharmaceuticals [Steven B.R 2009] [22]. Despite the critical role chemicals play in the economy and in our lives, the level of understanding about their characteristic and hazards they pose is generally low. According to [James H. & Robert P. 2002] [9] from the *Political Economy Research Institution* PERI revealed that chemicals are accumulating in our bodies and negative consequences for the environment are becoming increasingly clear.

During the twentieth century, chemistry changed the way people lived and the greatest perceived benefits came from pharmaceutical industries with development of organic medicinal molecules [Smita T. & Falguni M. 2012] [20]. Pharmaceutical chemistry encompasses major chemicals, reagents, solvents, catalysts and almost all types of organic reaction for synthesis of active pharmaceutical molecules. Therefore, many chemicals and chemicals processes are very hazardous, toxic and may have adverse effects on the environment and on human health. Industries associate with pharmaceuticals and fine chemicals are employing much more waste, which is not all suitable for environment and nature [Ankley G.T *et al.* 2007] [4].

When green chemistry was founded in the early 1990s,there was wide spread concern over potential adverse impact on human health and the environment from the processes, by-products, waste, pollution and industrial chemicals in people's daily lives. Rather than continue deferring to litigators, legislators, and regulators to reactively handle these critical problems, members of the chemistry community unified around a common goal to design chemical products and processes that reduce or eliminate the use and generation of hazardous substances" (Anastas P. 1999) [1] of Yale University, one of the green chemistry's founders.

An awareness of the potential impact that manufacturing process may have on the environment has become a major, and increasing factor of concern for the society. Much debate and discussions has been focused on the chemical industry, especially the pharmaceutical industry in the world. The main focus of the criticisms is the high E factor (environmental factor), defined as Kg of waste per Kg of designed products [Sheldon R.A 2000] [19]. A high E factor is indicative of inefficient process that generates large amounts of waste, increase the cost of medicines, and have a negative effect on the environment. The concept of Green chemistry has defined and interpreted in many ways depending on the particular area of chemistry in which one is employed or interested.

The limitations of a command and control system for environmental protection have become more obvious even as the system has become more successful. In industrialized societies with good, better, best, well-enforced regulations, most of the easy and inexpensive measures that can be taken to reduce environmental pollution and exposure to harmful chemicals have been executed. Therefore, small increases in environmental waste from pharmaceutical industry require relatively large investments in money and effort [Stanley E.M 2005] [21]. *Is there a better way? There is indeed. The better way is through the practice of Green chemistry***.** The potential for the future development of safer and greener chemistry will support Nigeria Global competitiveness and will help sustain Nigeria manufacturing in to the 21st century while preventing further erosion of good jobs.

Green Chemistry

The term Green chemistry was first used in 1991 by Anastas P. in a special program launched by the US (United State) Environmental Protection Agency (EPA) to implement sustainable development in chemistry and chemical technology by industry, academia and government. In 1996 the working party on Green chemistry was formed, acting within the framework of IUPAC (International Union of Pure and Applied Chemistry).One year later the Green chemistry Institute (GCL) was formed with 20 chapters across the world to facilitate contact between Governmental Agencies and industrial corporations with universities and Research Institutions to design and implement new technologies [Suresh D.D 2005] [23].

Green chemistry also called sustainable chemistry is a philosophy of chemical research and engineering that encourages the design of products and processes that minimizes the use and generation of hazardous substances [Ghanshyam D.S 2001] [8]. Zainab S.A 2009 [31] defined Green chemistry as technologies of the invention, design and application of chemical products and processes to reduce or eliminate the use and generation of hazardous substances and where possible utilize renewable raw materials. Steven B.R 2009 [22] also see Green chemistry as an innovative approach to designing chemical products and processes that reduce or eliminate the use or generation of hazardous substances while producing high quality products that are safer and healthier for the environment. In more comprehensive way, Green chemistry can be define as the practice of chemical science and manufacturing in a manner that is sustainable, safer, and non-polluting and that consumes minimum amount of materials and energy while producing little or no waste materials.

The practice of Green chemistry begins with recognition that the production, processing, use and eventual disposal of chemical products may cause harm when performed incorrectly [Stanley E.M 2005] [21]. Green chemistry is also known as: *clean chemistry, sustainable chemistry, environmentally benign chemistry and atom economy* Zainab S.A 2009 [31].

According to Anastas P. & Warner J.C 1998 [2, 3], this approach offers environmentally beneficial alternatives to more hazardous chemicals and processes and thus promotes pollution preventions. The following 12 principles of Green chemistry provide away for chemists to implement Green chemistry.

1. Prevention

It is better to prevent waste than to treat or clean up waste after it has been created.

2. Atom economy

Synthetic methods should be designed to maximize the incorporation of all materials used in the process in to the final product.

3. Less hazardous chemical syntheses

Synthetic methods should be designed, whenever practicable, to use and generate substances that poses little or no toxicity to human health and the environment.

4. Designing safer chemicals

Chemical products should be designed to achieve their desired function while minimizing their toxicity.

5. Safer solvents and auxiliaries

Unnecessary use of auxiliary substances (e.g solvents, separation agent etc) should be avoided whenever possible and made innocuous when used.

6. Design for energy efficiency

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of renewable feedstock

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, and 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 (as selective as possible) are superior to stiochiomtric reagents.

10. Design for degradation

Chemical products should be designed so that at the end of their function they break down in to innocuous degradation products and do not persist in the environment.

11. Real-time analysis for pollution prevention

Analytical methodologies need to be further developed allow for real-time, in process monitoring and control, prior to the formation of hazardous substances.

12. Inherently safer chemistry for accident prevention
Substances and the form of a substances used in a chemical process should be chosen so as to minimize the potential of chemical accidents, including releases, explosions and fires.

Technologies that enable green chemistry execution
In view of the above twelve 12 principles, this review article is limited to green solvents and green catalysts as the technologies which comprises an important part of almost all types of organic reactions.

Green Solvents
Walter L 2009 [30] explained that, the pharmaceutical industry has made significant efforts towards identifying organic solvents with reduces ecological footprint as compared to traditional reactions. solvents are key priority when greening chemistry, because they are used in high volumes and are typically volatile organic compounds (VOCs) leading to high risk for large amount of waste, air pollution, and other health concern [Smita T. & Falguni M.2012] [20]. Similarly, solvents are use to dissolved reactants and also to extract and purify products. Unfortunately, many organic solvents are volatile, flammable and may pose a risk to health and the environment. Jimenez G.C *et al.* 2004 [10] observed that, solvents can account for 80% of the mass in the pharmaceutical manufacturing industry; this resulted to a significant contribution to the high E factor for pharmaceutical products. Green solvents such as:
Water and Glycerol: 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 [smita T. & Falguni M. 2012] [20]. Glycerol on the other hand, was recently reported as a valuable (important) green solvent; glycerol may combine the advantages of water with low toxicity, low price, large availability and renewability [Jose I.G *et al.* 2010] [11]. The high polarity of glycerol allows for the simple reduction of different carbonyl compounds with sodium borohydride.
Super critical carbon dioxide CO_2: 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 carbon dioxide where it is held at or above its critical temperature (304.25K, 31.10ºc, 87.98ºF)and critical pressure(72.9atm, 7.39mPa 1,071psi) expanding to fill its container like gas but with density like that of liquid. Smita T. & Falguni M. 2012 [20] reported that, Super critical carbon dioxide $ScCO_{2S}$ work similarly with other problematic chemicals without hazardous effects with advantage of water. Oak R.S *et al.* 2001 [16] 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 [Oak R.S *et al.* 2001] [16].

Green Catalysts
Catalysis: 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 [Vivek Sharma 2015]. Recent advancement in catalysis has paved the way for many valuable applications, notably in the synthesis of APIs (Active pharmaceutical Ingredients) and intermediates. Dunn H. *et al.* 2013 [13] reported two types of catalysts technologies:
Chemocatalysis: chemocatalysis has been developed sufficiently to be used extensively in manufacturing today. It includes metal catalysts of various kinds and organocatalysis, both of which have transformed the field of organic synthesis (for pharmaceutical molecules) over the past few decades.
Biocatalysis: biocatalysts 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 favor green chemistry.
Chemists are working to develop new, longer-lasting catalysts to ensure industrial processes are cleaner, greener and more efficient [Vivek Sharma 2015]. In order to arrest the situation, much attention has been given on the research to find out the right catalysts that will enable pharmaceutical processes to be less polluting, operate with better atom economy, produce purer products and last longer [Tony H. 2009] [27].
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 [$AlCl_4^-$] and cannot be economically recycled, resulting in large quantities of corrosive waste [Tony H. 2009] [27]. 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.

Greener Pharmaceuticals
The development of new pharmaceutical products by organic synthesis over the past century has contributed to a revolution in medical care, enabling drastic reductions in hospitalization, suffering and death. However, this achievement is flawed if the environment is adversely impacted with the increasing emphasis on the green chemistry [Anastas P.T & Williamson T.C 1998] [2, 3]. Pharmaceutical industry can influence and improve the environmental performance with utilizing green chemistry. Green chemistry is being adopted to develop revolutionary drug delivery methods that are more effective and less toxic and could be a benefit to millions of patients [Kim A *et al.* 2008 and ScienceDaily 2007] [12, 25]. It's noted that pharmaceutical industries are in for big business because the incidence of infectious diseases is increasing in virtually every part of the world partly because some diseases have become drug-resistant and that is compelling the international community to urgently look for the ways of addressing the challenges. Pharmaceutical chemicals include medicinal drugs (including antibiotics, steroids, analgesics, anticancer),

veterinary drugs, materials for hygiene, diagnostic agents, nutraceuticals (from nutrition + pharmaceuticals eg vitamins, dietary supplements, policy phenols, herbal extracts), disinfectants, antioxidants and their packaging materials [Thomas V. & Valavanidis A. 2013] [29].

Pharmaceutical industry discovers, develops, produces and markets drugs or pharmaceutical drugs for uses as medications [McGuire, John L *et al.* 2007] [14]. 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 [Tudor O *et al.* n.d]. 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 [Korto G-K *et al.* 2013] [13].

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.

In 1990 the BHC after prolong research on the subject discovered a new synthetic route with only three steps and increased efficiency (U.S patent 4,981,995 and 5,068,448 both issued in 1991). In this process, most of the atoms of the reactants are incorporated into the desired products (Ibuprofen). This results only 1% of unwanted byproducts (very good atom economy or atom utilization). In both synthetic routes the starting chemical is 2-methylpropylbenzene, which is produced from the petrochemical industry. The innovation in the new method was in the second step. A catalyst of Nickel (Raney nickel) was the used thus decreasing substantially the steps of the synthesis [Cann MC & Cannelly M.E 2000] [5].

In the traditional synthetic route, each step had a yield of 90% so that the final product came to be 40% yield compared to the starting chemical. This resulted in the increased production of byproducts as waste. In the greener method of three steps the final yield is 77%, whereas the Raney nickel catalyst (Nickel, CO/Pt) can be recycled and reused. In the old synthetic route, $AlCl_3$ used as a catalyst had to be thrown away as waste [Cann MC & Cannelly M.E 2000] [5].

The amide groups are widely found in pharmaceuticals including the antidepressant maclobemide and other drug-like molecules. The catalytic transformation of a primary amide in to a secondary or tertiary amide generates very little waste, which is very promising for the green transformation of the pharmaceutical industry. Chen A. and his team from A* STAR institute of chemical and engineering sciences in collaboration with National University of Singapore (NUS), In 2014 reported that, the solid-state catalyst mesoporous niobium oxide is suitable for transmidation (the catalytic reaction of a primary amide with an amine to make secondary or tertiary amides) in the absence of any solvent. The team tested the niobium oxide catalyst in reactions of a wide range of primary amides with various 1^{o} and 2^{o} amines. The corresponding amides were all obtained in high yields. The only downside is that the reactions required a relatively high temperature (around 150^{o}C).

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 [U.S EPA 2012] [26].

Conclusion

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.

Green Chemistry

"*Hurt not the earth, neither the sea nor the trees*"--- Ronald C.D & Breslow R.I (1996) [18].

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