**Implementation of Green Technology & Green Chemistry in Pharmaceutical Industry: A newer approach for sustainability in Pharmaceutical Industry.**

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**ABSTRACT:**

 Emerging trends have nowadays been involved for the sustainability in Pharmaceutical industry. The concept of Green technology, Green Chemistry are growing attentions as the industries produces a significant amount of wastes and Green house gases with the utilization of large volume of water. The implementation of energy efficient system, using electric vehicles in logistics operations and independent verifications such as leadership in energy ,environmental design certifications that focusses on company’s building designs, construction are considered to be resource efficient which minimizes its carbon footprint. In order to minimize the impact on environment in a cost effective manner the designing of the chemical process with reduction in the use and creation of hazardous substances should be incorporated.

To achieve sustainability in operational perspectives integration of Green supply chain (GSC) can also be adopted. However, the potential risk and finalizing the risks involved in adopting the GSC initiatives within the pharmaceutical industry depends on fuzzy Delphi approach and fuzzy Analytical Hierarchy process (AHP).

 According to the data obtained during a survey conducted in top global pharmaceutical companies, pressures to deliver new drugs and regulatory risk are the top two barriers for GC adoption. Hence, wider adoption of green chemistry by the entire supply chain requires more effective and globally harmonized environmental regulations, use of life cycle assessment metrics, expanding GC education and establishing effective supplier management programmes.

 Large decline in Toxics Release Inventory (TRI) release from the pharmaceutical industry in U.S. have been observed with the adoption of GC as per the reports of researchers.

Recent studies of the global pharmaceutical supply chain revealed that inspite of lack of public disclosure, generic drug companies, API manufacturers and smaller R&D pharma companies exhibit interest and advances in GC principles. The current chapter aims to focus new technologies adoption of GC by pharmaceutical companies and API manufactures, to examine the drivers and barriers to greater adoption of GC by industry and to identify opportunities for wider acceptance of GC by pharma industry and API manufacturers in India.

**Keywords:** Green Chemistry, Green technology, Green Supply Chain, Pharmaceutical Industry, Active Pharmaceutical Ingredients.

 To enhance the standard of living across the world, pharma company has always been an assurance to deliver revolutionary drugs [1].During this process, from chemicals and waste management perspective, health and environmental concern in this are mainly related to release of pharmaceutical in the environment. Direct emissions from drug manufacturing, patient and animal excretion, aqua farming and disposal of unused or expired medicines are found to be various sources of release of pharmaceuticals to the environment [2]. In the recent times, many large pharmaceutical companies have moved to using green-chemistry practices for drug discovery, development and manufacturing. Their approach mainly focusses on profit, people and planet in contribution to the 12 principles of green chemistry which comprises of minimizing ingredients, waste, toxicity and energy [3].To quantify the waste generated from various process, the chemical industries includes E-factor, which is defined as the unit of waste generated per unit of product (API) & 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 [4]. In a report published in recent times by UK water Research Industry found several common drugs were present in the final effluent in high concentration enough to potentially affect our ecosystem upon a study conducted on 160 sewage treatment works. Delft Institute for Water Education in the Netherlands had predicted that with the trends prevailing, amount of pharmaceutical effluence into waterways could increase by two-thirds before mid-century.A particular concern is antimicrobial resistance (AMR), linked to discharge of antibiotics and other chemicals into the environment. Although antibiotics are essential for medical treatment, AMR has been labelled by the World Health Organisation as a "major threat to public health" and is expected to cause 10 million deaths annually by the year 2050 [5].With ecological approaches the branch of chemistry involves reducing or eliminating use of harmful substances in chemical processes as well as reducing harmful and toxic intermediates and products. Solvent, Reagent/catalyst and energy consumption are the three key components for a reaction to be called as “Green”. “Use and generation’’ is an another new aspect in the definition of “Green Chemistry”[6].

In 2005 the Pharmaceutical Roundtable started which was initially a collaboration between the ACS Green Institute and the pharma industry as a start up to include green chemistry in the process. Solvents were identified as the source of the majority of waste in the synthesis of small molecules by the Roundtable's benchmarking exercise, which was useful because this is a relatively non-competitive market. The Roundtable had focused on encouraging solvent providers to develop new solvents by using renewable raw materials and creating solvents with better environmental profiles, as well as on assisting chemists in making better solvent choices from the standpoints of the environment, health, and safety [7].

With the implementation of Green Chemistry (GC) principles the cost of discovering New Chemical Entity (NCEs) is not greatly reduced.One of the most critical contribution to GC in the drug discovery process is to design the APIs. The downstream persistence of drugs and their active metabolites in the environment is one of the problem that is poorly addressed till today. The FDA, EMEA and Ministry of Labor, Welfare and Health (MLWH), Japan, require environmental studies which include the potential to harm fish and plant life as part of marketing application. To evaluate the potential for endocrine disruption, till date no good tests are available. As an additional parameter in the drug discovery process, information related to rapidly degradation of the designed NCEs after release to the environment should be included. This serves to be an important area of research at the Carnegie Mellon Institute for Green Science, PA, USA [8].

The Green Aspiration Level (GAL) which is defined as the expected environmental impact for producing any pharmaceutical agent by assessing the complexity of its ideal synthetic route is one of the first significant green efficiency goal for any given manufacturing process. Here the direct route with the minimum number of synthetic stages is designed using commodity chemicals at the beginning of the drug development programme [9].

AstraZeneca in their article have mentioned some of the key features which they have adopted in maintaining sustainability in the drug discovery process for saving our planet. They have mentioned the modified technique of incorporating light into the development process, for photocatalysed carboxylation reaction the use of carbon dioxide in addition with visible light, use of easily and readily available greener materials by our chemists to synthesize the APIs will definitely proved to reduce the environmental footprint of the industry and along with late stage molecule modification techniques the labs , production will be more efficient with the vision to save the resources for future generations [10].

The most crucial variables to take into account for greener techniques are solvents and stoichiometric reagent. Various traditional solvents such as halogenated petroleum-based ones can be substituted with glycerol, ethyl lactate, water which will be more environmentally friendly. Another important factor that lowers the quantity of inorganic salts and/or reagents is a catalyst. Pharmaceutical businesses have thought about using a catalyst as a green alternative to consuming stoichiometric salts and chemicals. However, the application of catalysts to be widely employed has been constrained by the desire for the least expensive reagents [11].

Solvents play an important role in chemical reactions, to dissolve solids, reduce viscosity, modulation of temperature and recover products by means of extraction, recrystallization and also for cleaning purposes. They may further influence the particle size of the API and impact manufacturing costs by leading to difficult isolations or requiring milling. These solvents despite their advantages are associated with several ill-effects on human health and environment. Solvents are mostly derived from non-renewable resources like petroleum which are in contradictions to the basics of Green Chemistry. The only alternative to substitute these environmentally harmful solvents is with some use of benign solvents. The following four directions for the development of green solvents were discussed by Hungerbuhler et al.

* Harmful solvents can be substituted with safer alternatives having superior EHS (Environment, Health, Safety) characteristics, as improved biodegradability or a lower propensity for ozone depletion.
* Use of renewable resources or “bio-solvents” such as ethanol produced by fermentation of feed materials which contains sugar, starch or lignocellulosic compounds.
* Supercritical CO2 can replace organic solvents in polymer production, avoiding the usage of chlorofluorocarbons and reducing ozone depletion.
* There are fewer emissions to the air when using ionic liquids, which exhibit low or negligible vapour pressure [12].

Four classes of solvents have been listed by the Center for Drug Evaluation and Research (CDER) under US FDA (USA Food and Drug Administration). Based on their unacceptable toxicity or deleterious environmental impact Class I solvents includes benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethylene and 1,1,1-trichloroethane. Acetonitrile, methanol, methylene chloride, tetrahydrofuran, toluene and hexane are included under Class II solvents. Class III solvents (eg: acetic acid, acetone, ethanol, ethyl acetate, heptane, dimethyl sulfoxide) have the lowest toxic potential. Class IV solvents (i.e. isooctane, isopropyl ether, petroleum ether, and 2-methyltetrahydrofuran) have insufficient toxicological data [13].

There is more than one way to address the complex issue of pharmaceutical industry pollution. Since scientists are trying to find solutions to stop the production of waste, the issue is extremely important everywhere in the globe. With a view to advancing the idea of green chemistry to safeguard human health and the environment while retaining commercial viability, the US has created the American Chemical Society. Dr. Verma emphasised the microwave energy as an alternative source and said it could be utilised for reactions that can create a library of chemicals, particularly in the context of an environment-free solvent strategy for the treatment of waste, alkane, breakdown, and targets for drug discovery. Reducing the use of solvents is the basic idea behind green chemistry [14].

Solvents have been recognized as being of environmental concern particularly in source and synthesis of the solvent itself, its properties in use which includes accidental discharge and their disposal. The choice of solvent can have a significant impact on the result of a reaction. This means that switching from a "non-green" solvent to a "green" solvent may have unintended consequences. These unintended consequences includes increased waste or the necessity for harsher operating conditions that use more energy. In certain circumstances, the process may end up being less environmentally friendly overall. It is essential to take into account all of a solvent change's effects on the entire process in order to fully comprehend how it can damage a process's potential to be sustainable. In light of this, it is foolish and possibly unimportant to think that a liquid can be considered to be fundamentally "green." Use of a single solvent or a solvent system, rather than a combination of both, is what matters [15].

Classical organic solvents are mainly employed by the industrial chemical processes based on careful solvent selection and considering the role of the solvent in the entire process. Neoteric solvents as they provide advantages over organic, or aqueous solvents by improving the product separation are slowly being integrated into various industrial processes. Neoteric solvents include ionic liquids (ILs), deep eutectic solvents (DES), liquid polymers, supercritical carbon dioxide (scCO2), gas expanded solvents (GXLs) and switchable solvents. Before the adoption of neoteric solvents by the chemical industry, its price, availability, purity, regulations, disposal procedures, recycling procedures and costs have to be taken in considerations [16].

**DEPLOYING GREEN CHEMISTRY IN API SYNTHESIS**

 Pharmaceuticals is only one of several businesses that have made it a priority to find ways to enhance the environmental profile of production methods and finished goods. These strategies can include measures to optimise reaction conditions while synthesizing active pharmaceutical components, intermediates, or lead compounds in order to reduce waste, increase reaction efficiency and yield, and reduce the need for solvents and reagents. Numerous submissions for the 2009 Presidential Green Chemistry Challenge Awards, given annually by the US Environmental Protection Agency, offer strategies for green chemistry with applicability to the pharmaceutical sector.

Professor Bruce H. Lipshutz of the University of California at Santa Barbara's Department of Chemistry and Biochemistry created a method to improve catalytic activity and reaction efficiency, hence reducing the need for the organic solvents needed in several chemical reactions . Lipshutz and his team discovered that a mono-PEGylated, alpha-tocopherylated derivative of sebacid acid (PTS) enables several typical organic reactions catalysed by transition metals, particularly palladium and ruthenium, to use water as the only solvent, be carried out at room temperature, and yield high isolated yields of product. PTS can be utilised for Suzuki, Heck, and Sonogashira cross-couplings, which are palladium-catalyzed olefin metathesis processes. PTS removes the use of organic solvents in these processes by allowing the catalysis under aqueous conditions.

Leonard R. MacGillivray, a chemistry professor at the University of Iowa, invented a method for controlling chemical reactivity in organic solids. Small-molecule templates are used to assemble olefins (which undergo intermolecular [2+2] photodimerization) in discrete assemblies for solid-state reactions. The template, rather than long-range crystal packing, governs the solid-state arrangements of the olefins. This method was used by MacGillivray for the solid-state synthesis of ladderanes, which are building blocks for natural products, and he reported regiospecificity, no by products, and a 100% yield. This method allows molecules to react in geometries and orientations that are normally unavailable in solution.

Ohio State University chemistry professor.V. Rajan Babu and his team discovered a new codimerization of ethylene and various functionalized vinylarenes, 1,3-dienes, and strained alkenes (i.e., asymmetric hydrovinylation). This chemistry has applications in the enantioselective synthesis of NSAIDs such as ibuprofen, naproxen, fluriprofen, and fenoprofen from corresponding styrenes and ethylene. Under mild reaction conditions, the group developed highly catalytic protocols for the codimerization of ethylene and various functionalized vinylarenes, 1,3-dienes, and strained alkenes to produce 3-arylbutenes. This type of chemistry can be used to create specific NSAIDs. His work can also be used to synthesise steroid derivatives. Several 1-vinylcycloalkenes and 1-substituted 1,3-butadienes can also undergo efficient heterodimerization with ethylene, with yields of up to 99%. (1). For select substrates, phospholanes and phosphoramidites can be used as ligands in an asymmetric variation of this reaction, with yields up to 99% and enantiomeric excess of 95%. Other stereocenters in the ring can be installed using an exocyclic chiral centre. His research has also included the synthesis of several new ligands to improve enantioselectivity, as well as the use of hemilabile ligands and their synergy with highly dissociated counterions to improve selectivity.

Paul Wender, a chemistry professor at Stanford University in Palo Alto, California, developed a method known as function-oriented synthesis (FOS), which involves step economy in the organic synthesis of biologically active compounds, including compounds derived from natural products. Although natural products are a good source of potential drug targets, developing cost-effective synthetic routes to these complex molecules can be difficult. FOS addresses this issue by attempting to refine or improve the biologically active lead structure through the use of simpler scaffolds that are more easily synthesised. Wender has used the FOS method on a number of natural product lead compounds. These compounds include: arenes, which modulate protein kinase C and mimic more complex phorbols; simplified enediyne compounds for cancer treatment; simplified bryostatin analogues, which are also used as potential anticancer agents; laulimalide analogues with simplified structures that remove the inherent functional instability of natural laulimalide; and the design, synthesis, and optimization of polyarginine drug transporters, which are used to improve potency and circumvent multidrug [17].

Hence, advances in micellar catalysis, solid-state chemistry, catalytic asymmetric synthesis, and function-oriented synthesis for natural products are notable developments in green chemistry that can be applied to the synthesis of active pharmaceutical ingredients. Advances in micellar catalysis, solid-state chemistry, catalytic asymmetric synthesis, and function-oriented synthesis for natural products are notable developments in green chemistry that can be applied to the synthesis of active pharmaceutical ingredients.

**REDUCTION OF COST THROUGH GREEN CHEMISTRY**

The most basic method for lowering drug costs is to reduce the cost of the most expensive component of drugs: the API. In its most basic form, the process of producing any API consists of converting simpler commercially available raw materials into APIs via a series of chemical conversions. As a result, the cost of this process is primarily determined by the price of raw materials and the efficiency of the chemical process used to convert those materials into API.These same factors—raw material selection, number of synthetic steps, and the efficiency of the API production process—determine the amount and type of waste produced during drug manufacturing. Prior to manufacturing the supplies for Phase III clinical trials, the manufacturing method for an API is typically established and clearly defined in advance. The initial components, synthetic procedures, catalysts (if necessary), solvents, reaction and isolation conditions, etc., are fixed. Thus, prior to process validation in the context of the regulatory file, the information concerning associated compounds present, residual solvent levels, and physicochemical features of the API is well defined within the specifications. These production methods are established long before peak efficiency can be attained through process research because of the time constraints involved in getting a medicine through the clinical trial and approval processes.

However, the drug's production company can frequently increase the efficiency with which the raw components are turned into the API by optimising its processes. The cost and environmental impact of producing API are greatly decreased with careful application of the improvement and regulatory approval. It may be possible in some circumstances to change the process more drastically by using entirely or largely new synthetic beginning materials or approaches [18].

Green chemistry is an innovative approach to chemical design and manufacturing that aims to minimize the negative impact of chemical processes on human health and the environment. It involves the application of twelve fundamental principles that guide chemists in the development of sustainable and environmentally friendly processes. This chapter provides an overview of the principles of green chemistry and their significance in promoting a more sustainable future.

**Atom Economy:**

The principle of atom economy encourages the maximum utilization of atoms in a chemical reaction. It promotes the design of synthetic routes that minimize waste generation by emphasizing the use of renewable feedstocks and efficient catalysts. By improving atom economy, chemists can reduce the amount of waste produced and enhance resource efficiency.

**Pollution Prevention:**

Pollution prevention focuses on avoiding the generation of hazardous substances altogether, rather than managing or treating them after they are produced. It advocates for the design of processes that minimize or eliminate the use of toxic chemicals, thereby reducing the potential for environmental contamination and human health risks.

**Safer Chemicals:**

This principle emphasizes the use of inherently safer chemicals, which are less toxic or non-toxic to humans and the environment. Green chemists strive to develop alternative compounds that possess desired properties while minimizing hazards associated with toxicity, persistence, and bioaccumulation. Safer chemicals contribute to the reduction of risks throughout a chemical product's life cycle.

**Design for Energy Efficiency:**

Energy efficiency is a crucial aspect of green chemistry. Chemists are encouraged to design chemical processes that minimize energy consumption, utilize renewable energy sources, and optimize reaction conditions to reduce energy requirements. By doing so, they can contribute to the conservation of energy resources and reduce greenhouse gas emissions.

**Use of Renewable Feedstocks:**

The use of renewable feedstocks, such as biomass and bio-based materials, is an essential principle of green chemistry. By replacing non-renewable resources derived from fossil fuels, chemists can reduce the dependence on petrochemicals and mitigate the associated environmental impacts. This principle promotes the development of sustainable and bio-based alternatives for various chemical processes.

**Reduce Derivatives:**

Minimizing the production of unnecessary derivatives during chemical synthesis is an important principle in green chemistry. By designing synthetic routes that require fewer steps and produce fewer by-products, chemists can reduce waste generation, increase efficiency, and conserve resources. This principle also facilitates the development of more sustainable manufacturing processes.

**Catalysis:**

Catalysis plays a significant role in green chemistry by enabling efficient chemical transformations. Green chemists strive to develop and utilize catalytic systems that are selective, efficient, and use non-toxic and readily available catalysts. Catalysts enhance reaction rates, reduce energy requirements, and minimize waste production, contributing to the overall sustainability of chemical processes.

**Design for Degradation:**

Chemical products should be designed to degrade into harmless substances after their intended use. This principle aims to minimize the persistence of chemicals in the environment and reduce their potential for bioaccumulation. Designing products that break down into non-toxic compounds or are readily biodegradable promotes environmental sustainability and minimizes long-term impacts.

**Real-time Analysis for Pollution Prevention:**

The principle of real-time analysis involves the development and implementation of in-process monitoring techniques to ensure the early detection and prevention of potential environmental and health hazards. By continuously monitoring chemical processes, chemists can identify deviations from the desired conditions and take corrective measures to prevent the formation of unwanted by-products or toxic substances.

**Safer Solvents and Auxiliaries:**

Green chemistry encourages the use of environmentally friendly solvents and auxiliary materials. Chemists strive to identify and employ solvents that are non-toxic, non-flammable, and have low environmental impact. This principle promotes the development of sustainable alternatives to traditional solvents, such as water or bio-based solvents, which reduce potential hazards during chemical processes.

**Design for Sustainability:**

Designing chemical products and processes with sustainability in mind is a core principle of green chemistry. It involves considering the entire life cycle of a product, from raw material extraction to disposal. Chemists aim to develop sustainable processes that minimize waste, conserve resources, reduce energy consumption, and have a minimal environmental impact.

**Education and Collaboration:**

The final principle of green chemistry emphasizes the importance of education, collaboration, and dissemination of green chemistry knowledge. It encourages chemists to share information, promote green chemistry principles, and collaborate across disciplines to develop innovative solutions for sustainable chemistry. Education and awareness play a crucial role in fostering a greener and more sustainable chemical industry [19,20,21,22].

**SYNTHETIC STRATEGIES USING GREEN SOLVENTS**

The development of green solvents has gained significant attention in recent years due to their potential to mitigate the environmental impact of chemical processes. Green solvents, also known as environmentally benign solvents or sustainable solvents, offer several advantages over traditional solvents, such as lower toxicity, reduced waste generation, and improved energy efficiency. Here are many synthetic strategies employed to design green solvents,

**Replacement of Conventional Solvents:**

One of the primary strategies for designing green solvents is the substitution of conventional solvents with more environmentally friendly alternatives. For example, volatile organic compounds (VOCs) with high toxicity and significant contribution to air pollution can be replaced with non-toxic and non-volatile solvents. The use of water as a green solvent is a prominent example of this strategy, as water is abundant, non-toxic, and possesses unique properties that make it suitable for a wide range of applications [23].

**Renewable and Bio-Based Solvents:**

Another approach to developing green solvents is the utilization of renewable and bio-based feedstocks. Renewable solvents are derived from biomass or other renewable sources, minimizing the reliance on fossil fuels. Various natural products, such as vegetable oils, terpenes, and sugars, can serve as precursors for bio-based solvents. These solvents exhibit low toxicity, are readily biodegradable, and contribute to a reduced carbon footprint [24].

**Design of Task-Specific Ionic Liquids (TSILs):**

Ionic liquids (ILs) are a class of solvents composed entirely of ions. Task-Specific Ionic Liquids (TSILs) are tailor-made ILs designed to possess specific properties suitable for targeted applications. By carefully selecting the cation and anion components, researchers can optimize the physical and chemical properties of TSILs, making them effective and sustainable solvents. TSILs have been successfully employed in various applications, including catalysis, separation processes, and as reaction media [25].

**Supercritical Fluids:**

Supercritical fluids (SCFs) are substances maintained above their critical temperature and pressure, where they exhibit both gas-like and liquid-like properties. SCFs, such as carbon dioxide (CO2) and water, are considered green solvents due to their low environmental impact and unique solvent properties. SCFs offer advantages such as high diffusivity, tunable density, and selective solvation capabilities. They are particularly useful for extraction processes and as reaction media in various synthetic applications [26].

**Solvent-Free or Solid-State Reactions:**

Eliminating the need for solvents altogether is an ideal approach to achieving greener chemistry. Solvent-free or solid-state reactions involve conducting chemical transformations without the presence of a liquid solvent. These reactions offer benefits such as improved reaction rates, reduced waste generation, and simplified purification processes. Solid-state techniques, such as ball milling and mechanochemistry, have emerged as efficient alternatives for conducting solvent-free reactions[27].

Various examples of green solvents can be seen for forming natural products, medicines, and important intermediate products which can be used for further synthesis.

**1. Vegetable oils as a green solvent**

Vegetable oils are oleochemicals derived from the seeds of numerous plants. They are renewable resources having a triglyceride structure in which three hydroxyl groups of glycerol are substituted with various fatty acids, resulting in liquids or solid solids [28]. Vegetable oils are an important food component. Vegetable oils have been used in biopolymers and may be considered by scientists looking for a new source of green solvent. We observed the acylation and cyclization reaction that occurred in vegetable oil, particularly in maize oil. Vegetable oil utilisation and benefits have been explored. The reaction yields, reaction times, and sustainability of vegetable oils have been compared to the hazardous solvent, xylene. Due to the cost and efficacy of vegetable oils, this reaction is the first example of vegetable oils, and this idea should be concerned by additional synthetic techniques [29]. For 15 minutes, a combination of dibenzoylmethane (1), oxalyl chloride (2), and phenol (3) was cooked in maize oil at 120°C. The authors explained that compound 1's CH2 was easily acylated.

**2. Glycerol as a green solvent**

Glycerol is a polyalcohol and the second component of oleochemicals generated from natural oils. Glycerol has been used in a variety of industries, including the pharmaceutical and food industries, tobacco, and cellulose films [30]. Glycerol is a good green solvent because of its sustainability and low cost. In this regard, pharmaceutical businesses and scientists have become more interested in glycerol as an alternative to other organic solvents that are dangerous, volatile, poisonous, and harmful. Despite the fact that glycerol is a solvent and is used in many reactions, chemists and medical scientists must overcome various challenges:(i)Because of glycerol's viscosity, it should be fluidified with a co-solvent. Glycerol, on the other hand, is much less viscous up to 60°C and reactions can be carried out at higher temperatures; (ii) glycerol may join the reaction as a reagent because it has three OH groups that can be mentioned as acidic sites; and (iii) glycerol has enough length and donor atom to form complexes with metal catalysts, resulting in unwanted side products and/or catalysis unreactivity. There are two sides to glycerol, which may be applied to any solvents and reagents utilised in research. However, Safaei et al. synthesised 4H-pyrans utilising glycerol as the green solvent in a catalyst-free, one-pot, three-component method [31]. The yield of reactions is high, up to 93%, and the reactions produced a wide range of pyran derivatives. Furthermore, the reaction was performed in water and discovered that the yield of the reactions had fallen to 70%. Cyclization processes under atom economic and green solvent procedures are quite vital, prompting medicine experts to reorganise their medication design strategy.

Gu et al. recently published a glycerol cyclization procedure in which pyran derivative was produced using a three-component method [32]. Styrene, dimedone and p-formaldehyde were used in the reactions. The yield of the product was determined by the solvent used, and the best solvent was glycerol, with a yield of 68%. Other solvents yielded less than glycerol. Furthermore, the sustainability of glycerol was examined, and after three cycles, the output was found to be 65%. The reaction between dimedone and p-formaldehyde produces an intermediate product, which cyclizes with the styrene to form the pyrane ring. Lu and his colleagues devised a procedure in which pyrazolone, styrene analogue and p-formaldehyde were reacted in glycerol to produce pyrazolo-pyrane derivative [33]. The reaction was carried out at 110°C, and the yield was calculated to be 78%. The same reaction in solvent-free and ionic liquids produced no result and had a 48% success rate, respectively.

**3. Water as a green solvent**

Water has several distinct physical and chemical features, including significant hydrogen bonding, a high heat capacity, a big dielectric constant, and a wide temperature range. Water has numerous advantages over traditional organic solvents as a solvent. Furthermore, because it is inexpensive, easily available, nontoxic, nonpolluting, and nonflammable, water can be chosen as a green solvent. People do not refer to water as a chemical. Despite its numerous advantages, water is not often used as a sole solvent for synthetic methods in research labs and industry since most organic molecules are not soluble in water. Nature chooses water for its biological interactions, and scientists have been attempting to duplicate the synthetic reactions that occur in water for over a century. Water has long been avoided by scientists due to an old chemist's idea that insoluble reagents create no product. Sharpless, on the other hand, has replaced this old belief with the new belief that because reactions can be carried out "on" or "in" water, solubility is not critical for processes. Because the reactants were insoluble in water, Sharpless characterised processes such cycloaddition, Diels-Alder, nucleophilic opening of epoxide, and Claisen rearrangement as on-water [34]. Organic chemistry basic reactions are utilised to make drugs in medicinal chemistry.Wittig reaction is one of these reactions. The Wittig reaction is critical because it creates a new C-C bond. Morsch et al. have thus published a green protocol for the Wittig reaction, which is carried out in water at 25°C [35]. Sobral reported a green technique in which pyrrole and diethyl ketone were reacted in water to produce 2,2′-dipyrromethane. Sobral reported that the reaction yielded 80% and that it was proceeded as gram scaled [36].

Xu et al. reported the synthesis of isocoumarin in H2O. They discussed how the reaction of salicylic acid and alkyne with ruthenium catalyst produced isocoumarin with an 85% yield [37]. Pizzo and colleagues disclosed a reaction between aza compound and vinyl ether that produced pyridazine derivatives as the sole product and pyrrole derivative as a by-product (2%). Because of the limited solubility of aza compound and vinyl ether, the authors described the reaction as an on-water reaction[38]. Patel and colleagues published the synthesis of benzothiazole ring on water [39]. The reaction began with iodo-benzo-isothiocyanate and morpholine, yielding thiourea derivative that was not separated. Thiourea derivative was cyclized on water with a CuO-nanocatalyst and K2CO3 with a 92% yield.

 **SYNTHETIC STRATEGIES USING CATALYSTS**

**1.Nanocatalysts as a green solution**

Catalyst is one of the green chemistry rules that chemists and medical scientists should consider [40]. Catalysts are classified into two types: heterogeneous and homogeneous. Homogeneous catalysts outperform heterogeneous catalysts in terms of product yield. However, due of metal contamination of products, the separation and reusability of homogeneous catalysts are the more severe disadvantages when utilised for fine chemicals synthesis in the chemical and pharmaceutical industries. Less effective but more appealing heterogeneous catalysts are preferred since they are reusable and easy to isolate from the media.

Aside from heterogeneous catalysts, nanocatalysts have received increased attention as semi-heterogeneous catalysts due to their high surface-volume ratio, which results in more interactions between the surface of the catalyst and the reactant. Even if the catalyst is purified using particular filtration procedures, there is still contamination.

Magnetism has recently been used to obtain and extract magnetic nanocatalysts from medium with an external magnetic field [41-45]. They have provided more promising solutions for the chemical industries, and they appear to be good candidates for the active pharmaceutical ingredient (API) business [46].

Sharma et al. developed a nanocatalyzed cyclization reaction[47]. They created oxazole compounds by reacting benzyl amine and methyl acetoacetate. SEM, XRD, and FESEM were used to characterise the nanomagnetic catalyst. They highlighted how the absence of the nanocatalyst reduced the yield of oxazole derivatives to 5%.Under reaction conditions with nanocatalyst, the conversion of the process was 100%, indicating that no waste product was created. Gerbino and colleagues used a copper-based magnetically recoverable nanocatalyst to enable one-step synthesis of xanthones [48]. Under ligand-free conditions, salicylaldehyde and phenol derivatives were reacted in toluene. When utilised in the fourth cycle, reusable copper nanocatalyst was found to be 89% effective. When the copper nanocatalyst was replaced with a conventional catalyst, CuCl or CuO, the product yield was reduced to 65 and 62%, respectively.

**2. Biocatalysts as a green solution**

The term "biocatalyst" refers to a biological material that can be an isolated enzyme, a crude cell-free extract, an immobilised enzyme, or enzymes in entire microbial cells. Enzymes are crucial endogens that play an important function in living cells by catalysing all in vivo metabolic events to produce a required product for the organism. Enzymes have been used in the laboratory for over a century to simulate the activity of enzymes in biological reactions.

Scientists have employed enzymes such as oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases for a variety of reasons. These enzymes are used in a variety of industries, including food, pharmacology, medicine, and textiles. Enzymes have special features that manmade organic compounds cannot always replicate. Enzymes have excellent stereoselectivity, resulting in just one isomer, and can thus reduce medicine costs because chirality has a large effect on medicine costs when the candidate medicine includes more than one chiral centre. This chemical potential compels chemists and medical scientists to create biocatalysts for use in reaction flasks [49,50].

Savile and colleagues described an efficient biocatalytic technique for replacing a recently adopted Rh-catalyzed asymmetric enamine hydrogenation for the anti-diabetic drug sitagliptin. Current sitagliptin synthesis comprises enamine production followed by asymmetric hydrogenation at high pressure utilising a Rh-based chiral catalyst, in which sitagliptin was synthesised in 97% ee with a trace amount of Rh . Savile's synthetic approach demonstrated a green reaction, which is the direct amination of prositagliptin ketone to yield enantiopure sitagliptin (99.95% ee), followed by phosphate salt production to yield sitagliptin phosphate 90 [51].

**Case study: Green Chemistry in the synthesis of Lipitor**

Lipitor, the first medication in the world with yearly sales over $10 billion, contains the active component atorvastatin calcium. It is a medication that lowers cholesterol by preventing the liver's ability to synthesize cholesterol. This medication is an illustration of a competitive 3,5-dihydroxyheptanoic acid-7-substituted HMG-CoA reductase inhibitor. Ethyl (R)-4-cyano-3-hydroxybutyrate is the main chiral building block in all commercialized synthesis of atorvastatin. The initial steps in each of these procedures require the high-temperature reaction of an ethyl 3-hydroxy-4-halobutyrate with a cyanide ion in an alkaline solution. These procedures finally replace cyanide for halide in hot, alkaline conditions, creating a large amount of by-products and necessitating a difficult high-vacuum fractional distillation to purify the end product, further reducing yield. In order to overcome these problems for a workable and affordable procedure, S. K. Ma et al created a green, two-step, three-enzyme process for the synthesis in the production of atorvastatin in 2010. A ketoreductase (KRED) in conjunction with glucose and a NADP-dependent glucose dehydrogenase (GDH) for cofactor regeneration are used in the first phase to biocatalytically reduce ethyl-4-chloroacetoacetate. The isolated yield of the (S) ethyl-4-chloro-3-hydroxybutyrate product are 96% and >99.5%*ee*, respectively. By reacting with HCN at neutral pH and room temperature, a halohydrin dehalogenase (HHDH) is used to catalyse the replacement of the chloro substituent with cyano in the second phase. This made it possible to produce the essential hydroxynitrile intermediate in an economical and environmentally friendly manner. The overall process has an E factor (kg waste per kg product) of 5.8 when process water is not included [52].

**Case Study: The Green Synthesis of Artemisinin**

Artemisinin is a highly effective antimalarial drug derived from the Chinese herb Artemisia annua. Traditionally, artemisinin was extracted from the plant using organic solvents, which resulted in low yields and a negative environmental impact. In the early 2000s, researchers at the University of California, Berkeley, led by Professor Jay Keasling, embarked on a project to develop a greener and more sustainable synthesis route for artemisinin. The team employed synthetic biology techniques to engineer a strain of yeast, Saccharomyces cerevisiae, to produce artemisinic acid, a precursor of artemisinin. This approach eliminated the need for plant cultivation and reduced reliance on natural resources. The genetically modified yeast was designed to convert inexpensive and widely available sugars into artemisinic acid, providing a scalable and sustainable source of the precursor.

To optimize the process further, the researchers collaborated with pharmaceutical company Sanofi. Sanofi developed a green chemical conversion method, replacing the use of hazardous solvents with a greener solvent, which significantly reduced the environmental impact. This joint effort resulted in the successful production of semisynthetic artemisinin on a large scale, ensuring a stable supply of the life-saving drug [53].

**Case Study: Green Chemistry in the Synthesis of Ibuprofen**

Ibuprofen is a widely used nonsteroidal anti-inflammatory drug (NSAID) that offers pain relief and anti-inflammatory effects. The traditional synthesis of ibuprofen involves multiple steps, which often require the use of toxic solvents and reagents, leading to significant environmental concerns. However, a notable case study demonstrates the successful implementation of green chemistry principles in the synthesis of ibuprofen. Researchers from the University of York in the United Kingdom developed a greener synthesis route for ibuprofen using catalytic processes. They employed a catalyst composed of a readily available, non-toxic material called 2-methyl-1,3-propanediol (MPD) in the conversion of a precursor molecule into ibuprofen. This green catalytic process eliminated the need for hazardous solvents and reduced waste generation, leading to a more sustainable manufacturing method for the drug [54,55,56,57].

**Case Study: Green Chemistry in the Synthesis of Valsartan:**

Angiotensin II (AT-II) receptor antagonists, of which valsartan is a part, are a class of drugs. This class combines a high safety and tolerability profile with potent anti-hypertensive action. The tissues contract when AT-II receptors in the outer membrane of heart and artery vascular smooth muscle cells are activated. Despite variations in one's level of hydration, sodium intake, and other physiological factors, AT-II aids in the maintenance of constant blood pressure. It also carries out the regulatory functions of inhibiting sodium excretion by the kidneys, inhibiting norephedrine re-uptake, and promoting aldosterone biosynthesis. Valsartan is used to treat cardiovascular issues and heart failure because it reduces the rise in blood pressure brought on by hormone receptor interactions by inhibiting the effects of AT-II on its receptors. The multistep synthesis of Valsartan/hydrochlorothiazide was first described in 1994. Most of the reported works share the biphenyl unit as a structural component, and the production of this unit is a crucial step in the synthesis.  Suzuki-Miyaura couplings are used in the documented preparation techniques for valsartan. The common flaw in the main synthetic routes to valsartan shown in is the use of expensive boronic acid substrates in the cross-coupling step. In 2007, Goossen and coworkers published a four step valsartan synthesis employing decarboxylative coupling, and Beutler and coworkers revised the three chemical steps of the original synthesis to increase throughput and do away with the usage of halogenated solvents. In 2010, Gosh and colleagues described a quick and easy way to make valsartan using Negishi coupling of oxazoline moieties rather than the more expensive organoboronic acid coupling. Pandarus et al. (2013) reported the heterogeneous Suzuki-Miyaura coupling reaction between 2-chlorobenzonitrile and 4-tolylboronic acid under batch conditions to produce 4-methyl-2-biphenylcarbonitrile over the functionalized organosilica matrix[52].

**Future Prospects**

The pharmaceutical industry, like many other sectors, has been increasingly recognizing the importance of sustainability and environmental responsibility. As concerns about climate change and resource depletion continue to grow, there is a growing demand for eco-friendly practices in all industries, including pharmaceuticals. The implementation of green technology and green chemistry in the pharmaceutical sector can offer several potential benefits and opportunities:

* Reduced environmental impact: The adoption of green technology and green chemistry can lead to a reduction in harmful emissions, waste generation, and the consumption of non-renewable resources. This can significantly lower the industry's carbon footprint and contribute to global efforts to combat climate change.
* Cost savings: Many green technologies and practices are designed to be more efficient and less resource-intensive. By adopting these approaches, pharmaceutical companies can potentially reduce operational costs, improve energy efficiency, and optimize resource utilization.
* Enhanced reputation and market appeal: As consumers and investors become more environmentally conscious, companies that prioritize sustainability are likely to gain a competitive advantage. Emphasizing green initiatives can improve a pharmaceutical company's reputation and attract environmentally-conscious customers and investors.
* Regulatory incentives: Governments and regulatory bodies worldwide are increasingly promoting sustainable practices. By incorporating green technology and green chemistry into their operations, pharmaceutical companies may be eligible for incentives, tax benefits, or preferential treatment when seeking approvals for new products.
* Innovation and research opportunities: Embracing green technology and green chemistry requires continuous research and development of new sustainable methods and materials. This opens up opportunities for collaboration and innovation within the pharmaceutical industry and with other sectors that focus on sustainability.
* Access to new markets: Some countries and regions have stricter environmental regulations, making it challenging for conventional pharmaceutical products to enter those markets. By adopting green practices, companies can gain access to new markets and expand their global reach.
* Risk management: Implementing sustainable practices can help pharmaceutical companies mitigate potential risks associated with climate change, resource scarcity, and changing regulatory landscapes

In summary, the implementation of green technology and green chemistry in the pharmaceutical industry presents an innovative approach for sustainability. By embracing eco-friendly practices, pharmaceutical companies can not only contribute to a healthier environment but also position themselves for long-term success by attracting environmentally-conscious customers, investors, and partners. As technology and awareness continue to advance, the future prospects for sustainable practices in the pharmaceutical industry appear promising.

**Conclusion**

In conclusion, the implementation of green technology and green chemistry in the pharmaceutical industry represents a transformative and imperative approach towards sustainability. This newer approach not only addresses the pressing environmental challenges facing our planet but also lays the foundation for a more resilient and responsible pharmaceutical sector.

Throughout this chapter, we have delved into the multifaceted benefits that arise from embracing eco-friendly practices in pharmaceutical manufacturing, research, and development. By adopting green technologies, pharmaceutical companies can significantly reduce their ecological footprint, minimize waste generation, and optimize resource utilization. These endeavours not only align with the global call for environmental stewardship but also position these companies as leaders in the pursuit of a greener future.

Furthermore, we have explored the potential cost savings and long-term economic advantages associated with sustainable practices. By employing more efficient and resource-conserving methods, pharmaceutical companies can not only improve their bottom line but also foster a culture of innovation, spurring the development of new and cutting-edge green technologies.

The shift towards sustainability is not only driven by ethical considerations but also by the demand from consumers, investors, and regulatory bodies. Companies that prioritize environmental responsibility and invest in green chemistry will undoubtedly gain a competitive advantage, attracting a growing cohort of eco-conscious customers and investors who seek to support businesses aligned with their values.

While the journey towards a fully sustainable pharmaceutical industry may present challenges, the potential rewards are both tangible and intangible. Governments and regulatory bodies worldwide are increasingly recognizing the significance of green initiatives, offering incentives and favourable treatment for companies that incorporate sustainable practices into their operations.

As the pharmaceutical industry embarks on this transformative path, collaboration, research, and continuous innovation will be essential. By fostering cross-industry partnerships and sharing knowledge, the sector can overcome obstacles and create a more sustainable and interconnected ecosystem.

In closing, the implementation of green technology and green chemistry in the pharmaceutical industry is not just a means to an end; it is a pivotal step towards safeguarding the health of our planet and its inhabitants. Through our collective commitment to sustainability, we can usher in a new era of pharmaceutical excellence—one that balances medical progress with environmental responsibility, securing a brighter and healthier future for generations to come.

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