

Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE DOI: 10.53555/jptcp.v29i04.4373

SUSTAINABILITY IN PHARMACEUTICALS: AN IN-DEPTH LOOK AT THE GREEN PHARMACY PRINCIPLES

Parul Srivastava^{1*}, Ankita Wal², Versha Chaturvedi³, Pranay Wal⁴, Ashish Srivastava⁵, Anil Yadav⁶, Pranjal Sachan⁷

^{1*,2,3,4,5,6}PSIT-Pranveer Singh Institute of Technology, Pharmacy, Kanpur

*Corresponding Author: Parul Srivastava *PSIT-Pranveer Singh Institute of Technology, Pharmacy, Kanpur

Abstract:

Green chemistry, a cornerstone of sustainable practices, is transforming the pharmaceutical industry by minimizing or eliminating the use and production of harmful substances. This review delves deep into the **12 Green Pharmacy Principles**, a guiding force for designing eco-friendly and health-conscious medication production processes.

We explore how these principles are being implemented across various aspects of drug development, from molecule design and synthesis to production, distribution, and disposal. Exciting advancements like biocatalysis, renewable feedstocks, innovative solvents, and energy-efficient methods are discussed, showcasing their potential to minimize environmental impact and create economic opportunities. By embracing these green principles, the pharmaceutical industry can pave the way for a healthier planet and ensure the development of safer and more sustainable medications for generations to come.

Keywords: Photocatalysis, Ionic Liquids, Supercritical Fluids, Microwave Irradiation, Green Chemistry, Biocatalysts, and Biomass.

1. Introduction:

Being green has recently become a trend in product marketing and a flashpoint for environmentalists. (The colour green represents chlorophyll and the colour of the dollar.) To be green, chemists must apply green chemistry principles to all facets of the chemical sciences, including basic and applied research, production, and teaching.[1] Chemical products should be created such that they break down in the environment after use and do not linger there afterward, according to the Environmental Protection Agency's definition of "green chemistry" components with a low environmental impact.[2] Savings from effective synthesis without the use of "exotic" reagents, decreased energy needs, and the substitution of organic solvents with water are significant even at the laboratory scale, with millions of dollars in savings possible at the industrial scale.[3] Green chemistry is an ethical, multidisciplinary method of science that emphasises chemical, ecological, and social responsibility while fostering innovation and the growth of creative research The utilisation of natural resources, economic development, and environmental preservation are all balanced in an effort to achieve and preserve this equilibrium.[4,5,6,7,8] Trends in Green Chemistry: which is defined as "a programme for the design, development, and implementation of chemical products and processes that decrease or eliminate the use or production of hazardous substances," a number of significant trends are involved in both the production of substances that are harmful to both human health and the environment as well as the achievement of the program's main objectives.[9,10,11,12] Researchers

study catalytic and biocatalytic techniques to produce highly selective, pure compounds without producing dangerous by-products. Creating less dangerous and more sustainable chemicals; creating and testing new, non-toxic, renewable reaction media like supercritical fluids, ionic liquids, and water; and creating and testing new reaction environments like those that use microwave, ultrasound, and light [13.14,15]. According to the goals, green chemistry "changes stable industrial practicegenerates, pollutes, then cleans, and in the late 20th century, becomes the heart and soul of industry. "Green chemistry, sometimes referred to as environmentally friendly, safe, and sustainable chemistry, refers to the development and application of chemical goods and procedures that reduce or completely do away with the usage and production of dangerous substances [16,17,18,19,20]. By minimising exposure to dangerous chemicals, green chemistry seeks to diminish and possibly even eliminate the risk, negating the need for exposure control. If hazardous substances are not used or produced, there is no need to be concerned about removing them from the environment or restricting exposure to them. Green chemistry, sometimes referred to as sustainable chemistry, is a type of chemical engineering and examination. [21,22] It is about reducing waste, raw materials, dangers, energy, environmental effects, and costs [23]. It is a branch of chemistry and chemical engineering that is concerned with producing products and methods that use hazardous materials as little as possible [24,25]. The study, creation, and use of chemical products and processes are intended to reduce or end the production and use of dangerous substances for the environment and human health. [26,27,28] As the term implies, proponents of "green chemistry" work to change how people view chemicals, especially man-made organic molecules. By (re) designing chemicals and the methods used to make them at the molecular level, problems are to be avoided. [30,31,32,33,34,35] What could ultimately lead to a significant overhaul in chemical synthesis methods, raw materials, by-products, and end products has started to develop in recent years, albeit with little debate or publicity. The phrase "green chemistry" was first used by Anastas from the US Environmental Protection Agency (EPA). The US Green Chemistry Program was formally formed by the EPA in 1993. [36,37,38] It has since acted as a focal point for activities all around the country, including the Presidential Green Chemistry Challenge Awards and the annual Green Chemistry and Engineering Conference. That is not to claim that there was no green chemistry research done prior to the early 1990s; it simply lacked a name. Since the early 1990s, both Italy and the United Kingdom have spearheaded substantial programmes in green chemistry, as well as, more recently, the Green and Sustainable Development Goals. [40,41,42,43] In Japan, the Chemistry Network was established. The Royal Society of Chemistry provided funding for Green Chemistry to print its debut issue in 1999. We may therefore confidently predict that green chemistry is here to stay [44.45.46]. A good working definition of green chemistry is as follows: green chemistry efficiently uses raw materials (preferably renewable ones), reduces waste, and stays away from the use of dangerous and toxic chemicals and solvents in the production and usage of chemical products. [47,48,49] As Anastas has shown, building environmentally friendly products and processes (benign by design) is the overarching principle. Introduction: Can the Pharmaceutical Industry Embrace Green Chemistry? Although the groundwork for "Green and Sustainable Chemistry" and "Green Engineering" had long been laid, there had been a lack of coordinated initiatives involving business, academia, government, and environmental organisations. [50,51] Twenty years ago, a collaboration was formed with the intention of fostering innovative production techniques and advancing products that are environmentally friendly and sustainably produced on a large scale. Industry, academic institutions (universities and research institutes), and governments worked together to identify fresh approaches to enduring problems, not just in manufacturing but also in the creation of safer consumer goods [52,53,54]. The goals were unmistakable: to start and enhance collective knowledge and to provide technological improvements at a lower cost. It also proves that purchasing "green" products is a wiser financial decision in the long run. At this point in time, lowering pollution is the most important step toward sustainability [55,56,57]. The effective use of the planet's limited natural resources (such as electricity and water) and the promotion of collaboration among all stakeholders with environmentally friendly ideas and goods are the most dynamic. It is leading to important movements toward "greener" feedstocks, cleaner solvents, unconventional techniques, and innovative thinking. The pharmaceutical industry

has been implementing more "green" practises and technological operations for many years. All of these measures will boost the industry's environmental credentials while also reducing costs and materials for manufacturing processes, putting them on the road to sustainability. In developed nations, the research divisions of several large pharmaceutical corporations have made great strides in developing new methods, improving biocatalytic reactions, using fewer solvents, and reducing waste. According to researchers[59], it took the pharmaceutical industry several years to translate green ideas into quantifiable goals for environmentally friendly research, development, and production.[60] Pharmaceutical companies, for example, have stringent safety and health regulations in place, as well as environmental standards for their products[61][.Safety, efficiency, dependability, and economy are the four pillars of change, and promoting them is seen as a competitive advantage, a move that is better for the environment, and something that will bring about financial advantages. One of the biggest problems the world is currently facing is pollution [62]. Pharmaceutical products, which mostly consist of prescription medications but can also include other personal care items, may be regarded as environmental contaminants due to their extensive use in both human and veterinary medicine [63,64,65]. The European Union (EU) market, which is second in the world in terms of consumption only to the United States of America, consumes around 100,000 tonnes of pharmaceutical products annually (USA). Additionally, 559 active pharmaceutical substances are found in environmental sectors such as soil, groundwater, and surface water [66,67]. A new phrase, the "green pharmaceutical notion," has been coined in this context and is described as the collection of all appropriate steps to reduce environmental impact. The discovery of novel chemicals as well as production, distribution, dispensing, and disposal should all follow these safety precautions. Additionally, to reduce the pollution brought on by pharmaceutical items, healthcare professionals (such as doctors and pharmacists) and end users (patients) should take part in the measures [68]. Pharmacy trash, which is mostly made up of outdated pharmaceuticals, must be disposed of. Pharmacists are responsible for administering prescription and over-the-counter (OTC) prescriptions as well as disposing of pharmaceutical waste. Based on this analysis, the International Pharmaceutical Federation (FIP) Board of Pharmacy Practice and the Board of Pharmaceutical Science created a document titled "Green Pharmacy Practice: Taking Responsibility for the Environmental Impact of Medicines" to offer recommendations for pharmacists in a variety of practise settings [69]. The primary objectives are to summarise and analyse the pertinent academic literature on pharmaceutical contamination in the environment. We think that pharmacists ought to be more involved in this area, and we want to suggest future study topics for its regulation and implementation in Romania (figure-1).[70]

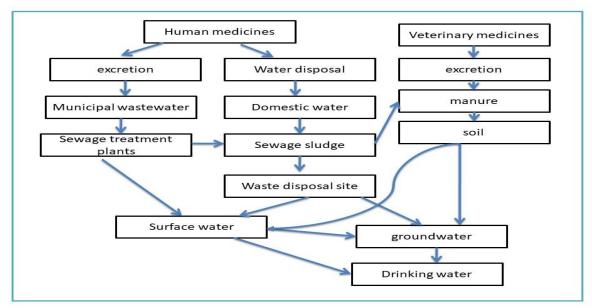


Figure 1 illustrates how pharmaceuticals infiltrate the environment.

2.History:

A number of pre-existing theories and research programmers (such as atom economics and catalysis) gave rise to green chemistry in the years before the 1990s, as the public's awareness of chemical pollution and resource depletion expanded [71]. Green chemistry's emergence in Europe and the US coincided with a shift in the way environmental problems were approached, moving away from command-and-control regulation and mandated reductions in industrial emissions at the "end of the pipe" in favor of a number of pre-existing theories and research programmers (such as atom economics and catalysis) gave rise to green chemistry in the years before the 1990s, as the public's awareness of chemical pollution and resource depletion expanded [72]. Green chemistry's emergence in Europe and the US coincided with a shift in the way environmental problems were approached, moving away from command-and-control regulation and mandated reductions in industrial emissions at the "end of the pipe" in favor of being proactive in pollution prevention through innovative production technology design. The middle to late 1990s saw the emergence of the body of concepts [73,74] currently known as "green chemistry," as well as a surge in the term's popularity (which prevailed over rival terms like "clean" and "environmental"). Through its pollution prevention programmers, funding, and expert coordination, the Environmental Protection Agency (EPA) played a crucial early role in the development of green chemistry in the United States. At the same time that the Royal Society of Chemistry in the UK launched the Green Chemistry Network, researchers from the University of York contributed to the founding of the journal Green Chemistry [75]. of being proactive in pollution prevention through the design of innovative manufacturing technology The middle to late 1990s saw the emergence of the body of concepts currently known as "green chemistry," as well as a surge in the term's popularity (which prevailed over rival terms like "clean" and "environmental").[76] Through its pollution prevention programmers, funding, and expert coordination, the Environmental Protection Agency (EPA) played a crucial early role in the development of green chemistry in the United States. At the same time that the Royal Society of Chemistry in the UK launched the Green Chemistry Network, researchers from the University of York contributed to the founding of the journal Green Chemistry [77].

3.Green pharmacy trends include:

Green chemistry is a "programme for the design, development, and application of chemical products and processes that reduce or eliminate the use or production of substances that are hazardous to human health and the environment," with a number of key trends helping to realise the main objectives of the green programme. study on catalytic and biocatalytic techniques to produce pure chemicals that are extremely selective without producing potentially dangerous by-products; b. c)). Creating novel, risk-free, sustainable raw materials like biomass into less toxic, environmentally friendly substances; creating and analysing new non-toxic, renewable reaction media such as supercritical fluids, ionic liquids, and water. (f). creating and testing new reaction conditions, like microwave, g. research on alternative purification techniques for polluted air and water, like photocatalytic processes, to enhance their quality [78]. According to the stated objectives, "green chemistry alters established industrial practices-generates, pollutes, then cleanses, and in the late 20th century, becomes the heart and soul of industrial ecology." A new generation of scientists and engineers is being produced to evaluate the economics of the production and development methods and materials used to safeguard the environment and natural resources. Green chemistry is a Hippocratic oath for chemists. The creation and use of chemical goods and procedures that restrict or stop the use and manufacturing of dangerous substances is known as green chemistry, also known as environmentally friendly, secure, and sustainable chemistry. Instead of reducing the risk, green chemistry strives to diminish and possibly even eliminate it by limiting exposure to dangerous chemicals, thus negating the need for exposure control. If there is no use or production of hazardous substances, there is no need to be concerned about removing them from the environment or restricting exposure to them. Green chemistry aims to reduce waste, raw materials, risks, energy use, and costs.[79] 4. principle. The twelve principles cover a range of methods to lessen the effects of chemical manufacturing on the environment and human health, as well as the objectives of research for the advancement of green chemistry technology [20].

Some of the guiding principles are to use as many raw materials as possible in the final product, to use renewable feedstocks and energy sources as much as possible, to use safe, environmentally friendly compounds, such as solvents, and to make processes that use less energy [21] (fig. 2,3).

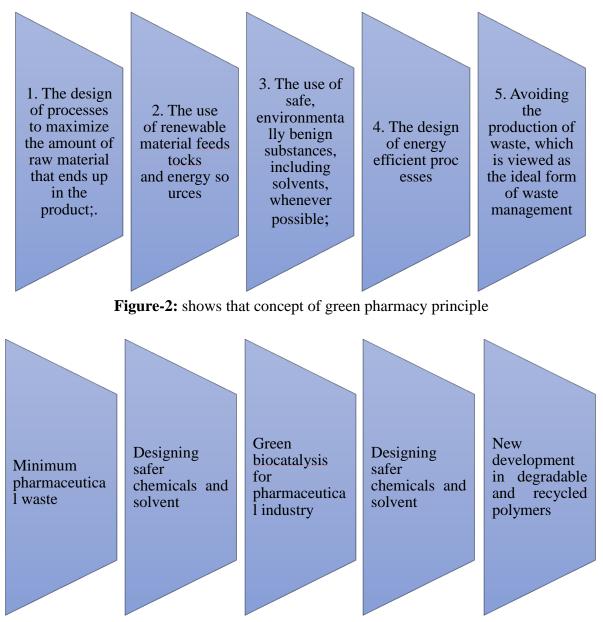


Figure -3: shows that concept of green pharmacy principle

4. There are twelve green chemistry tenets:

They developed twelve guiding principles for green chemistry in their 1998 book, Green Chemistry Theory and Practice. According to green chemistry principles, toxic or dangerous molecules should be eliminated or reduced from the synthesis, production, and application of chemical products, as well as the use of substances that are damaging to both human health and the environment. It is impossible to create a green chemistry method that can satisfy the requirements of all twelve principles at once, but it aims to apply as many principles as is practical during various stages of synthesis (figure-4).[**80**]

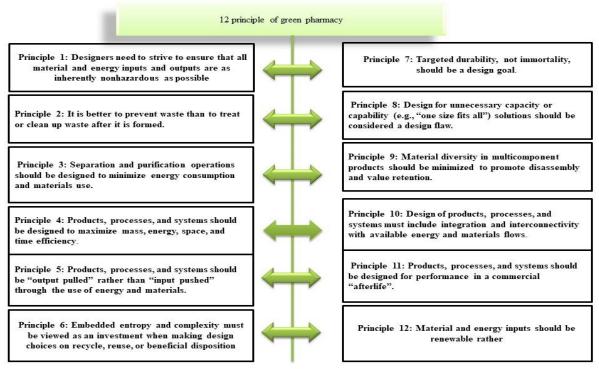


Figure 4 illustrates the twelve tenets of green pharmacy

4.1 One Principle:

innate rather than circumstantial. Although the adverse impacts of fundamentally dangerous substances (whether toxicological, physical, or global) can be lessened, doing so necessitates a significant investment of time, money, resources, and energy. This is generally a poor economic and environmental strategy. Designers should evaluate the fundamental character of the chosen material and energy inputs to make sure that they are as benign as is practical as a first step toward a sustainable product, process, or system. The development of essentially benign materials and energy sources is a goal of molecular designers. If the inputs are intrinsically dangerous, the threat will be eliminated during the process-typically during purification or clean up procedures-or included in the finished product. The final transfer of any hazards to an off-site storage and disposal facility will be necessary if they are removed from the final product throughout the manufacturing process as a result of improved operating circumstances. Carefully planned safety measures are required at every level, but they could go wrong. What if these hazards aren't completely avoided but rather are incorporated into the finished item? As long as the risk is frequently recycled and reused, there are ways to embed risks into products or processes, but doing so requires resources to be spent on continuing monitoring and control. Additionally, these methods depend on the conveyance of these hazards in order to maintain "closed-loop" cycling, which raises the chance of release due to mishaps, spills, and leaks. System inputs should always be intrinsically safer. As a result, there will be less failure potential and less need for control, monitoring, and containment resources. [81]

4.2 Two Principle:

Therapy is not as effective as prevention. It is common to criticise proposals for "zero-waste" industrial processes or service systems for omitting to take into account enthalpy and thermodynamic rules. An important distinction that is sometimes overlooked is that the idea of waste is human. In other words, neither energy nor a substance is fundamentally useless. Instead, it results from a dearth of applications that have not yet been thought of or created. Therefore, material or energy that can no longer be successfully employed for beneficial purposes by current processes or systems is described as waste. Regardless of where it comes from, waste generation and disposal need time, effort, and money. Furthermore, spending on monitoring and control needs to be increased even further for

hazardous waste. Despite what might be implied, it goes without saying that waste should be avoided whenever possible, yet there are many instances where waste isn't accidentally created-rather, it's purposefully built into the process. Waste-free design approaches are based on the same fundamental idea at every scale: inputs are meant to be a component of the desired output. The architecture of current fossil-fuel-based power production systems, which inherently produce waste at each life cycle step, is an example of this idea, which is known as "atom economy" at the molecular level and can be extended across design sizes as "material economy." Although garbage is created during mining and processing, consumption accounts for the majority of waste production. Greenhouse gases are released with the burning of fossil fuels. Particulate matter and other pollutants play a role in the causes and effects of global climate change. In contrast to fusion energy, power generation systems do not need to produce waste. Although it has not yet been achieved, fusion energy has the potential to move energy systems toward sustainability. Fusion will stop the production of chemical combustion products since no fossil fuels are needed. Furthermore, fusion energy does not create dangerous fission products like nuclear energy does. The use of this technique in energy systems illustrates how fundamental design principles can be used to create systems, processes, and other elements that minimise waste generation. [82]

4.3 Three Principle:

The objective is separation. Product separation and purification consume the most energy and resources in many production processes. While some traditional separation techniques make heavy use of potentially harmful chemicals, others make heavy use of energy in the form of heat or pressure. Designing products correctly from the start enables them to self-separate based on inherent physical and chemical properties like solubility and volatility rather than external factors, which cuts down on waste and processing time. Similar design techniques can be applied to create the final product, process, or system from constituent parts that have the desired properties. The intended output is separated using this technique from a complicated matrix of undesirable and superfluous material, using the least amount of energy and resources. Additionally, the elements of the undesirable matrix are typically categorised as "rubbish." Time, money, and resources are required for handling, transportation, disposal, and possibly monitoring. Additionally, early design choices can affect how simple it is to separate and purify products for later use and recycling. The cost and difficulty of separating materials and components is one of the biggest obstacles to recovery, recycling, and reuse. Avoiding persistent links between two materials will help you avoid these issues. Fasteners that are intended for disassembly should be incorporated into the fundamental design plan at all scales. "Reversible fasteners," especially threaded fasteners, can significantly increase the ease of material recovery, recycling, and reuse in everything from cellular phones to automobiles. To cut down on harvesting time and costs, separation and purification are considered beforehand. At the molecular level, separation and purification techniques like column chromatography and distillation, for example, are typically inefficient. intended output at all design scales and throughout the life cycle. Distillation uses a lot of energy for both cooling and heating, whereas column chromatography might use a lot of hazardous solvents. On the other hand, chemical reaction products that self-separate from the reaction medium would not require these additional resources. Polymers can be used to modify the solubility of substrates, labels, and catalysts for separation and reuse. To avoid wasting resources and energy, separation and purification are considered early in the design process. This is done at all design sizes and throughout the life cycle.[83]

4.4 Four Principle:

Boost the effectiveness of time, space, energy, and mass. The implications are widely spread over the product and process life cycles, yet they could be categorised as "inefficiencies" because processes and systems usually use more time, space, energy, and materials than is necessary. Resources are wasted over the course of a system's existence if it is created, put to use, or used inefficiently. The standard design strategies used by engineers to promote efficiency can be applied even more widely to increase intensity. Constraints on time and space could be considered together with material and

energy flow while attempting to eliminate waste. Real-time monitoring is also necessary in optimised systems to guarantee that the system keeps operating at the parameters that were anticipated. In chemical manufacture, massive batch reactors are typically only partially utilised during the reaction time, frequently at dilution levels that are substantially greater than necessary. Utilizing process intensification techniques, such as micro reactors that run continuously at extremely low volumes with efficient mixing, high productivity can be generated from small amounts of material. It is possible to use molecular, product, and process procedures that have been created for optimum effectiveness and intensity. Examples of how this holds true across the hierarchy of system sizes include spinning-disk reactors rather than batch reactors; powder coatings; digital information rather than printed media; and eco-industrial facilities to stop urban development. **[84]**

4.5 Five Principle:

conditions. In chemical manufacture, massive batch reactors are typically only partially utilised during the reaction time, frequently at dilution levels that are substantially greater than necessary. Utilizing process intensification techniques, such as micro reactors that run continuously at extremely low volumes with efficient mixing, high productivity can be generated from small amounts of material. It is possible to use molecular, product, and process procedures that have been designed for maximum efficiency and intensity. Examples of how this holds true across the hierarchy of system sizes include spinning-disk reactors rather than batch reactors; powder coatings; digital information rather than printed media; and eco-industrial facilities to stop urban development. It is "dragged" to completion as opposed to requiring tremendous effort or resources. Le Chatelaine's idea can be applied to design to cut down on the number of resources needed to convert inputs into desired outputs. This happens at the molecular level in chemical transformations like condensation reactions, where water is withdrawn from the product stream to "pull" the process to completion. This comparable method can be applied at many design scales, though not always in the expected setting. In terms of timeliness, quality, and quantity, "just-in-time" manufacturing produces items that perfectly satisfy end-user demand. This word can be used more widely, with the end user being the person who will ultimately purchase the product or someone else further down the supply chain. Equipment, materials, and labour must only be accessible in the quantities and at the times necessary to perform the operations for the production line. Only the necessary units are produced in the appropriate quantities at the necessary times by perfectly aligning production rates with demand. Planning industrial processes for final output eliminates overproduction, processing delays, inventories, and resource inputs. For instance, direct metal deposition generates less waste in the end than metal casting.[85]

4.6 Six Principle:

Keep the intricacy. Spending on materials, energy, and time typically has an impact on how complicated a product is, whether at the macro, micro, or molecular level. Recycling extremely complicated, high-entropy substances could be detrimental and lead to value loss (down-cycling). High complexity should be linked to reuse, whereas low complexity should be linked to value-preserving recycling or beneficial disposition when applicable. It is also important to acknowledge that natural systems have benefits in terms of complexity that should not be forfeited needlessly in manufacturing transformation or processing. However, the complexity of a brown paper bag may not warrant the time and effort needed to collect, sort, process, remanufacture, and redistribute it as an entire shopping bag. Recycling silicon computer chips has a high level of complexity, so recycling a silicon chip to recover the value of the original ingredients may not be cost-effective. End-of-life design alternatives for recycling, reusing, or proper disposal should be based on the material and energy expended as well as the complexity that results across all design scales. **[86]**

4.7 Seven Principle:

Durability, not immortality. Products that last well beyond their useful economic life are usually linked to environmental problems such as solid waste management, persistence, and bioaccumulation.

It is essential to produce chemicals with a definite lifetime in order to prevent the immortality of harmful molecules in the environment. This technique must be balanced with the design of devices that are strong enough to endure anticipated working conditions for the intended lifetime in order to prevent premature failure and disposal. In order to achieve the targeted lifetime with the least amount of extra material and energy introduced during the life cycle, maintenance and repair must also be taken into account. Focusing on endurance rather than immortality as a design goal lowers the danger to human and environmental health. At the end of life, the quality of life is significantly reduced. For instance, the single largest non-recyclable portion of municipal solid waste, for instance, has been single-use disposable diapers made of a variety of materials, including non-biodegradable polymers. [Despite having a short usable life, this product continues to pose a serious environmental risk well beyond its intended use. One alternative is Eco-fill, a new starch-based packaging material that competes with conventional polystyrene packaging and is made of food-grade inputs (starch and water) that can easily be dissolved in domestic or industrial water systems at the product's end of life. By combining endurance but not immortality into this product, Eco-fill meets its intended usage without incurring long-term environmental obligations. Another instance at the molecular level is the use of polylactic acid, which is naturally generated. to create plastics and fibres instead of petroleumbased, non-biodegradable polyacrylic acid.[87]

4.8Eight Principle:

Make sure you have what you need and don't have too much of what you don't. It's important to account for the necessary product flexibility and process agility during the design phase. On the other hand, excessive design and underused capacity or capability may result in high material and energy expenditures. Additionally, there is a propensity to plan for the worst-case scenario or optimise performance for extreme or unrealistic conditions, allowing the same product or process to be used regardless of local geographical, temporal, or physical constraints. This necessitates incorporating, then discarding, and handling components whose function will not be achieved in the majority of operational settings. Avoiding the propensity to create an eternal, universal solution (such as PCBs or chlorofluorocarbons) can help reduce resource waste. Chlorine-based drinking water disinfection is a prime example. Before it is dispersed from a central location, the water is cleansed. Water closer to the drinking water treatment plant in the system will, however, have higher-than-necessary concentrations of disinfection products since some of them dissolve over time. This is done to ensure that the water is disinfected all the way to the end consumer. An alternative, and potentially more sustainable, method is to install actuators and control systems throughout the distribution system to adjust the chlorination dose. For example, tri halo methane, for example, is produced during the chlorination process and is less damaging to the environment and people's health. Although this example does not move us closer to a non-chlorinated disinfection system, it does demonstrate how the present system can be significantly improved, albeit gradually. This approach is applicable to a range of design scales. Reduce the usage of resources and energy that are underutilised or inefficient. For instance, less reactive reagents like enzyme catalysts can be used in place of more reactive ones. To ensure that the water is disinfected until it reaches the end user, there are alternatives to "off the shelf" solutions, such as technologies that focus on the unique needs and preferences of end users. Because some disinfection by products dissipates over time, water closer to the drinking water treatment plant in the system will have higher-than-necessary amounts of disinfection by products. Installing actuator and control systems throughout the distribution system to change the chlorination dose is an alternative and potentially more sustainable approach. Tri-halo methane is a type of methane that has three halo atoms, and although this example does not use a chlorine-free disinfection system, it does show a significant, albeit incremental, improvement over the current system. This reduces the risks to the environment and human health from chlorine production and subsequent chlorination by chemicals. This method can be used on a variety of design scales. Reduce the usage of underutilised and inefficient resources and energy. Enzyme catalysts that function under benign circumstances can be used to substitute more reactive compounds. Technologies that meet the specific needs and wants of end users are alternatives to "off the shelf" solutions.[88]

4.9 Nine Principle:

The variety of materials should be less. Multiple components are found in many things, including cars, food packaging, computers, and paint, to name a few. Metals, glass, and plastics are all employed in the manufacture of automotive parts. Chemical additives such as thermal stabilisers, plasticizers, colours, and flame retardants are used in particular plastics. This variety raises concerns when endof-life decisions are made that have an impact on how simple it is to disassemble products for recycling and reuse. Forward-thinking designs that limit material diversity while accomplishing necessary functions enhance final disposition options. In order to prevent the need for additives later in the manufacturing process, this is accomplished at the process level by including the necessary functionality into the polymer backbones. Tailoring polymer characteristics can have a positive environmental impact when additives are leached. It's possible this is a problem, especially when recycling is necessary. On a product level, some auto designers are minimising the quantity of plastic required by creating innovative polymer forms that are simpler to break down and recycle. This technology is now being used to produce multilayer components like doors and instrument panels. Components, for instance, can be made from a single material that has all the desired design characteristics, like metal-licenced polyolefins. Thanks to this mono-material design concept, it is no longer necessary to disassemble the door or instrument panel for recycling or recovery. This idea is demonstrated at the molecular level. The First Day of Mark in the Year 2003: Science and Technology in the Environment. At the end of the day, life expectancy substantially declines when durability is valued above immortality, endangering both human and environmental health. It is preferable to use "one-pot," "cascade," or "self-assembly" reactions in place of multistep ones.[89]

4.10Ten Principle:

Integrated regional material and energy fluxes. To take advantage of the current framework of energy and material flows, products, processes, and systems should be designed inside a unit operation, production line, manufacturing facility, industrial park, or neighbourhood. Utilizing current energy and material flows lessens the need to produce energy and/or acquire and refine raw materials. The heat produced by exothermic reactions can be used in this method at the process scale to drive additional processes with high activation energies. Chemical by products or the results of purification procedures can be used as feedstock in later reactions. Cogeneration energy systems can produce steam and electricity simultaneously, improving efficiency. As a result, energy and "waste" materials can be gathered everywhere. Production lines, buildings, and industrial parks all include system procedures and finished goods. Regenerative braking is another example of this strategy used in hybrid electric vehicles. In these systems, the heat produced by braking is trapped and used to reverse the electric motor, which is typically a waste of energy. As a result, the motor is transformed into an electric generator that generates electricity that is used to power the vehicle's forward motion after being stored in a battery. The connection between the drive train and the regenerative braking system significantly lowers the vehicle's fuel requirements and improves fuel efficiency. As this example demonstrates, it is important to consider the energy and material availability for a given product or process. Energy inputs originate from a range of sources, such as recycled materials and waste heat from nearby activity. Materials that use less energy and raw materials, need less processing, and are easier to get rid of could have a big impact on the life cycle.[90]

4.11 Eleven Principle:

It is described as renewable in terms of sustainability. Bio-based polymers, wastewater treatment employing natural ecosystems, and recovering biomass feedstock are just a few examples. Despite the fact that all human activities and actions have an impact on the environment, eliminating those behaviours can help to create products, procedures, and systems that are more environmentally friendly. This is more a sign of immaturity than a defect in the product's quality. Mobile phones, personal digital assistants, and laptop computers are frequently retired as fashions change and technology develops, but the actual components are still completely functional and thus valuable. Designing products with recoverable components lowers end-of-life costs and prevents the creation of duplicate components in later product generations. For example, 90% of the time, Xerox equipment is made to be remanufactured. An example of a system is converting old industrial structures into homes.[91]

4.12Twelve Principle:

Renewable resources are employed as opposed to being exhausted. The long-term survivability of products, processes, and systems can be significantly impacted by the source of materials and energy inputs. It has far-reaching effects to determine if a chemical or energy source is renewable or diminishing. Consumption of a finite resource brings the supply closer to exhaustion with each unit used. This cannot be sustained in the definitional sense. In addition, the repetitive extraction processes required to obtain virgin materials create long-term environmental harm. On the other hand, renewable resources can be employed in cycles when the destructive processes are not necessary, or at least not as frequently. Biological materials are frequently referred to as "renewable". However, if the waste output of a process can be recycled, this would surely be considered renewable from the perspective of sustainability if it could be gathered and utilised as an alternative feedstock or recyclable input that retains its value. A few examples include the recovery of biomass feedstock; wastewater treatment using natural ecosystems; and bio-based polymers. A more sustainable supply of goods, services, and systems can be created by lowering behaviours that irreversibly and considerably modify the sustainable supply of a resource, even though all human activities and actions have some impact on the environment. Instead of using finite resources, renewable energy is used. The place where energy and materials come from can have a significant impact on how long a product lasts. From a sustainability standpoint, a material is said to be renewable if it can be recovered and utilised as a replacement feedstock or recyclable input while maintaining its value. Bio-based polymers, wastewater treatment employing natural ecosystems, and recovering biomass feedstock are just a few examples. Despite the fact that all human activities and actions have an impact on the environment, eliminating those behaviours can help to create products, procedures, and systems that are more environmentally friendly.[92]

5. Green chemistry has benefits for the pharmaceutical industry:

5.1Human health: • Cleaner air: Less lung damage from harmful chemical emissions into the environment. • Cleaner water: Drinking and recreational water is cleaner because less hazardous chemical waste is released into the environment. • The chemical industry has made it safer for workers by using fewer hazardous substances, requiring less protective equipment, and lowering the risk of accidents. • A broader range of safer consumer products will be available, some of which will replace few [93]

5.2 Reduced Environment: The phrase "less environment" refers to a situation where a lot of chemicals end up in the environment either intentionally (e.g., pesticides), accidentally (e.g., manufacturing emissions), or as a result of disposal. Green chemicals are recycled or broken down into harmless substances. There is less chance of smog, ozone depletion, or global warming occurring; there is less damage to plants and animals from environmental toxins; and there is less chemical disruption of ecosystems. Reliance on landfills is reduced, especially for hazardous trash.[94]

6.Green chemistry's main purpose is:

to create chemical goods and procedures that minimise or completely do away with the usage of risky and toxic compounds. Due to a shortage of green chemistry, this objective is also the most difficult in terms of effort, cost, and level of expertise to complete. There is no universal agreement on what is regarded as safe, and switching from an outdated, conventional product or process to a new, "green" one takes time. New product and process design is also sometimes difficult and expensive. Another reason for the absence of green chemistry is the high implementation costs, a lack of knowledge, and the absence of any recognized alternatives. Human resources and abilities are not enough to be employed as substitutes for chemical raw materials or green technology **[95]**. The transition to ecofriendly goods and procedures entails risks that are not evenly distributed throughout the supply chain, and funding for further study is scarce. Ionic liquids are seen as having a future in green chemistry. Despite the fact that they are without a doubt helpful, it's increasingly important to consider if chemical synthesis lives up to expectations. Ionic liquids do not appear to be particularly eco-friendly when the 12 principles for identifying green chemicals are used. There is now a school of thought that predicts ionic liquids will be widely used within the next ten years. Ionic liquids are moderately volatile in part because of their low vapors pressure, but this is just one of many factors **[96]** that affect how green a substance actually is. Hazardous liquids based on ions like imidazole and fluoro-anion, for example, cannot evaporate and leak their contents into the environment. This technique makes it simple for ionic liquids to penetrate the biosphere because the majority of them are water soluble.

7.Problems:

In recent decades, the pharmaceutical business has shifted to a new strategy to deal with concerns such as pollution, the use of limited natural resources, and the utilization of renewable sources with long-term sustainability. As a result, applying green chemistry concepts could be considered as a further stumbling obstacle [97]. With growing awareness of environmental pollution and expanded testing processes, the pharmaceutical business is under increased pressure to improve both manufacturing efficiency and product efficacy. The commercialization of green technologies is also limited by capital expenditure. Green process commercialization needs various improvements along the entire long and global supply chain. Going green isn't always the most cost-effective option, but it has been shown to be beneficial in the long run.[98] (Fig-5)

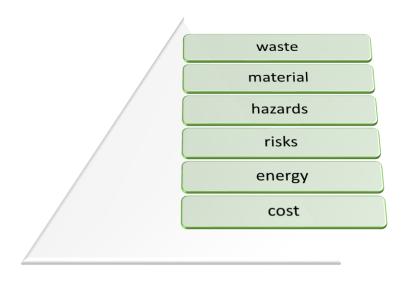


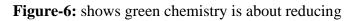
Figure-5: demonstrates the issues and difficulties in green pharmacy (A)Pharmaceutical industries (B), chemical reactions (C), waste generation (D), air pollution (E), environmental pollution (D), environmental challenges (G), environmental laws (H), and IPR

regulations for design implementation (I). For an explanation of the colour references in this figure legend, go to the article's online version.

8. The goal of green chemistry is to reduce:

A manner of thinking and acting that lessens the damaging impacts of pollution on the environment is known as "green chemistry." Green chemistry can also be seen as a method for lowering pollution. **[99,100]** (Fig-6)





9. What advantages come with employing green chemistry??

One cannot overstate how important chemistry is to our daily lives. The development of more environmentally friendly chemical products is necessitated by the fact that technological advancements in the chemical industry also raise fresh environmental issues and potentially harmful side effects. **[101]** A well-known example is the chemical DDT. One of the objectives of green pharmacies is to employ new and appropriate chemicals as well as materials to lessen their harmful effects on the environment. Goal number two is to create procedures that use renewable raw resources rather than nonrenewable ones. 3-Create methods that are less likely to cause explosives, fires, or the release of hazardous materials. 4. Rearranging the order and procedure of chemical transformation to get rid of by-products creates safer products. Sixth, develop items that break down in the environment more quickly than ones that are already on the market. 7-When it comes to chemical processes, it's crucial to keep in mind that using poisonous, long-lasting solvents to extract ants must be kept to a minimum. Improve energy efficiency by creating low-temperature, low-pressure procedures that make use of fresh catalysts. 9-Develop trustworthy and efficient methods for observing processes in order to enhance controls. **[102]**

10. The most typical uses of green pharmacy are as follows:

• Minimal climatic change • Minimal resource depletion • Food access • Environmental friendliness. 11Green Chemistry Abilities:

Innovative techniques, synthesis methodologies, reaction conditions, catalysts, and other green chemistry ideas are being developed by chemists from all over the world. New scholarly studies into different synthesis techniques have been stimulated by commercial applications of green chemistry. Here are a few instances: 1. Phosgene and ethylene chloride have been replaced by biphenyl carbonate in the production of polycarbonates. 2. The most polluting reaction in industry is the oxidation

reaction. Utilizing green chemistry has led to the use of less harmful chemicals, including transition metal complexes with extremely high oxidation states and molecular ozone as the primary oxidant. 3.0 An environmentally friendly tool: acetaldehyde is made by oxidizing ethylene with oxygen in the presence of a catalyst, as opposed to ethanol or acetylene when it is hydrated with HaS04. 4. Traditional methylation processes use toxic alkyl halides or methyl sulphate, but dimethyl carbonate is used instead, leaving no inorganic ions behind. 5.In 1996, Dow Chemical received the Greener Reaction Award for its blowing agent for polystyrene foam production that is made up entirely of carbon dioxide. Polystyrene foam is a typical material for packaging and shipping. Foam sheets have traditionally been made with CFCs and other ozone-depleting chemicals, constituting a significant environmental threat. According to Dow Chemical, supercritical CO is just as effective as a blowing agent. Polystyrene might be recycled more easily if it didn't contain dangerous compounds. because the coy that was used in the process was recycled. The technique produces no net carbon emissions compared to other sectors. 6-Propylene oxide (PO) is a chemical component found in food additives, polyurethane, and detergents. Chlorohydrin, which is used in conventional PO production, yields coproducts like t-butyl alcohol, styrene monomer, and cymene. As a byproduct of its production, a sizable amount of waste is created. In order to create a new method for producing propylene oxide that uses hydrogen peroxide and propylene to eliminate the majority of waste, Dow and BASF worked together. In order to create propylene oxide from hydrogen peroxide and propylene, Dow and BASF collaborated to develop a novel process. Most of the garbage is removed by 7. CFCs have been used as refrigerants in refrigerators and air conditioners for a very long time. The advantages of CFCs include their low toxicity and lengthy shelf life. They offer stability and safe incombustibility, but in the process, they weaken the ozone layer. Other hydro chlorofluorocarbons (HCFCs) and hydro fluorocarbons (HFCs) have largely replaced CFCs in the last ten years. HCFCs and HFCs are certainly safer for the ozone layer. Multi-component substances called "cheats" interact with metal ions to increase solubility. They can be found in a variety of industrial operations and cleaning products. Phosphates and amino carboxylic acids, such as ethylenediaminetetraacetic acid (EDTA), are present in conventional cheaters [103] (e.g., sodium tripolyphosphate). Unfortunately, conventional materials are not appropriate because EDTA is not biodegradable and phosphates are usually thought to be environmentally harmful due to their potential to produce eutrophication. A biodegradable chelating agent comprised primarily of renewable resources has been created by Kazoo Nobel. Tetrasodium N, N-diabetic acid L. The novel chemical glutei acid (GLDA) will be used in automatic dishwashing detergents to replace phosphates. In a technique that produces almost no waste, the flavors enhancer monosodium glutamate is used to create GLDA (MSG). MSG is a renewable resource that is produced from easily accessible corn sugar. Pharmaceutical activities include drug research, manufacturing, prescribing, dispensing, and disposal, all of which cause environmental pollution. On MSG, cyanomethylation of the primary amino nitrogen is followed by in situ alkaline oxidation. All of these methods need to be backed up by ways to keep active pharmaceutical ingredients from getting into the environment.

12.R&D in pharmaceuticals:

The pharmaceutical sector develops and produces pharmaceuticals. The development of new bioactive molecules frequently uses chemical synthesis, which increases the danger of contamination due to the use of a variety of organic and inorganic solvents. To decrease this harmful effect on the environment, chemists have developed the idea of "green chemistry," which can be regarded as environmentally beneficial. Aqueous synthesis, solvent-free synthesis, and enzymes are a few examples of "green chemistry" methods. Another method for creating new therapeutic products while protecting the environment is biotechnology. Pharmaceutical research typically yields a significant number of molecules before an actual medicinal product can be examined and approved. a quantitative structure-activity link assessment that creates the relationship. One method for minimising the number of molecules that are synthesised is to compare the structural and biological characteristics of freshly designed molecules even before they are produced. The creation of medical chemicals that readily biodegrade once they enter the environment, notably water and soil, is another

issue the pharmaceutical business must deal with. Nowadays, phase I (driven by Cytochrome P450) and phase II mechanisms in the liver are used to metabolise pharmaceuticals. In the case of pro-drugs, this transition results in the excretion of more hydrophilic metabolites, but it can also result in the creation of the active molecule. The pharmaceutical business must also develop technology to produce "greener pills" that work therapeutically when needed. Co crystallisation for higher bioavailability, salt production, cyclodextrin encapsulation, and creating amorphous forms for increased solubility are just a few examples. These dosing strategies are also environmentally benign. One such drug that degrades quickly in wastewater treatment due to photodegradability is Valrico acid. Using microbes (Streptomycin sp.) as bioremediation agents, for instance, can help carbamazepine be broken down. If the anticipated ambient concentration of the active pharmaceutical ingredient in water is equal to or more than 1 g/l, producers must submit environmental risk assessments in order to get marketing authorization for new pharmaceutical products. While the Food and Drug Administration recommends 0.01 g/l, the European Medicines Agency does not.[**104**]

13.Dispensing and disposal of pharmaceutical products:

Concerns about the distribution of pharmaceutical active ingredients may be a factor in the rise in environmental pollution, according to numerous studies. Free or inexpensive medicines run the risk of producing an excess of unneeded drugs. Shipments that are advertised to the general public remotely usually end up being lost or destroyed. As a result, some medications are no longer available, while others-like phoney or counterfeit medications-might spread too widely. Patients may not comprehend how to use their medical treatment if labels are inaccurate or handwritten. It is possible to misuse a doctor's prescription. The following risk-mitigation strategies spring to mind in this context: developing databases to track the usage and return of pharmaceutical supplies; as well as employing legible labelling. Outline the proper procedures for implementing patient counselling requirements and legislation governing online pharmacies. Patients also run the risk of contaminating the environment with active prescription ingredients. The accumulation of unused or expired medications and, as a result, their improper disposal can be caused by self-medication, keeping excessive stocks of pharmaceuticals at home, excessive direct-to-consumer advertising, polytherapy, particularly in the elderly, patient noncompliance with medication therapy, and adverse effects. Patients should be informed about the proper use of pharmaceutical products and the proper disposal of leftover or expired medications through education campaigns and take-back activities, also known as pharmaceutical-return programmes.[105]

14.handling of pharmaceutical waste:

There are a few management strategies that should be looked into in order to reduce the environmental impact of pharmaceutical waste. Pharmaceutical waste includes items like used and outdated medications, containers holding pharmaceutical residues (such as blister packs, vials, bottles, and bags), gloves, and masks. Sharp and soft trash, as well as hazardous (infected) and non-hazardous waste, can all be categorized. Due to their extreme mutagenic, teratogenic, and carcinogenic characteristics, cytotoxic medicines are categorised as harmful and geotaxis pharmaceutical waste. Before being properly disposed of, all pharmaceutical waste should be collected in containers with corresponding colours. Pharmaceutical waste is typically disposed of using incineration, a heat treatment technique involving high-temperature burning. Compact waste treatment is an alternative strategy. Sterilization, radiofrequency irradiation, microwave, hot oil systems, and alkaline hydrolysis are all options. Low-temperature gasification (up to 550°C), autoclave, and chemical processing are other options. Due to the high risk of pollution, some disposal techniques, like land filling, open burning, or mechanical destruction, are only used in specific situations. Because people flush unneeded prescriptions down the toilet, wastewater can contain active pharmaceutical compounds. Human medicine almost always causes active pharmaceutical substances to be excreted in urine and faeces, increasing the amount of these substances in wastewater. Despite the fact that most medications cannot be eliminated completely, contaminants can be removed from wastewater using common biological, physical, and chemical techniques. This means that wastewater treatment needs

to be improved in many ways, such as by using coronation, reverse osmosis, ultrafiltration, and carbon-activated sludge from recycled **water [106]**.

Conclusion:

The study of green chemistry is not a recent subject. This new approach to sustainable development is based on the principles of green chemistry. A lot of work still needs to be done to create a perfect strategy that begins with non-polluting components. It goes without saying that the future chemical industry's objective will be to create safer products and procedures using fresh ideas obtained from basic research. The education and training of a new generation of chemists is also essential to the advancement of green chemistry. Encourage green chemistry practises among students at all grade levels. The main objective of each industry is to make money from readily available raw materials, so when it comes to green chemistry education, "The Most Difficult Part of Green Chemistry Is Following Its Rules." comes to mind. The study of green chemistry is not a recent one. It is a new conceptual material and basic capital through long-term industrial activity. Chemical processes must use raw materials, water, and energy in ways that are both environmentally responsible and economically viable in order to meet today's demands without endangering those of future generations. The use of a green chemistry approach, whose goal is to produce chemical processes and products that are safe for both human health and the environment, can help strike a balance between the use of natural resources, economic expansion, and environmental preservation. It takes the proper legislative support in the form of chemical regulation to implement the green chemistry concept, which ensures chemical safety. By reducing or eliminating hazardous or dangerous molecules from the synthesis, manufacture, and use of chemical products, green chemistry aims to reduce or eliminate the use of substances that are harmful to human health and the environment. It is based on twelve principles. While developing a green chemistry process, it tries to apply as many of the twelve principles as possible during various stages of synthesis, even though it is impossible to satisfy the needs of all twelve at once. The objectives of environmental protection and financial gain are achieved by green chemistry in a variety of ways. Biocatalysts, catalysis, and the application of enzymes are a few instances. alternative reaction mediums (water, ionic liquids, and supercritical fluids); alternative renewable raw materials (biomass); and alternative renewable raw materials' conditions of reaction (microwave activation). Thanks to special catalytic reactions and various new catalyst types, catalysis-the cornerstone of green chemistry-offers many advantages in terms of process utilisation, selectivity, energy reduction, and the use of alternative reaction media. The enormous potential of microorganisms and enzymes in the selective transformation of synthetic compounds has thrust biocatalysts to the fore of the "green" programme. The foundation of green chemistry, catalysis, offers a number of benefits in terms of process utilisation, selectivity, energy reduction, and the use of alternate reaction media, thanks to unique catalytic reactions and types of new catalysts. Photocatalytic reactions, which are unique ways of cleaning contaminated air and water, also contribute to this.

References:

- Valavanidis A, Vlachogianni T, Fitrakis K. Laboratory experiments of organic synthesis and decomposition of hazardous environmental chemicals following green chemistry principles. In International Conference "Green Chemistry and Sustainable development", Thessaloniki 2009 (pp. 25- dot et all.
- 2. Begawan AS. Green Chemistry, 12 Principles in Practice Research and Innovations in Chemical Sciences: An Approach towards.:126.
- 3. Margate D. Mechanic-chemical organic reactions without the use of solvents. Kim Ind. 2005;54(7-8):351-8.(https://doi.org/10.1021/acs.chemrev.7b00417)
- 4. Kolb VM. Green organic chemistry and its interdisciplinary applications. CRC Press; 2017 Apr 21.(https://doi.org/10.1201/9781315371856)
- 5. Vojvodić V. Environmental Protection: Green Manufacturing in the Pharmaceutical Industry and Cost Reduction. Kim Ind. 2009;58(1):32-3.

- Riđanović L, Ćatović F, Riđanović S. The Green Chemistry-Ecological Revolution in the Classroom. 8th Research/Expert Conference with International Participations "QUALITY 2013", Neon, B&H, June 06–08, 447-452..
- Juke M, Vorkapić-Furač J, Filipović-Kovačević Ž, Đaković S. Green chemistry open the way for clean ecologically acceptable chemical process. Kemija u industry. 2004 Jan 1; 53(5):217-24. (https://doi.org/10.15255/KUI.2002.046)
- 8. Sheldon RA. Utilisation of biomass for sustainable fuels and chemicals: Molecules, methods and metrics. Catalysis Today. 2011 Jun 10;167(1):3-13..
- 9. Main D, Stanković MI, Petrolia S. Ibuprofen: Gain and Properties, Hem. Ind. 57 (5) 199-214.
- 10. Ivanković A, Dronjić A, Buganda AM, Talia S. Review of 12 principles of green chemistry in practice. Int J Green Energy. 2017;6(3):39-48.
- 11. Anastas PT, Kirchhoff MM, Williamson TC. Catalysis as a foundational pillar of green chemistry. Applied Catalysis A: General. 2001 Nov 30;221(1-2):3-13.
- Zhang Y, Bash BR, Demesne ES. Life cycle assessment of an ionic liquid versus molecular solvents and their applications. Environmental science & technology. 2008 Mar 1;42(5):1724-30. (https://doi.org/10.1021/es0713983)
- 13. Walton T. Solvents and sustainable chemistry. Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2015 Nov 8;471(2183):20150502.(https://doi.org/10.1098/rspa.2015.0502)
- 14. Hill Jar HW, Brady DG. Properties, environmental stability, and melding characteristics of polyphenylene sulphide. Polymer Engineering & Science. 1976 Dec;16(12):831-5.(https://doi.org/10.1002/pen.760161211)
- 15. Samaria C. Use of solvents and environmental friendly materials for applications in Green Chemistry.(https://doi.org/10.6092/UNIBO%2FAMSDOTTORATO%2F2840)
- 16. Kärkkäinen J. Preparation and characterization of some ionic liquids and their use in the demonization reaction of 2-methylpropene. Oulu: University of Oulu; 2007 Mar 9.
- 17. Hoofer MI, Caldera K, Bedford G, Criswell DR, Green C, Herzog H, Jain AK, Kheshgi HS, Licker KS, Lewis JS, Lightfoot HD. Advanced technology paths to global climate stability: energy for a greenhouse planet. science. 2002 Nov 1;298(5595):981-7.
- Garnett T. Fruit and Vegetables & UK Greenhouse Gas Emissions–Exploring the Relationship. Food Climate Research Network. Surrey, UK Centre for Environmental Strategy, University of Surrey. 2006.
- 19. Ivanković A, Elko K, Telic S, Lasik M. Biodegradable packaging in the food industry. J. Food Safe. Food Qual. 2017 Mar 1;68:26-38.
- 20. Ivanković A, Dronjić A, Buganda AM, Talia S. Review of 12 principles of green chemistry in practice. nt J Green Energy. 2017;6(3):39-48.(. doi: 10.11648/j.ijrse.20170603.12)
- 21. Ivanković A, Dronjić A, Buganda AM, Talia S. Review of 12 principles of green chemistry in practice. nt J Green Energy. 2017;6(3):39-48.(doi: 10.11648/j.ijrse.20170603.12)
- 22. Paquette LA, Eds.: P. Anastas, T. Williamson. Green chemistry: Frontiers in benign chemical synthesis and processing.
- 23. Williams RT, editor. Human pharmaceuticals: assessing the impacts on aquatic ecosystems. Allen Press/ACG Publishing; 2005.(https://doi.org/10.3390/toxics10050272)
- 24. Hardwar M, Neel am K. The advantages and disadvantages of green technology. Journal of Basic and Applied Engineering Research. 2015 Oct;2(22):1957-60.
- 25. Sharma H, Mahalaxmi K, Satyannarayana B. 29 An Overview on Importance of Green Chemistry and its uses in Environmental Fields. Research and Innovations in Chemical Sciences: An Approach towards.:236.
- 26. Anastas PT, Warner JC. Green chemistry. Frontiers. 1998;640:1998.
- 27. Amato I. The Slow Birth of Green Chemistry: Government funding, public concern, and tantalizing research problems may finally coax mainstream chemists into lending their skills to environmental protection. Science. 1993 Mar 12;259(5101):1538-41.

- 28. Anastas PT, Kirchhoff MM. Origins, current status, and future challenges of green chemistry. Accounts of chemical research. 2002 Sep 17;35(9):686-94. (https://doi.org/10.1021/ar010065m)
- 29. Anastas PT, Heine LG, Williamson TC. Green chemical syntheses and processes: introduction. (https://doi.org/10.1021/ar010065m)
- 30. Choy YK. 28 years into "Our Common Future": sustainable development in the post-Brundtland world. WIT Transactions on The Built Environment. 2015 Oct 6;168:1197-211.
- 31. Clark JH. Green chemistry: today (and tomorrow). Green Chemistry. 2006;8(1):17-21.
- 32. Knight DJ. EU Regulation of Chemicals: Reach. smothers Rapa Publishing; 2006.
- 33. Hester RE, Harrison RM, editors. Chemicals in the environment: assessing and managing risk. Royal Society of Chemistry; 2006.
- 34. Manger LE. Feedstock's for the Future. Incas Sump. Ser 2006 (Vol. 921, pp. 40-51).
- 35. Ragauskas AJ, Williams CK, Davison BH, Britovsek G, Carney J, Eckert CA, Frederick Jar WJ, Haslett JP, Leak DJ, Iota CL, Myelin JR. The path forward for bio fuels and biomaterials. science. 2006 Jan 27;311(5760):484-9.
- 36. Toma A, Cretan O. Green pharmacy–a narrative review. Cumuli Medical. 2018 Oct;91(4):391.
- 37. Haughton CG, Roomy IS. Green pharmacy and pharmEcovigilance: prescribing and the planet. Expert Review of Clinical Pharmacology. 2011 Mar 1;4(2):211-32.
- 38. Proskurova IO, Kubarieva IV, Yevsieieva LV, Bolder GE. Analysis of handling practice with unused medicines in home first aid kits of the Ukrainian households. Journal of Advanced Pharmacy Education & Research Jul-Sep. 2019;9(3).
- 39. Kreisler J. Greener Pharmacy. Integrative Medicine. 2007;6(4).
- 40. Toured E, Rig B. Knowledge and need assessment on pharmaceutical products in environmental waters. Final report KNAPPE (036864) on specific support action project priority. 2008;1163.
- 41. Kemmerer K. Pharmaceuticals in the environment. Annual review of environment and resources. 2010 Nov 21;35:57-75.
- 42. Baron M. Towards a greener pharmacy by more eco design. Waste and Biomass Valorisation. 2012 Dec;3(4):395-407..
- 43. Haughton CG. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. II. Drug disposal, waste reduction, and future directions. Environmental Health Perspectives. 2003 May; 111 (5):775-85..
- 44. Bustling J. Our common future. By World commission on environment and development (London, Oxford University Press, 1987, pp. 383£ 5.95.).
- 45. National Research Council. Board on Sustainable Development, 1999. Our Common Journey: A Transition towards Sustainability.
- 46. Grade TE, Life RJ. Industrial ecology's first decade. Taking stock of industrial ecology. 2016:3-20.
- 47. Allen DT, Shunned DR. Green engineering: environmentally conscious design of chemical processes. Pearson Education; 2001 Sep 6.
- 48. Keoleian GA, Monterey D. Sustainable development by design: review of life cycle design and related approaches. Air & Waste. 1994 May 1;44 (5):645-68.
- 49. Anastas PT, Zimmerman JB. Peer reviewed: design through the 12 principles of green engineering.
- 50. Hawke P, Loins AB, Loins LH. Natural capitalism: the next industrial revolution Earth scan.
- 51. Anderson RC. Mid-course correction: toward a sustainable enterprise: the interface model. Chelsea Green publishing company; 1998.
- 52. Choi YH, Verpoorte R. Metabolomics: What you see is what you extract. Phytochemical Analysis. 2014 Jul;25(4):289-90.
- 53. Chemat F, Abert Vian M, Ravi HK, Khadhraoui B, Hilali S, Perino S, Fabiano Tixier AS. Review of alternative solvents for green extraction of food and natural products: Panorama, principles, applications and prospects. Molecules. 2019 Aug 19;24(16):3007.

- 54. Henderson RK, Jiménez-González C, Constable DJ, Alston SR, Inglis GG, Fisher G, Sherwood J, Binks SP, Curzons AD. Expanding GSK's solvent selection guide–embedding sustainability into solvent selection starting at medicinal chemistry. Green Chemistry. 2011;13(4):854-62.
- 55. Alfonsi K, Colberg J, Dunn PJ, Fevig T, Jennings S, Johnson TA, Kleine HP, Knight C, Nagy MA, Perry DA, Stefaniak M. Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. Green Chemistry. 2008;10(1):31-6.
- 56. Thorne T. Dictionary of contemporary slang. A&C Black; 2014 Feb 27.
- 57. Jones RB. Use of smokeless tobacco in the World Series, 1986 through 1993. American Journal of Public Health. 1995 Jan;85(1):117-8.
- 58. Prat D, Pardigon O, Flemming HW, Letestu S, Ducandas V, Isnard P, Guntrum E, Senac T, Ruisseau S, Cruciani P, Hosek P. Sanofi's solvent selection guide: A step toward more sustainable processes. Organic Process Research & Development. 2013 Dec 20;17(12):1517-25.
- 59. Daughton CG. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ Health Perspect. 2003;111(5):754–774.
- 60. Daughton CG, Ruhoy IS. Green pharmacy and pharmEcovigilance: prescribing and the planet. Expert Rev Clin Pharmacol. 2011;4(2):211–232.
- 61. International Pharmaceutical Federation (FIP). Green pharmacy practice: Taking responsibility for the environmental impact of medicines 2015. Available from: https://fip.org/files/fip/publications/2015-12-Green-Pharmacy-Practice.pdf.
- 62. Kreisberg J. Greener pharmacy proper medicine disposal protects the environment. Integrative Medicine. 2007;6(4):50–52.
- 63. KNAPPE. Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters, KNAPPE Final Report. 2008 Available from: https://cordis.europa.eu/docs/publications/1245/124584761-6_en.pdf.
- 64. Executive Agency for Health and Consumers. Study on the environmental risks of medicinal products, final report. . 2013 Available from: https://ec.europa.eu/health/sites/health/files/files/ environment/study_environment.pdf.
- 65. Kümmerer K. Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry. Green Chem. 2007;9:899–907.
- 66. Kümmerer K. Pharmaceuticals in the Environment. Annu Rev Environ Resour. 2010;35:57–75.
- 67. Baron M. Towards a Greener Pharmacy by More Eco Design. Waste Biomass Valor. 2012;3:395–407.
- 68. Daughton CG. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. II. Drug disposal, waste reduction, and future directions. Environ Health Perspect. 2003;111(5):775–785.
- 69. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Official Journal of the European Union, L 311/28.11.2001. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1527866260154&uri =CELEX:02001L0083-20121116.
- 70. Directive 2001/82/EC of the European Parliament and of the Council on the community code relating to veterinary medicinal products. Official Journal of the European Union, L 311/28.11.2001. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1527866863497&uri=CELEX:0200 1L0082-20090807.
- 71. Amiard-Triquet C, Amiard JC, Mouneyrac C. Aquatic ecotoxicology. Advancing tools for dealing with emerging risks. 1st ed. Academic Press; 2015.
- 72. Heberer T. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol Lett. 2002;131:5–17.
- 73. Kummerer K. The presence of pharmaceuticals in the environment due to human use--present knowledge and future challenges. J Environ Manage. 2009;90:2354–2366.

- 74. Zhang Y, Geissen SU. Prediction of carbamazepine in sewage treatment plant effluents and its implications for control strategies of pharmaceutical aquatic contamination. Chemosphere. 2010;80:1345–1352.
- 75. Caracciolo AB, Grenni P, Falconi F, Caputo MC, Ancona V, Uricchio VF. Pharmaceutical waste disposal: assessment of its effects on bacterial communities in soil and groundwater. Chem Ecol. 2011;27:43–51.
- 76. Repice C, Dal Grande M, Maggi R, Pedrazzani R. Licit and illicit drugs in a wastewater treatment plant in Verona, Italy. Sci Total Environ. 2013;463-464:27–34.
- 77. Gamarra JS Jr, Godoi AF, de Vasconcelos EC, de Souza KM, de Oliviera CM. Environmental Risk Assessment (ERA) of diclofenac and ibuprofen: a public health perspective. Chemosphere. 2015;120:462–469.
- 78. Owens B. Pharmaceuticals in the environment: a growing problem. The Pharmaceutical Journal. 2015 . Available from: https://www.pharmaceutical-journal.com/news-andanalysis/ features/pharmaceuticals-in-the-environment-a-growing-problem/20067898.article.
- 79. Brandt KK, Amézquita A, Backhaus T, Boxall A, Coors A, Heberer T, et al. Ecotoxicological assessment of antibiotics: A call for improved consideration of microorganisms. Environ Int. 2015;85:189–205.
- 80. Meffe R, de Bustamante I. Emerging organic contaminants in surface water and groundwater: a first overview of the situation in Italy. Sci Total Environ. 2014;481:280–295.
- 81. Bu Q, Wang B, Huang J, Deng S, Yu G. Pharmaceuticals and personal care products in the aquatic environment in China: a review. J Hazard Mater. 2013;262:189–211.
- 82. Oldenkamp R, Huijbregts MA, Hollander A, Ragas AM. Environmental impact assessment of pharmaceutical prescriptions: Does location matter? Chemosphere. 2014;115:88–94.
- 83. Eissen M, Backhaus D. Pharmaceuticals in the environment: an educational perspective. Environ Sci Pollut Res Int. 2011;18:1555–1566.
- 84. Brown KD, Kulis J, Thomson B, Chapman TH, Mawhinney DB. Occurrence of antibiotics in hospital, residential, and dairy effluent, municipal wastewater, and the Rio Grande in New Mexico. Sci Total Environ. 2006;366(2-3):772–783.
- 85. Agunbiade FO, Moodley B. Occurrence and distribution pattern of acidic pharmaceuticals in surface water, wastewater, and sediment of the Msunduzi River, Kwazulu-Natal, South Africa. Environ Toxicol Chem. 2016;35(1):36–46.
- 86. Al-Khazrajy OS, Boxall AB. Risk-based prioritization of pharmaceuticals in the natural environment in Iraq. Environ Sci Pollut Res Int. 2016;23(15):15712–15726.
- 87. Calisto V, Esteves VI. Psychiatric pharmaceuticals in the environment. Chemosphere. 2009;77:1257–1274.
- 88. Chen Y, Yu G, Cao Q, Zhang H, Lin Q, Hong Y. Occurrence and environmental implications of pharmaceuticals in Chinese municipal sewage sludge. Chemosphere. 2013;93:1765–1772.
- 89. Chitescu CL, Kaklamanos G, Nicolau AI, Stolker AA. High sensitive multiresidue analysis of pharmaceuticals and antifungals in surface water using U-HPLC-Q Exactive Orbitrap HRMS. Application to the Danube river basin on the Romanian territory. Sci Total Environ. 2015;532:501–511.
- 90. Evans S, Bagnall J, Kasprzyk-Hordern B. Enantiomeric profiling of a chemically diverse mixture of chiral pharmaceuticals in urban water. Environ Pollut. 2017;230:368–377.
- 91. Fent K, Weston AA, Caminada D. Ecotoxicology of human pharmaceuticals. Aquat Toxicol. 2006;76:122–159.
- 92. Isidori M, Lavorgna M, Nardelli A, Parrella A, Previtera L, Rubino M. Ecotoxicity of naproxen and its phototransformation products. Sci Total Environ. 2005;348:93–101.
- 93. Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ. Illicit drugs and pharmaceuticals in the environment--forensic applications of environmental data. Part 1: Estimation of the usage of drugs in local communities. Environ Pollut. 2009;157:1773–1777.

- 94. Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ. Illicit drugs and pharmaceuticals in the environment--forensic applications of environmental data, Part 2: Pharmaceuticals as chemical markers of faecal water contamination. Environ Pollut. 2009;157:1778–1786.
- 95. Kosjek T, Heath E. Occurrence, fate and determination of cytostatic pharmaceuticals in the environment. Trends Anal Chem. 2011;30(7):1065–1087.
- Lees K, Fitzsimons M, Snape J, Tappin A, Comber S. Pharmaceuticals in soils of lower income countries: Physico-chemical fate and risks from wastewater irrigation. Environ Int. 2016;94:712– 723.
- 97. Li WC. Occurrence, sources, and fate of pharmaceuticals in aquatic environment and soil. Environ Pollut. 2014;187:193–201.
- Lissemore L, Hao C, Yang P, Sibley PK, Mabury S, Solomon KR. An exposure assessment for selected pharmaceuticals within a watershed in Southern Ontario. Chemosphere. 2006;64: 717– 729.
- 99. Lolić A, Paíga P, Santos L, Ramos S, Correia M, Delerue-Matos C. Assessment of non-steroidal anti-inflammatory and analgesic pharmaceuticals in seawaters of North of Portugal: occurrence and environmental risk. Sci Total Environ. 2015;508:240–250.
- 100.Moldovan Z, Schmutzer G, Tusa F, Calin R, Alder AC. An overview of pharmaceuticals and personal care products contamination along the river Somes watershed, Romania. J Environ Monit. 2007;9:986–993.
- 101.Riva F, Zuccato E, Castiglioni S. Prioritization and analysis of pharmaceuticals for human use contaminating the aquatic ecosystem in Italy. J Pharm Biomed Anal. 2015;106:71–78.
- 102.Scott TM, Phillips PJ, Kolpin DW, Colella KM, Furlong ET, Foreman WT, et al. Pharmaceutical manufacturing facility discharges can substantially increase the pharmaceutical load to U.S. wastewaters. Sci Total Environ. 2018;636:69–79.
- 103.Shraim A, Diab A, Alsuhaimi A, Niazy E, Metwally M, Amad M, et al. Analysis of some pharmaceuticals in municipal wastewater of Almadinah Almunawarah. Arab J Chem. 2017;10:719–29.
- 104. Van De Steene JC, Stove CP, Lambert WE. A field study on 8 pharmaceuticals and 1 pesticide in Belgium: removal rates in waste water treatment plants and occurrence in surface water. Sci Total Environ. 2010;408:3448–3453.
- 105.Vazquez-Roig P, Andreu V, Blasco C, Picó Y. Risk assessment on the presence of pharmaceuticals in sediments, soils and waters of the Pego–Oliva Marshlands (Valencia, eastern Spain). Sci Total Environ. 2012;440:24–32.
- 106. Wen ZH, Chen L, Meng XZ, Duana YP, Zhang ZS, Zeng EY. Occurrence and human health risk of wastewater–derived pharmaceuticals in a drinking water source for Shanghai, East China. Sci Total Environ. 2014;490:987–993.
- 107.Zuccato E, Castiglioni S, Fanelli R. Identification of the pharmaceuticals for human use contaminating the Italian aquatic environment. J Hazard Mater. 2005;122:205–209. 50. Jones OA, Lester JN, Voulvoulis N. Pharmaceuticals: a threat to drinking water? Trends Biotechnol. 2005;23:163–167.
- 108.Burns EE, Carter LJ, Kolpin DW, Thomas-Oates J, Boxall ABA. Temporal and spatial variation in pharmaceutical concentrations in an urban river system. Water Res. 2018;137:72–85.
- 109.Puckowski A, Mioduszewska K, Łukaszewicz P, Borecka M, Caban M, Maszkowska J. et al. Bioaccumulation and analytics of pharmaceutical residues in the environment: A review. J Pharm Biomed Anal. 2016;127:232–255.
- 110.Rice J, Proctor K, Lopardo L, Evans S, Kasprzyk-Hordern B. Stereochemistry of ephedrine and its environmental significance: exposure and effects directed approach. J Hazard Mater. 2018;348:39–46.
- 111.Barra Caracciolo A, Topp E, Grenni P. Pharmaceuticals in the environment: biodegradation and effects on natural microbial communities. A Review. J Pharm Biomed Anal. 2015;106:25–36.

- 112.Kodešová R, Kočárek M, Klement A, Golovko O, Koba O, Fér M, et al. An analysis of the dissipation of pharmaceuticals under thirteen different soil conditions. Sci Total Environ. 2016;544:369–381.
- 113.Alygizakis NA, Gago-Ferrero P, Borova VL, Pavlidou A, Hatzianestis I, Thomaidis NS. Occurrence and spatial distribution of 158 pharmaceuticals, drugs of abuse and related metabolites in offshore seawater. Sci Total Environ. 2016;541:1097–1105.
- 114.Brambilla G, Testa C. Food safety/food security aspects related to the environmental release of pharmaceuticals. Chemosphere. 2014;115:81–87. 58. He BS, Wang J, Liu J, Hu XM. Eco-pharmacovigilance of non-steroidal anti-inflammatory drugs: necessity and opportunities. Chemosphere. 2017;181:179–189.
- 115.Carlier L, Baron M, Chamayou A, Couarraze G. Greener pharmacy using solvent-free synthesis: Investigation of the mechanism in the case of dibenzophenazine. Powder Technol. 2013;240:41– 47.
- 116.Ott D, Kralisch D, Denčić I, Hessel V, Laribi Y, Perrichon PD, et al. Life cycle analysis within pharmaceutical process optimization and intensification: case study of active pharmaceutical ingredient production. ChemSusChem. 2014;(12):3521–3533.