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GREEN CHEMISTRY AND IT'S APPLICATION IN BIOTECHNOLOGICAL INDUSTRY

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ABSTRACT

Industrialization has significantly impacted the global economy, leading to social movements that have transformed green chemistry since the 1940s. This has led to changes in industrial positions and sustainable processes, improving environmental impact and public awareness. The function of a chemical product is where sustainable chemistry begins, focusing on economic and ethical considerations. Green chemistry serves as a crucial building block for sustainable chemistry, addressing greener synthesis and the more benign qualities of chemicals. Sustainable chemistry aims to develop chemical products and procedures that reduce or eliminate hazardous compound usage and manufacturing. In order to decrease or eliminate the use or manufacture of hazardous compounds in all stages of a specific synthesis or process, green chemistry employs a set of principles that were developed in response to scientific findings concerning pollution awareness. By adhering to all the beneficial principles of green chemistry, chemists and pharmaceutical scientists may drastically lower the danger to human health and the environment. It is obvious that the principles of green chemistry are to increase the environmental friendliness of chemical processes and reactions. Considerations include things like energy efficiency, atom efficiency, safe reactants, renewable resources, and pollution control. This article discusses the potential benefits of green chemistry for industrial biotechnology, highlighting the need for a close relationship between green chemistry and biotechnology, despite advancements in "greener" chemistry, and emphasizes the need for updated biotechnological processes.

KEYWORDS: Green Chemistry, Environment, Industrial Biotechnology, Sustainable Chemistry, green solvent, nanoparticles, catalysts.

INTRODUCTION

Biotechnology is a promising frontier technology for the future, enabling safer and more ethical production of pharmaceuticals and medical services in the healthcare industry. Stem cell research offers potential for replacing tissues and organs in degenerative disorders like Alzheimer's and Parkinson's. Biotechnology also enhances the utilization of industrial raw materials in energy transformation and pharmaceutical industries, transforming carbs, oils, lipids, proteins, and fibers. Biomass can provide alternative energy sources like biodiesel and bioethanol. From an environmental perspective, biotechnology offers new ways to protect and enhance the environment, including air, soil, water, and waste.[2] Biotechnology is a multidisciplinary field that focuses on using cells, microorganisms, and other organisms to create new products through novel processes. Biotechnological processes, such as fermenting sugar into alcohol, have been used for millennia. Advancements in genomic sciences, genetic engineering, and metabolic engineering have led to the main biotechnology breakthrough. Genetic engineering allows for the genetic modification of microbes to target specific metabolic characteristics, resulting in more selective chemical processes. This approach enhances the selectivity of chemical processes, offering benefits over traditional methods. Genetic engineering also provides new ways to produce desired products, sometimes at lower manufacturing costs and using safer, more environmentally friendlyingredients. This field has been used for millennia, but genomic sciences have significantly influenced the chemical industry.[3]

The way people lived was altered by chemistry during the 20th century. And the pharmaceutical sectors, with the creation of organic drug compounds, were thought to have the most advantages. Major chemicals, reagents, solvents, catalysts, and nearly every sort of organic reaction are included in pharmaceutical chemistry, which is used to create active pharmaceutical compounds. Many of the chemicals used in this are extremely dangerous, poisonous, and may have negative impacts on both the environment and human health. Pharmaceutical and fine chemical industries use far more complicated chemistry and generate proportionately much more waste, which is completely unsuitable for the environment and nature.[8]

The chemical industry's history has evolved significantly, starting in the 1800s with a narrow application due to manufacturers' limited capacities. Today, it produces a wide range of materials and is a crucial component of contemporary civilization, despite its limited scope. The chemical industry's rapid growth has led to a focus on optimizing existing processes rather than developingnew ones. However, environmental concerns were not addressed during the industry's early years.Over the past two decades, the industry has been a major contributor to environmental issues due to the massive waste generated by traditional manufacturing processes. The sector is shifting towards greener chemistry by addressing key factors like excessive waste, low efficiency, toxic reagents, and hazardous solvents, aiming to create eco-friendly procedures.[4]

Early in the 1990s, the US Environmental Protection Agency (EPA) created the term "Green Chemistry" to encourage cutting-edge chemical technologies that lessen or do away with the use or production of hazardous compounds in the development, production, and use of chemical goods.[8] Green chemistry is often referred to as clean chemistry, benign chemistry, or sustainable chemistry. The pharmaceutical business and other sectors are growing quickly, which aids in the quick expansion and progress of the medical and healthcare industries. As a result, there are fewer fatalities and sufferings.[7] By-products and pollutants from the production of chemicals, such as polluted solvents, depleted reagents, and air pollutants, have the potential to be produced in large quantities. These parameters can be significantly influenced by the pharmaceutical industry. The pharmaceutical industry faces a challenge and opportunity for improvement due to increased waste per kilogram product due to stricter medical and regulatory requirements for pharmaceutical purity compared to less sophisticated compounds.[9] In order to safeguard their environment, individuals are becoming more conscious of the issue and attempting to adopt "green chemistry." Green chemistry, refers to developing chemical products and procedures that reduce or halt the usage and manufacturing of dangerous compounds. It comprises decreasing or eliminating the use of hazardous materials in chemical processes as well as damaging and toxic intermediates and products. This new field of chemistry incorporates ecological techniques.[7] These "green chemistry" ideas have completely changed how new projects and research are planned, and they have had an influence on all of chemistry's subfields. Alongside this shift in perspective, there have also been substantial advancements in biotechnology, which in certain cases can offer useful alternatives or tools for putting some of the 12 principles of green chemistry into practice[3] . The 12 principles of green chemistry are predicated on the reduction or elimination of hazardous solvents from chemical analyses and processes, as well as the avoidance of residue production. The usage of renewable and safe raw resources, as well as the atomic and energy economies, play important roles in this. Furthermore, catalysis can aid in the acceleration of chemical processes. For instance, in reduced trash production and energy savings. One of the guiding principles also addresses the deliberate creation of chemicals, ensuring that, upon reaching the end of their useful lives, they disintegrate and turn into environmentally safe degradation products while also preventing bioaccumulation. As a result, it can be seen that these principles are focused on the planning of the product, from its synthesis and processing to its analysis and final destination. The primary goal is to reduce the dangers that industrial operations pose to the environment and to workers[1] . Making procedures other than those that require stoichiometric reagents, which are mostly to blame for the significant quantity of waste, is a key component of green chemistry. Thus, the use of catalytic processes not only offers a solution to the waste problem but also generates processes that are more energy and raw material efficient and, as a result, more environmentally friendly. Here, it is thought that using biocatalysts is a potential option.[4]

Biocatalysts have been used for centuries. Enzymes have been utilized in industrial production processes since the 1930s, when they were first used consciously. The growth of biotechnological methods is due to ongoing advancements in the synthesis of enzymes as well as their use in transformation procedures. There is a steady rise in biocatalytic processes used in industrial applications today, from bulk chemicals to specialty chemicals. The rising need for chirality and functionality, notably in the pharmaceutical business, technological advancements in bio(techno)logy, and the need for sustainability are the primary reasons behind the adoption of biotechnology on an industrial scale.[4]

In this sense, biotechnology is a science that may be used as a tool to enhance procedures in almost countless applications. The conversion of conventional chemical processes into "green" processes, where the fusion of biotechnology and green chemistry results in so-called "white biotechnology," may be the crucial science. This field, which includes the application of biotechnological methods in the industrial manufacture of fine chemicals, biofuels, and agricultural goods, among many others, has quickly developed in recent decades. White biotechnology's major goal is the creation of "clean" processes that reduce greenhouse gas emissions, energy and water use, and industrial waste production. The upstream and downstream processes, from early cell cultivation and raw material supply to the final challenge of obtaining the target material with the desired characteristics after separation and purification procedures, still present significant challenges when combining these two principles (biotechnology and green chemistry). Since these processes may be extremely energy, chemical, and water-intensive, they should all be carefully considered. Both procedures need to be taken into account since they have the potential to render a biotechnological process non-green and unsustainable, regardless of the employment of genetically modified strains.[3]

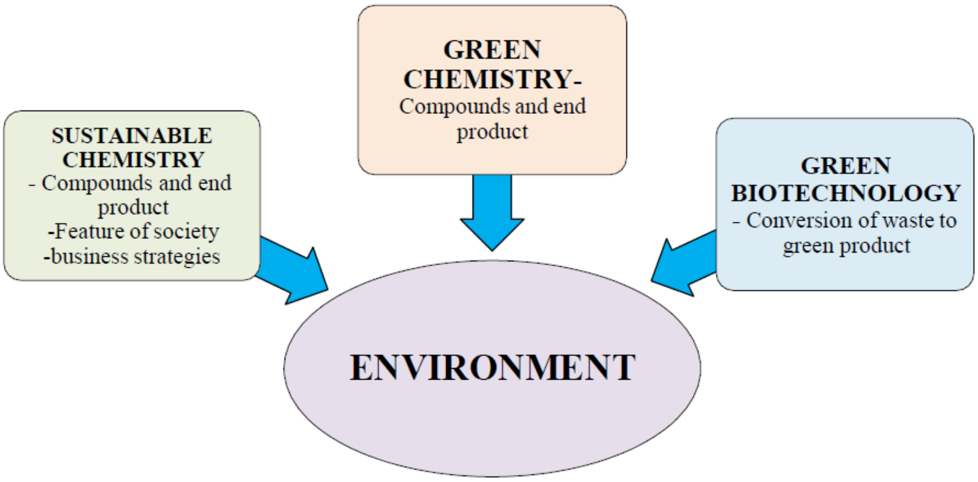

Fig. 1: Green chemistry, green biotechnology, sustainable chemistry and their relation to environment.

PRINCIPLES OF GREEN CHEMISTRY

The area of chemistry known as "green chemistry" focuses on creating chemical compounds without endangering the environment.[7] Due to its application of cutting-edge scientific answers to actual environmental problems, green chemistry is a very successful method of preventing pollution.[8] Paul Anastas and John Warner formulated the 12 principles of green chemistry.[7] The principles include guidelines for applying novel chemical compounds, as well as new synthesis and technical techniques, for professional chemists.[10] The elimination and reduction of toxic, hazardous, or dangerous compounds that are produced during synthesis and manufacturing are explained by the concepts of green chemistry.[7]

1. Prevention

The first green chemistry principle is founded on the idea of prevention, which is further supported by the idea that[7] - It is preferable to avoid waste than to treat or clean it up after it has been produced.[12] Synthesis should be conducted using minimal waste production, as unreacted starting substances or reagents are often preventable waste products. In universities and colleges,conducting research on a smaller scale can lower the cost of disposing of waste from chemical laboratories.[11] The pharmaceutical industry cannot completely eliminate waste product generation, so the only solution is to reduce solvent usage or replace one with another. For example, in the "green synthesis" process of sertraline, methanol is used as the sole solvent, reducing the number of solvents used. Environmental Factor (E) can describe a waste measurement. Roger Sheldon outlined the "E factor." It is the weight ratio between the waste produced during synthesis and the weight of the product that results.[7]

2. Atom economy

The goal of synthetic techniques should be to incorporate as many materials as possible into thefinal product.[5]

The efficiency of a chemical reaction is measured by the "atom economy," which is computedas the ratio of the total mass of atoms in the intended product to the total mass of atoms in the reactants.[11]

$$\% \text{ Atom Economy} = \frac{\text{Mol. weight of the intended product}}{\text{Mol. Weight of all reactants}} \times 100$$

In 1991, Berry Trost of Stanford University created the atom economy. The intermediates that areproduced throughout the reaction but are useless increase waste and reduce atom economy. Atomic economy is thought to be more effective than reaction yield as a percentage.[7] A particularly goodexample is the synthesis of ibuprofen by the BHC firm, which generates less waste and byproducts. The three-step catalytic green synthesis (BHC) is more economical than the six-step brown synthesis (BOOTS) by 77% and 40%, respectively. The percentage of atom economy increases to 99% from 77% when taking into account the recovered acetic acid produced in step 1 of green synthesis.[12]

3. Less Hazardous Chemical Syntheses

This principle emphasizes selecting chemicals that are the least dangerous and produce only beneficial byproducts.[11] When possible, synthetic ways should be created to utilize and produce materials that are safe for the environment and human health.[5] The majority of the many-staged chemical synthesis operations, which employ toxic chemicals, are carried out. Green chemistry's duty is to rethink these processes since there is a possibility of contamination even when the resultdoes not include these harmful compounds.[7] The core of green chemistry is redesigning current transformations to include less dangerous substances.[11]

4. Designing Safer Chemicals

Chemical products should be made with the least amount of toxicity possible while yet performing the necessary function.[10] Designing a chemical requires knowledge about its structure. One of thebiggest challenges in creating a safe chemical is keeping a chemical's basic efficacy and usefulness while reducing its toxicity. In other words, wherever possible, it is advisable to refrain from employing potentially toxic or dangerous substances while still making sure that their efficacy is maintained.[7] Pharmaceutical goods often contain chiral compounds, which can be life-saving. One of the two enantiomers can cure errors, while the other isomer causes more serious flaws. To create safer products, it's crucial to separate the two chiral forms using catalysts capable of catalyzing significant reactions resulting in only one of the two mirror image forms. Chemical characteristics of a molecule, such as its polarity, solubility in water, etc. so that they can alter it to produce the desired results.[11] In order to maintain the potential of new compounds by reducingthe usage of harmful solvents or substances, this principle is employed in the development of newchemicals.[7]

5. Safer Solvents and Auxiliaries

Auxiliary compounds should be used sparingly and rendered harmless when necessary (e.g., solvents, separation agents, etc.).[8] To carry out the continuing reaction, the majority of chemicalreactions utilize solvent or another reagent. These used solvents or auxiliaries might be poisonousor pose a risk to human health. The use of solvents during reactions is essential and cannot be avoided, but they should be selected in a way that reduces the amount of heat required overall for the synthesis process and has the least amount of toxicity possible.[7] Alcohol, benzene (known to be carcinogenic), CCl_4, $CHCl_3$, perchloroethylene, and CH_2Cl_2 are hazardous and volatile solventsthat are frequently utilized in syntheses. Solvent and other byproducts (such as chromatography supports) are also used and produced in huge quantities throughout the purification process. Now, safer green solvents like ionic liquids have taken their place.[11]

6. Design for Energy Efficiency

Chemical processes' energy needs should be understood in terms of their effects on the environment and the economy, and they should be kept to a minimum. Synthetic procedures are to be carried out at room temperature and pressure whenever possible.[12]

i. Microwave irradiation: Microwave-based reactions have been carried out on solid supports like clay, silica gel, etc. with no solvents used or very little solvent. The reactions proceed more quickly than thermal heating does. One process that produced quantifiable quantities of the products without the need for acid catalysts was the Beckmann rearrangement of oximes in the solid state using microwave irradiation.[11]

ii. Sonochemistry (Ultrasound energy): With outstanding yields, reactions utilizing ultrasonic energy are carried out at RT. For instance, using ultrasonic energy increases yields from Ullmann'scoupling, which occurs at higher temperatures and provides poor yields when done conventionally.[11]

7. Use of Renewable Feedstocks: When technically and practically possible, a raw material or feedstock should be renewable rather than diminishing.[10] For green synthesis, the feedstock should substitute for conventional petroleum sources, for example, the commercial synthesis of adipic acid now uses glucose instead of benzene to some extent, and the reaction is carried out inwater.[11]

8. Reduce derivatives: The use of blocking groups, protection/deprotection, and temporary alteration of physical/chemical processes are examples of unnecessary derivatization that should be reduced or avoided wherever feasible since they need extra reagents and can produce waste.[8] Making the required product without the usage of chemical derivatives is one of the key aspects of green chemistry. Derivative usage should be avoided as much as possible because it generates trash.[7]

9. Catalysis: The best stoichiometric reagents are those that are catalytic (or as selective as feasible).[10] This idea encourages the use of biodegradable catalysts since they use less energy and are better for the environment. Using a catalyst, a reaction with great atom economy can be generated. Since the catalyst doesn't deplete throughout the reaction and doesn't generate waste, itmay be utilized repeatedly.[7]

10. Design for Degradation: Chemical goods should be made to disintegrate into harmless, hazard-free chemicals after serving their purpose rather than building up and remaining in the environment. Functional groups that promote a molecule's biodegradation can now be added to it. To guarantee that the products will be biodegradable, functional groups that are amenable to hydrolysis, photolysis, or other cleavage have been used.[11]

11. Real-time analysis for pollution prevention: Further development of analytical techniques is required to enable real-time process monitoring and control before hazardous chemicalsemerge.[8] When a chemical reaction is taking place, it should be observed. This can avoid the production of hazardous byproducts and the possibility of lethal reactions since the reaction can be halted quickly while being observed.[7]

12. Inherently Safer Chemistry for Accident Prevention: When using substances in a chemicalprocess, care should be taken to choose them in a way that reduces the possibility of releases, explosions, and fires.[8] Pollutants into the environment, such benzene, which causes cancer Another significant addition to green chemistry is nanoscience and nanotechnology. Because nanotechnology is used to create tiny and submicroscopic mechanical and electrical devices, significant material savings are possible. It has been shown that attempting to recycle process solvents for financial gain raises the risk of a chemical mishap or fire.[11]

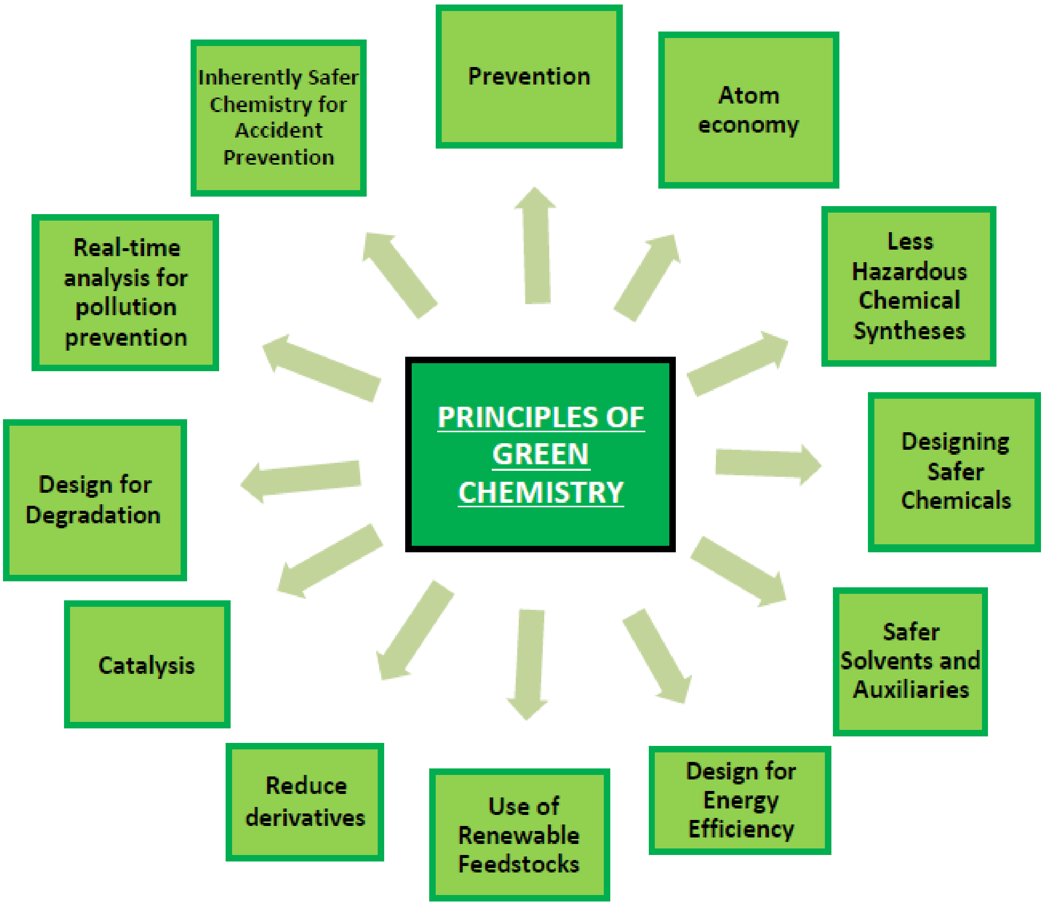

Fig. 2: Twelve principles of Green Chemistry.

GREEN CHEMISTRY IN INDUSTRY

Green solvents:

Solvents affect safety and health concerns as well as defining a significant amount of a process's environmental performance. In the industry, logistical, safety, and financial factors are taken into account while choosing solvents for chemical operations and managing the waste solvent.[8]

Conventional solvents are hazardous and detrimental to the environment, even yet they are often utilized in synthesis procedures where flammable organic solvents are required. Thus, in a numberof industries, the use of conventional solvents is currently being replaced with green solvents.[7]

The pharmaceutical industry has worked hard to find organic solvents that are lessharmful to the environment than conventional reactions.[8] Excellent types of solvents are available. Achieving success in a reaction technique may depend on selecting the appropriate solvent for the particular reaction. When choosing a solvent for a reaction, the following characteristics should be taken into account.

- Chemical compatibility between products and reagents.
- Handling reagent problems.
- The procedure's temperature.[7]

There is a lot more potential for green solvents such ethyl lactate, water, liquid polymers, ionicliquids, bio-ethanol, and supercritical fluids.[8]

Water as solvent: There is growing interest in using water as a solvent due to the ongoing need for synthesis processes to take a more sustainable approach. One of the finest methods for green chemistry to reduce the amount of dangerous chemicals released into the environment is to utilize water as a solvent during chemical synthesis. Reactions involving water as a solvent are frequently carried out under benign experimental circumstances, allowing the catalysts to be reused and lowering the overall cost of the product.[7] Since the dawn of nanoscience and nanotechnology, water has been utilized in the creation of several nanoparticles, making it the most economical andreadily accessible solvent.[13]

This review discusses a method for synthesizing chromeno-isoxazole/isoxazolines under onwater conditions. The process involves hydrolysis of hydrophobic glycidyl ethers in pressured water, using air as the terminal oxidant, sodium nitrite as the catalyst, and molecular iodine as the iodine source. The 1,3-Dipolar cyclo-additions of hydrophobic nitrones were investigated in aqueous suspensions and homogeneous organic solutions, showing faster reactions in water suspensions. The rearrangement of benzil is a base-catalyzed process using water between 300 and 380°C (near critical water). Synthesis of benzothiazoles and benzothiazolines can be done easily and cleanly using water, with aromatic, heteroaromatic, and styryl aldehydes transformed into 2-substituted benzothiazoles in high yields.[8]

Glycerol: Glycerol is a transparent, colorless, odorless, viscous liquid with a pleasant taste. As atrihydric alcohol, it has a dielectric constant of 42.5, making it a polar protic solvent. It is insolublein hydrocarbons but soluble in water and short-chain alcohols. It is weakly soluble in organic solvents like dichloromethane, ethyl acetate, and diethyl ether. Glycerol crystallizes at low temperatures and has a molecular weight of 92.09 and a specific density of 1.26.[14] Bioethanol and biodiesel production is an example of green technology. "Glycerol" is one of the several byproducts that are produced and discarded during the biodiesel synthesis process. There is lots of potential use for this glycerol in the food, explosive, and pharmaceutical sectors.[7] Glycerol offersinnovative solutions for replacing volatile organic solvents by combining water's low toxicity andhigh boiling point with ionic liquids' low vapor pressure and high boiling point. Its solubility, easy product separation, and benefits like catalyst recycling, microwave assistance, and biphasic and emulsion modes make it a valuable alternative. Various carbonyl reduction techniques have usedglycerol as an alternate green reaction medium. Glycerol's strong polarity makes it possible to reduce various carbonyl compounds easily using sodium borohydride and to reduce ethyl acetoacetate in an enantioselective manner.[8]

Ionic liquids: In the context of green solvents, we might want to talk about ionic liquids (ILs), which are, at least temporarily, regarded as both designer solvents and green solvents due to theirminimal vapor pressure requirements and inherent lack of detrimental effects on volatile organic compounds.[7] Ionic liquids (ILs) are nonmolecular solvents created by combining organic and inorganic cations with melting temperatures below 100 degrees Celsius. They are used in the preparation of task-specific ILs and derivatives like polymeric ILs, IL-based surfactants, and magnetic ILs due to their unique properties, including low vapor pressure, high thermal and chemical stability, ease of synthesis, and impressive tuneability. ILs are increasingly investigated as a replacement for traditional organic solvents in analytical procedures.[15] Ionic liquids can have an anionic or cathodic character, making them either hydrophilic or hydrophobic.[13]

The following are some benefits of using ionic liquids as solvents: (i) many organic compounds, metals, and gases dissolve easily in them; (ii) ionic liquids have constructive thermal stability when used in a wide temperature range (ionic liquids have a synthesis temperature range that is 3-5 times larger than that of water); (iii) ionic liquids do not coordinate when used in place of other polar solvents or alcohols; (iv) ionic liquids do not evaporate as volatile organic solvents; and (v) because of the presence of cations and anions, ionic liquids are amphilites.[13]

Simple salts, which consist of a single anion and cation, and binary ionic liquids, which include equilibrium, are the two primary groups of ionic liquids. For instance, [EtNH3][NO3] is a simple salt, but mixtures of 1,3-dialkylimidazolium chlorides and aluminum(III) chloride (a binary ionic liquid system) contain a variety of ionic species, and the mole fractions of these compounds determine the properties and melting point of these mixtures. Ionic liquids at room temperature, like BMIM-PF6 [1-Butyl-3-methylimidazolium hexafluorophosphate], have been utilized as a direct substitute for traditional organic solvents in multiphase bioprocess reactions. This includes two-phase biotransformation procedures and liquid-liquid extraction of the antibiotic erythromycin.[8]

Supercritical carbon dioxide: Supercritical carbon dioxide (scCO2) has benefits over water and functions similarly to other hazardous chemicals without posing any risks. Using scCO2 as a reaction medium allows for the performance of several reactions, including hydrogenation, epoxidation, radical reactions, Palladium-mediated C-C bond synthesis, ring closure metathesis, biotransformation, and polymerization. It has been shown that liquid (near critical) carbon dioxide may be used as a solvent to load Ibuprofen into mesoporous silica, producing a material with a high Ibuprofen content.[8]

Catalyst

In chemical reactions, a green catalyst may be extremely helpful by enabling more efficient operations, lowering environmental impact, and substituting chemicals impact of procedures and by bringing down their expenses. This may be accomplished by creating the right catalyst, which would be inexpensive, easily prepared, repeatable, and completely environmentally benign.[8] Because they may perform a single reaction several times and are employed in smaller quantities than stoichiometric reagents, catalysts are preferred.[11]

They can lower a transformation's temperature, increase a reaction's selectivity, cut down on wastederived from reagents, and maybe prevent unintended side reactions that might result in clean technology. In addition to heavy metal catalysts, phase transfer catalysts such as crown ethers andzeolites, which are softer catalysts, are finding more and more commercial use.[11] Catalysts support the process without becoming consumed or mixed with the finished product. They ought to be applied wherever practical. Among the advantages of catalysts are: (i) higher yields of products; (ii) the ability to perform reactions in situations where they would not ordinarily be able to; and (iii) enhanced selectivity. Furthermore, there are major benefits to using catalysts in terms of reduced waste, improved raw material use, and energy consumption. Selectivity improvements in catalysts have made some "green" synthesis procedures incredibly practical.[13] It has been reported that immobilized metal complex-based catalytic devices can catalyze pharmaceutically valuable processes, such the selective oxidation of steroidal substances. In one research, different functionalized allenes are stereo selectively cycloisomerized to five or six membered oxygen or nitrogen containing heterocycles using chloroauric acid (HAuCl4) as a catalyst in water.[8]

This catalytic system may be reused once the substrate has been fully converted, making it more ecologically friendly than conventional gold catalysts in organic solvents. There has been a report of a mild, chemo-selective process for aldehydes and ketones that is both affordable and sustainable. It does not need the use of ligands or precious or non-precious metals. Molecular oxygen has been created as the oxidant for Wacker oxidation of higher alkenes and aryl alkenes, whereby colloidal palladium nanoparticles are used. Under the absence of a co-catalyst are thought to promote its reoxidation when stabilized in ethylene carbonate. It has been claimed that a streamlined one-step process may be used to create various mesoporous solid sulfonic acids, whichcan serve as ecologically acceptable substitutes for conventional acids like sulfuric acid and its chemical derivatives.[8]

Biocatalyst

The most prevalent and effective catalysts in nature are enzymes.[11] Catalysts that are extremely enantioselective, enzymes frequently produce enantiomeric excesses greater than 99%. The production of enzymes from microbes in the quantity required by industry became possible with the advent of molecular biology techniques, particularly after Mullis discovered the polymerase chain reaction, and the heterologous expression in genetically optimized hosts. This paved the way for the long-awaited use of enzyme catalysis in synthetic industrial processes.[6] The oldest known biocatalyzed conversion in human history is ethyl alcohol production from molasses by the enzyme invertase. Enzymes are crucial instruments in the synthesis of chemical compounds. The largest- scale biocatalytic process in the pharmaceutical business is the enzyme penicillin acylase's conversion of Penicillin G's fermentation product into 6-amino penicillanic acid. This process yields a wide range of chemically modified penicillins, amino acids, vitamins, fructose syrup, and biopharmaceuticals. The benefits of biocatalyzed reactions include being carried out in an aqueous media, requiring just one step for conversions, not requiring the protection of functional groups, being quick, and being stereo-specific.[11] One new instrument for green technology is biocatalysis. Enzymes have great stereo and regioselectivity and are very efficient. Reactions can be carried out in water at ambient conditions, which minimizes the energy input and the need for organic solvents. Biocatalysts may catalyze several organic processes such as epoxidation of terpenes andfatty acids, formation of polymers, polylactides and polyesters, manufacture of 1,3-propanediol from corn etc. Candida Antarctica Lipase is one of these biocatalysts; it catalyzes the processes of alcoholysis, ammoniolysis, and perhydrolysis. These rates of reactivity are on par with or even higher than those found in organic media.[8] However, the cost of enzymes can be high, and biocatalysis is still the exception rather than the rule when it comes to the organic synthesis of vitamins, fine compounds, flavor and aroma, and medications.[6]

In order to find enzymes with greater selectivity and wider substrate acceptance, biotechnology companies frequently investigate promising new classes of enzymes. For instance, they may use directed evolution to select mutants of thermostable enzymes or other biotechnology techniques to evolve customized enzymes with improved industrial performance.

In response, contract manufacturing businesses seek to lower process costs even further, boost output, and enhance product quality. One such initiative is the development of disposablebioreactors that enable quick downstream purification.[6]

Nanoparticles

One billionth of a meter is called a nanometer, and it has a width of ten atoms. One example that may be used to compare with actual items is hair, which has a diameter of 150,000 nanometers. The interdisciplinary fields of biology, chemistry, physics, food, medicine, electronics, aerospace, and medicine are all involved in the rapidly emerging field of nanotechnology, which studies the design, production, assembly, and characterization of materials with a scale smaller than 100 nanometers as well as the use of small functional systems made from these materials.[18] Atomically or molecularly-sized nanoparticles (NPs) serve as a link between bulk materials and NPs with a dimension of 1–100 nm. Due to their tiny sizes, extensive surface area with free dangling bonds, and more reactivity than their bulk counterparts, they have surprising and fascinating features.[17] It is a science that operates at the nanoscale and provides several areas of focus for the many scientific disciplines, including bioengineering, dentistry, and pharmaceuticals. The use of green chemistry is important for the prospects of nanomaterials in the future. The goal of this field of nanoscience should be to create safe, environmentally acceptable nanoparticles that are widely used in nanotechnology. The morphology of included particles, including their size, physicochemical characteristics, and form, is greatly influenced by the solvents and reducing operators used in the NP reduction process. This morphology has an impact on how NPs are used.[16]

Traditional Synthesis methods of nanoparticles

Two fundamental approaches that include different preparation techniques and have been known since ancient times are utilized in the creation of nanoparticles, which can have a natural or synthetic origin and display distinct features at the nanoscale.[18]

"Top-down" and "bottom-up" are distinct approaches for synthesizing NPs. A top-down strategy uses a variety of size reduction processes, including as grinding, milling, sputtering, thermal/laser ablation, etc., to break down acceptable bulk material into smaller fine particles.[16] This method uses a variety of thermal, chemical, and physical processes to supply the energy required for the production of nanoparticles. The "bottom-up" strategy, which is the second method, involves collecting and assembling atoms or molecules of gas or liquid.[18] While "bottom-up" approaches include chemical reduction, electrochemical procedures, and sonodecomposition, "bottom-to-top" methods synthesize NPs by self-assembling atoms into new nuclei that develop into nanosize particles by chemical and biological means.[16]

The real process for creating nanoparticles is environmentally dangerous and poisonous. The disadvantage of the conventional synthesis procedure is that byproducts pollute the colloidal solution. Green nanoparticle synthesis was therefore developed as a solution to this problem. Thesenanoparticles may be employed for large-scale manufacturing and are both economical and environmentally beneficial. This adheres to certain green chemistry tenets, including prevention, the synthesis of less hazardous compounds, the design of safer chemicals, and the real-time prevention of pollution. Nanotechnology in pharmacy is still in its early stages of development. Prior until now, nanoparticles were created via chemical and physical processes. The large-scale manufacture of nanoparticles is a result of growing demand for them. As a result, the commercial process for creating metal nanoparticles was created. However, the need for clean, nontoxic, and environmentally acceptable ways to manufacture nanoparticles is becoming more widely recognized due to the usage of harmful solvents or high energy in these processes. Chemically produced nanoparticles are less biocompatible than those made by green synthesis. The following are the three main advantages of employing green synthetic nanoparticles: Affordable, non-toxic, eco-friendly, and non-toxic.[7]

Green synthesis method

Biological organisms such as bacteria, actinobacteria, yeasts, molds, algae, and plants, or their byproducts, can be used to complete synthesis in a single step. The creation of nanoparticles is carried out by reduction of molecules found in plants and microbes, including proteins, enzymes, phenolic compounds, amines, alkaloids, and pigments. Reducing chemicals used in the reduction of metal ions and stabilizing agents intended to prevent the generated nanoparticles from clumping together unintentionally are hazardous to the environment and the cell when employed in conventional chemical and physical processes. Moreover, it is believed that the size, shape, and surface chemistry of the generated nanoparticles are hazardous. Biocompatibility nanoparticles arecreated using a green synthesis approach that uses naturally occurring substances found in the biological organisms used.[18] The process of creating nanoparticles via biological processes is outlined in Figure 3.

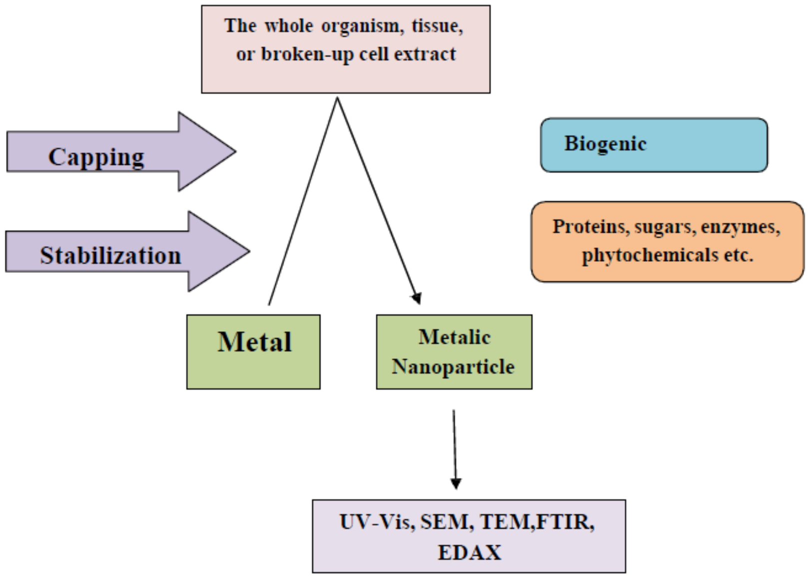

Fig 3: Synthesis of nanoparticles via biological processes.

Yeast, fungus, bacteria, plants, and other microbes, parasites, can all be utilized to synthesizenanoparticles.[7] Table 1. lists a few examples of microorganisms utilized in green synthesis.

Table 1: Examples of microorganisms utilized for green synthesis ofnanoparticles.

Source	Examples
Fungi	Aspergillus clavatus, Aspergillus fumigates[7], Aspergillus flavus[17], Trichoderma viride[16] etc.
Bacteria	Serratia sp[7], Pseudomonas antarctica, Pseudomonas proteolytica, Arthrobacter kerguelensis, Pseudomonas meridiana, Arthrobacter gangotriensis, Bacillus indicus and Bacillus cecembensis[16], Aeromonas hydrophila, Bacillus mycoides, Bacillus subtilis[17] etc.
Yeast	Rhodosporidium diobovatum, Saccharomyces boullardii[7], F. oxysporum[16] etc.
Plant	Tridax procumbens, Melia azedarach[7], Cassia auriculata, Euphorbia condylocarpa, Gloriosa superba, Gum karaya[17] etc.
Algae	L. majuscule, R. hieroglyphics, C. vulgaris, C. prolifera, S. Platensis and S. fluitans, S. subsalsa, P. pavonica[16] etc.

Characterization

Following NP synthesis, several spectroscopic techniques must be used to analyze the morphologyand other delicate conformational aspects. The most often used systems include: dynamic light scattering (DLS), energy dispersive X-ray examination (EDAX), scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), Fourier transmissioninfrared (FTIR) spectroscopy, and so on(Fig:4).[16]

UV–visible spectroscopy

To investigate the size and form of NPs in aqueous suspension, UV-Vis spectra were used. NPs with sizes between about 2 and 100 nm are often characterized using wavelengths between 300 and 800 nm. Because of its surface plasmon resonance, the ZnO particles produced using aloe vera extract showed significant UV absorption spectra, with the absorption peak falling between 358 and 375 nm.[17]

FT-IR

The purpose of FT-IR spectroscopy is to gather information about the various utility groups from the highest points in the range. It also looks at the characteristics of functional groups or metabolites that are present on the surface of NPs and may be in charge of their reduction and stabilization, as well as information about capping and stabilizing the NPs.[16]

XRD Spectroscopy

XRD provides details on the size, phase identification, and translational symmetry of metallic nanoparticles. To gather structural information, X-rays are used to penetrate the nanomaterials and compare the diffraction pattern produced with standards. The face-centre cubic phase of CeO2 NPs is demonstrated by the XRD peaks at angles (2h) of 28.51, 33.06, and 47.42, which correspond to the 111, 200, and 220 planes, and the typical diffraction peaks. Using the Scherer equation, the XRD examination verified the presence of Pb NPs' crystalline pattern and their average particle size of 47 nm.[17]

SEM & TEM

SEM and TEM are typically used to characterize the shape and size of NPs. ZnO NPs (25–55 nm) were seen in the electron microscopy examination, which is consistent with the XRD analysis. Polyaniline films entirely encased green produced carbon nanotubes for SEM and TEM examination. TiO2 particles were typically agglomerated into spherical shapes in the 10–30 nm range during TEM investigation. Additionally, a crystalline form was revealed by the selected area electron diffraction (SAED) examination.[17] In the direction of TEM determination, the new generation of high-resolution SEM (HRSEM) allows a determination better than anything 1 nm. Collaborations might be broken down using this process, such as the adsorption and uptake of metallic NPs by cells. The size and shape of the ensuing NPs are made clear by TEM and SEM analysis. The spherical and monodisperse Ag NPs are shown by the TEM data.[16]

DLS & EDAX

The size distribution distributed in liquid and the elemental contents of NPs are analyzed using the DLS and EDAX, respectively.[17]

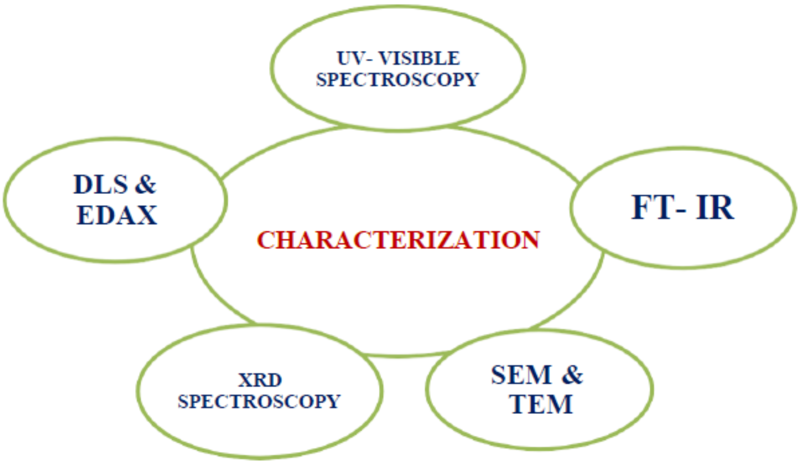

Fig 4: Characterization techniques of nanoparticles.

Green synthesis of drugs

To avoid releasing hazardous and poisonous byproducts into the environment, green procedures are created throughout the drugs synthesis process. Nearly every green chemistry concept has been used for the same purpose. For example, catalysis, cleaner solvents, less risky chemical synthesis,prevention, and atom economy.[7]

CASE STUDY

Sildenafil Citrate

The phosphodiesterase inhibitor sildenafil citrate (Viagra), the first successful oral therapy for erectile dysfunction, has significantly contributed to Pfizer's earnings since 1998. Its success can be attributed to the integration of green chemistry into the commercial manufacturing process. Pfizer's UK laboratories used a linear 11 step synthesis for 2-pentanone, yielding 4.2%. However, due to toxic substances and poor yield, it was not suitable for large-scale production. The placement of a crystalline intermediate in the synthesis led to toxic chlorosulfonic acid, resulting in hazardous waste.

Convergent strategies improve manufacturing processes by creating advanced intermediate components simultaneously. This allows for easier accumulation of intermediates and easier filtering of impurities. Modified chemistry for sildenafil citrate improved total yield by shifting chlorosulfonation earlier and positioning cyclization as the last step using safe reagents. The process of sulfonation allowed workups to naturally purify, eliminating harmful residues, and by performing the final step at high concentration, solvent waste was further reduced. Green solvents like water, t-butanol, and ethyl acetate were introduced to replace ether and chlorinated solvents, simplifying the process and reducing waste, resulting in significant energy savings.[9]

Sertraline

The medicine sertraline is an antidepressant. Pfizer introduced sertraline to the market in 1991. Itspharmacological action is demonstrated by its inhibition of serotonin absorption. An excess of aluminum chloride was required for the classic Friedel craft acylation method of synthesizing sertraline, and carbon disulphide—a hazardous solvent—was used to carry out the reaction. Tetrahydrofuran was employed as a solvent after titanium tetrachloride was utilized in the condensation reaction of the synthesis method, producing titanium waste.

Tetrahydrofuran was swapped out for ethanol in the green synthesis of sertraline, increasing the imine formation to over 95%. Moreover, since titanium tetrachloride (TiCl4) is no longer neededfor imine creation, no titanium waste is produced.[7]

Celecoxib

Celebrex, a COX-2 anti-inflammatory drug, contains celecoxib, which has a straightforward synthesis technique. However, its high daily dose of up to 800 mg necessitates more process work due to the need for bulk medication. Scientists optimized ring formation to reduce environmental impact after cyclization produced regioisomers and unreacted hydrazine, resulting in increased solvent and waste disposal costs.

The use of methanol and isopropanol as safe solvents has led to a 35% reduction in waste generation and a 50% increase in reactor throughput. The cleaner product also reduced the need for harmful solvents like methylene chloride and hexane, reducing the annual solvent requirementfrom 5200 metric tons.[9]

Quinapril

Quinapril is an anti-hypertensive medication used to treat heart failure and hypertension by lowering blood pressure. It inhibits the angiotensin-converting enzyme, demonstrating its therapeutic action. The first production process used unwanted solvents, including dicyclohexyl carbamidimide, methyl chloride, hydroxy benzotriazole, and toluene, resulting in the formation ofa diketopiperazine impurity.

The green strategy aimed to decrease dietopiperazine production by replacing acetic acid with N- carboxy anhydride, a readily available substance. This self-activated anhydride produced direct amide coupling, eliminating the need for chlorinated solvent and DCC and its waste product, dicyclohexylurea.[7]

CONCLUSIONS

In conclusion, the integration of green chemistry principles in the biotechnological industry represents a pivotal shift towards sustainable and environmentally friendly practices. The adoptionof green solvents, such as ionic liquids or supercritical fluids, reduces the ecological footprint of processes, minimizing the generation of hazardous waste. Bio-based catalysts, derived from microorganisms or enzymes, not only enhance reaction efficiency but also facilitate milder operating conditions.

Nanoparticles, being instrumental in various applications, play a key role in targeted drug delivery and diagnostics. Their synthesis through green methodologies, such as plant-mediated or microbial-assisted routes, ensures reduced energy consumption and avoids toxic by-products. Thegreen synthesis of drugs, employing renewable feedstocks and eco-friendly methodologies, underscores a commitment to both human health and environmental sustainability.

Overall, the amalgamation of green chemistry and biotechnology not only optimizes manufacturing processes but also addresses global concerns about pollution and resource depletion. As the biotechnological industry continues to advance, embracing these green principles is imperative for fostering a harmonious coexistence between technological progress and ecological well-being. This symbiotic relationship holds the promise of a more sustainable and resilient future for both industry and the planet.

REFERENCES

1. De Marco BA, Rechelo BS, Tótoli EG, Kogawa AC, Salgado HR. Evolution of green chemistryand its multidimensional impacts: A review. Saudi pharmaceutical journal, 2019 Jan 1; 27(1): 1-8.
2. Jayalakshmi C and Thangaraj N.2018, Impact of Biotechnology In Our Environment. Int J Recent Sci Res, 9(5): 26825-26827.

3. Fasciotti M. Perspectives for the use of biotechnology in green chemistry applied to biopolymers, fuels and organic synthesis: from concepts to a critical point of view. Sustainable Chemistry and Pharmacy, 2017 Dec 1; 6: 82-9.
4. Wenda S, Illner S, Mell A, Kragl U. Industrial biotechnology—the future of green chemistry?.Green Chemistry, 2011; 13(11): 3007-47.
5. Pleissner D, Kümmerer K. Green chemistry and its contribution to industrial biotechnology. Sustainability and Life Cycle Assessment in Industrial Biotechnology, 2020; 281-98.
6. Ciriminna R, Pagliaro M. Green chemistry in the fine chemicals and pharmaceutical industries.Organic Process Research & Development, 2013 Dec 20; 17(12): 1479-84.
7. Msingh R, Pramanik R, Hazra S. Role of green chemistry in pharmaceutical industry: A review. J. Univ. Shanghai Sci. Technol, 2021; 23: 291-9.
8. Talaviya S, Majmudar F. Green chemistry: A tool in Pharmaceutical Chemistry. NHL Journal of Medical Sciences, 2012; 1(1): 7-13.
9. Cue BW, Zhang J. Green process chemistry in the pharmaceutical industry. Green Chemistry Letters and Reviews, 2009 Dec 1; 2(4): 193-211.
10. Dhage SD. Applications of green chemistry principles in every day life. International Journalof Research in pharmacy and chemistry, 2013; 3(3): 501-18.
11. Patil HI, Singh MC, Gaikwad P, Lade KS, Gadhave NA, Sawant SD. Green Chemistry: Why And How-For Sustainable Chemical Industry and Environmentally Commendable Civilization. Journal of Pharmacy Research, 2011 Dec; 4(12): 4798-804.
12. Himaja M, Poppy D, Asif K. GREEN TECHNIQUE-SOLVENT FREE SYNTHESIS AND ITS ADVANTAGES. International Journal of Research in Ayurveda & Pharmacy, 2011 Jul 1; 2(4).
13. Soltys L, Olkhovyy O, Tatarchuk T, Naushad M. Green synthesis of metal and metal oxide nanoparticles: Principles of green chemistry and raw materials. Magnetochemistry, 2021 Oct 31; 7(11): 145.
14. Gu Y, Jérôme F. Glycerol as a sustainable solvent for green chemistry. Green Chemistry, 2010; 12(7): 1127-38.
15. Pacheco-Fernández I, Pino V. Green solvents in analytical chemistry. Current Opinion in Green and Sustainable Chemistry, 2019 Aug 1; 18: 42-50.
16. Gour A, Jain NK. Advances in green synthesis of nanoparticles. Artificial cells, nanomedicine,and biotechnology, 2019 Dec 4; 47(1): 844-51.
17. Hussain I, Singh NB, Singh A, Singh H, Singh SC. Green synthesis of nanoparticles and

its potential application. Biotechnology letters, 2016 Apr; 38: 545-60.

18. Nadaroglu H, GÜNGÖR AA, Selvi İN. Synthesis of nanoparticles by green synthesis method.International Journal of Innovative Research and Reviews, 2017 Aug; 1(1): 6-9.