

Introduction of green chemistry

The accelerated progress in science and technology nowadays has led to economic development in the world, but such economic development also causes environmental degradation which is manifested by climate change, the emergence of ozone holes and the accumulation of destructive organic pollutants in all parts of biospheres. So, the present situation required a solution to balance the use of natural resources and environmental conservation. In the last two decades, awareness of environmental protection has increased by using the concept of "Green Chemistry".

Green or Sustainable chemistry is defined as a branch of science which utilizes a set of principles for the invention, design, development and implementation of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. The processes of green chemistry developed to date include mainly all areas of chemistry, including organic, inorganic, biochemical, polymeric, toxicological, environmental, physical, technological, etc. The approach in chemistry is to protect human health and the environment and it represents a significant departure from the traditional methods previously used. Green chemistry addresses the various hazards that can be caused by the chemicals, which include physical hazards (being explosive or flammable), toxicity (being carcinogenic or cancer-causing, or lethal), or global hazards (climate change or stratospheric ozone depletion). Green chemistry applies across the life cycle of a chemical product, including its synthesis (the path to making chemicals), manufacture (the actual making of chemicals), and ultimate disposal. Molecular structures of the chemicals decide their properties, which can be modified by changing the structures of the chemicals.

Prior to green chemistry, the main aim was to minimize exposure to chemicals, but green chemistry emphasizes the design and creation of chemicals that are not hazardous to people or the environment. It has been applied to a wide range of industrial and consumer goods, including paints, dyes, fertilizers, pesticides, plastics, medicines, electronics, dry cleaning, energy generation, water purification, etc. Its concept is aimed at the promotion and development of future sustainable ways of life in which guiding principles and trends of green chemistry are observed not only for their basic benefits to the environment or health but also to advance new technologies/sciences, generations, and jobs.

The goals of green chemistry in environmental protection and economic profit are achieved through several dominant directions such as catalysis, biocatalysts, the use of alternative renewable raw materials (biomass), alternative reaction media (water, and supercritical fluids), alternative reaction conditions (microwave activation, and ultrasound) as well as new photo catalytic reactions. Foremost, among the essential changes are the demands of shifting energy production and chemical fabrication from a fossil resource to a renewable biomass or bioenergy feedstock.



Origin of green chemistry


The term green chemistry was first given by Paul T. Anastas an organic chemist working in the Office of Pollution Prevention and Toxins at the Environmental Protection Agency (EPA), and John C. Warner who developed the twelve principles of Green Chemistry in which the early origins of pollution control and hazard awareness of pollution were observed. In this time period, Environmental Protection Agency evolved with strict command and control with end-of-the-pipe-line technology to active efforts to prevent pollution before it happened with risk analysis early in the process. Green chemistry includes a new approach to the synthesis, processing and application of chemical substances in such a manner to reduce scourge to health and the environment like; Clean Chemistry, Atom Economy, and Environmentally benign chemistry.

The next time period was between 1993 and 1998. During this time, a frame of chemical philosophy evolved. It is a combination of several chemical concepts and a conceptual framework that can be used in the design of chemical processes to achieve environmental and economic goals by way of preventing pollution. This comprises ambient reaction conditions, renewable feedstocks and minimization of reaction steps.

The third time period was from 1999 to now which has seen an explosion of green chemistry based on scientific articles.

Genesis of the Green Chemistry Movement:

- The Pollution Prevention Act of 1990.
- Mandated a national policy of *preventing pollution* rather than treating it once it is formed.



Anastas, P. A. & Warner, J. C. (1998).

Advantages and disadvantages of green chemistry

Advantages

- Plants and animals suffer less harm from toxic chemicals in the environment.
- Lower potential for global warming, ozone depletion, and smog formation.
- Less chemical disruption of ecosystems.
- Less use of landfills, especially hazardous waste landfills.

Disadvantages

- High implementing costs.
- Lack of information.
- No known alternative to chemical raw material or alternative process technology.
- Lack of human resources and skills.
- Requirement of time.

Principles of green chemistry

Green Chemistry is a rapidly developing and important area in the chemical sciences. It aims to protect the environment not by cleaning up, but by inventing new chemical processes that do not pollute the environment. It is the utilization of a set of principles developed by Paul Anastas and John Warner that will help to reduce the use and generation of hazardous substances during the manufacture and application of chemical products. The principles of green chemistry include:















-  Prevention of waste
-  Increment of atom economy
-  Less hazardous chemical syntheses
-  Design safer chemical
-  Safer solvent and auxiliaries
-  Design for energy efficiency
-  Usage of renewable feedstocks
-  Reduce derivatization
-  Catalysis process
-  Design for degradation
-  Real-time analysis for pollution prevention
-  Inherently safer chemistry for accident prevention

Figure1. Twelve principles of green chemistry.

1. Prevent waste

The first principle of green chemistry deals with the design of chemical synthesis to prevent waste (Leave no waste to treat or clean up) than to treat or clean up waste after it has been created. Waste can be defined as the production of any material that does not have realized value or the loss of unutilized energy. It is the prevention of waste generation, which is more favourable for humans and the environment, and ultimately cheaper than treating waste and destroying it after it has emerged. Organic waste, which is harmful to humans and the environment, is primarily produced at certain stages of synthesis, so-called "Dirty reactions" where toxic reactants and solvents are used, and due to the harsh reaction conditions, a large number of toxic byproducts are formed. These are the most common basic reactions of organic synthesis (halogenation, oxidation, alkylation, nitration and sulfonation) that are applied in different industrial branches.

This is often measured by the E-factor or environmental impact factor, presented by Roger Sheldon and defined as the ratio of the total mass of waste (byproducts) from the process per total mass of product. The E factor takes into account waste byproducts, leftover reactants, solvent losses, spent catalysts and catalyst supports, and anything else that can be regarded as waste. A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero.

Table 1. E-factor in the chemical industry.

Industry	Product tonnage	E-factor (Kg waste per kg product)	Waste produced (t)
Oil Refinery	$10^6 - 10^8$	0.1	$10^5 - 10^7$
Bulk chemicals	$10^4 - 10^6$	< 1- 5	$10^4 - 5 \times 10^6$
Fine chemicals	$10^2 - 10^4$	5 - 50	$5 \times 10^2 - 5 \times 10^5$
Pharmaceuticals	$10 - 10^3$	25 - 100	$2.5 \times 10^2 - 10^5$

For example, a large amount of waste is coproduced during drug manufacturing (more than 100 kilos per kilo of active pharmaceutical ingredient (API) in many cases). However, when companies applied green chemistry principles to the design of the API process, dramatic reductions in waste are often achieved, sometimes as much as tenfold. A good example is the new "green" production process of sertraline by which the introduction of more benign solvent ethanol as the sole solvent eliminates the need to use distillation and recovery of four solvents (methylene chloride, tetrahydrofuran, toluene and hexanes) resulting in a reduction in solvent consumption from 250 to 25 litres per kg of sertraline. By eliminating waste, reducing solvents, and maximizing the yield of key intermediates, green chemistry has demonstrated significant innovation in the manufacture of an important pharmaceutical agent.

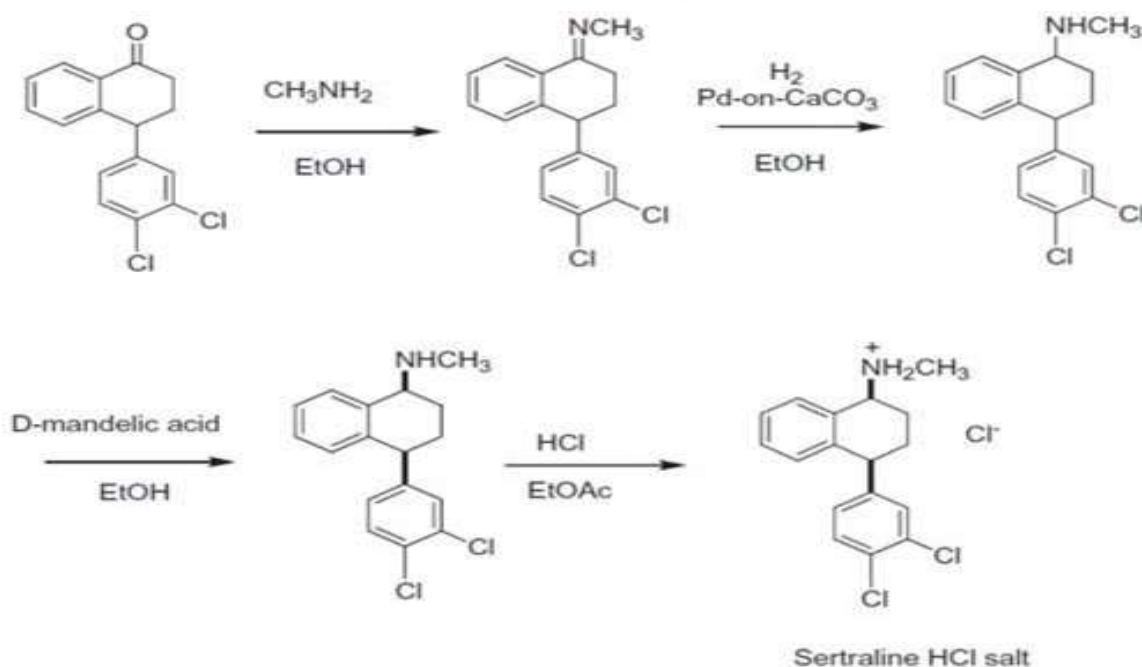


Figure 2. Green synthesis of sertraline

2. Maximize atom economy

The second principle of green chemistry can be simply stated as the "atom economy" also known as the atom efficiency of a reaction. Atom economy, which was developed by Barry Trost of Stanford University (USA), for which he received the Presidential Green Chemistry Challenge Award in 1998, asks the question "what atoms of the reactants are incorporated into the final desired product(s) and what atoms are wasted?". Therefore, atom economy targets the design synthesis so that

the final product contains the maximum proportion of the starting materials. Thus, chemists must not only strive to achieve maximum percent yield, but also design synthesis that maximizes the incorporation of the atoms of the reactants into the desired product.

$$\% \text{ Atom economy} = \frac{\text{Molar mass of desired product}}{\text{Molar mass of all reactants}} \times 100$$

The synthesis of Ibuprofen is an example of maximising the atom economy. The main problem of the old synthesis was the utilization of input raw materials was only about 40% and consists of six synthetic steps. While the new "green" method of ibuprofen synthesis involves only three steps, and 80% of input raw material was utilized.

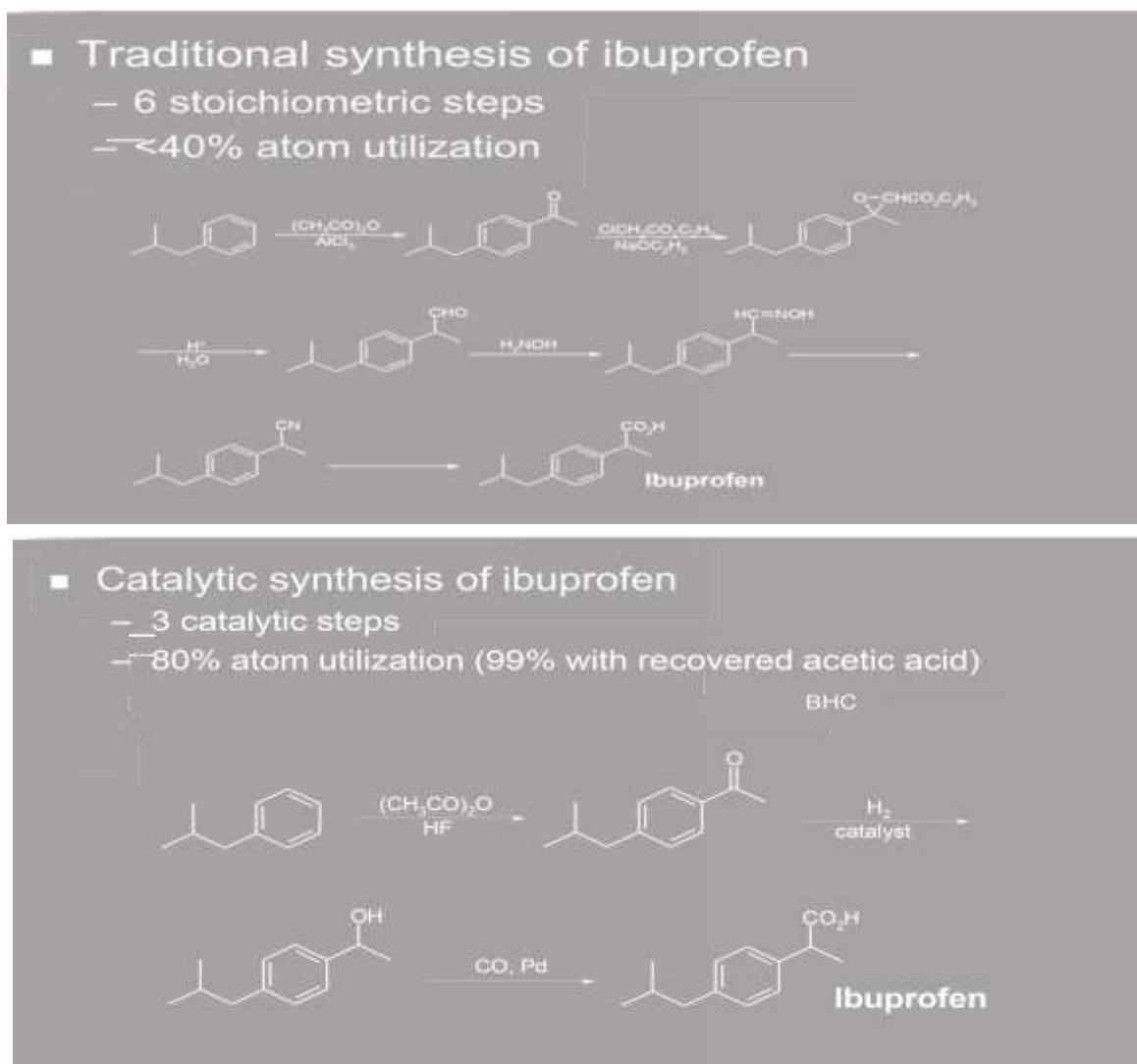


Figure 3. Comparison of classic and the green synthesis of ibuprofen.

3. Design less hazardous chemical synthesis

The third principle of green chemistry targets to use and generate substances with little or no toxicity to either humans or the environment. Chemists use toxic substances all the time and unless—and until—replacement chemicals along with new synthetic protocols are developed, inherently toxic materials will continue to be used.



Reactions based on rearrangement, cycloaddition or multi-component coupling reactions were already known and constituted one category of efficient reactions. Cascade or tandem reactions metathesis, C–H activation, and enzymatic reactions are rather new approaches and demonstrate good examples of cleaner, more efficient synthetic tools available to organic chemists. For example, a new polycarbamate (which is a category of organic compounds) synthesis process is conceptually simple and is based on the substitution of toxic carbonyl dichloride (COCl_2) with CO_2 . This procedure also consequences in the removal of dichloromethane (CH_2Cl_2) as a solvent. The total reaction contains ethylene oxide ($\text{C}_2\text{H}_4\text{O}$), CO_2 and bisphenol-A ($\text{C}_{15}\text{H}_{16}\text{O}_2$) to produce polycarbamate and ethylene glycol $\text{C}_2\text{H}_6\text{O}_2$ as shown below.

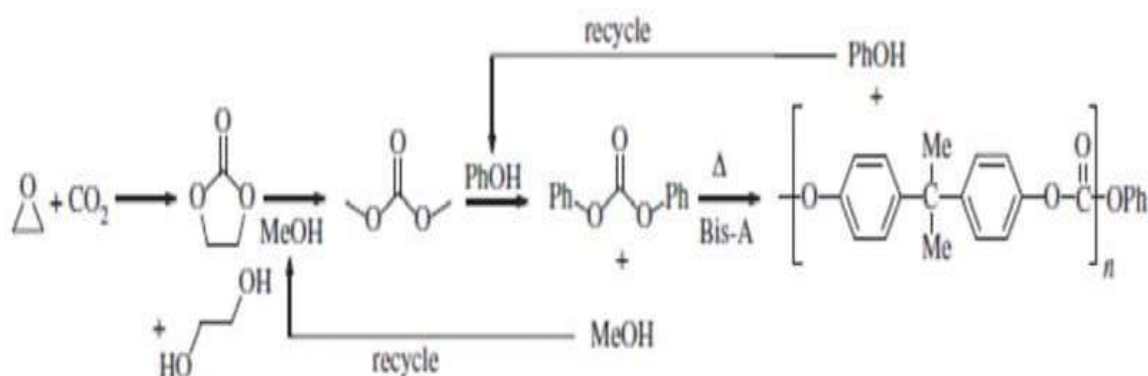


Figure 4. Synthesis of polycarbamate.

4. Design safer chemicals and products

The fourth principle of green chemistry purposes is that chemical products should be designed to preserve the efficiency of function while reducing toxicity. Minimizing toxicity, while keeping function and efficiency can be considered one of the most challenging parts of designing safer products and processes, and achieving that requires understanding not only chemistry but also the principles of toxicology and environmental science. Moreover, the goal of producing safe chemicals (non-carcinogenic, mutagenic, and neurotoxic) is the equilibrium between optimal performance and chemical product function, confirming that toxicity and hazard are reduced to the lowest possible level. In other words, the use of toxic chemicals should be avoided and replaced wherever possible, however, should take into account their efficacy.

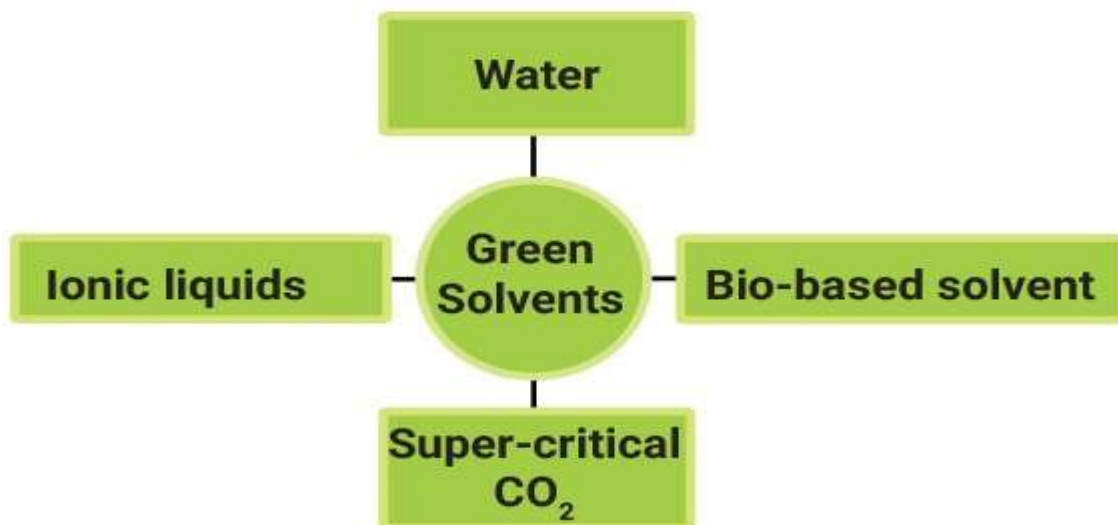


This principle has been used in the development of new pesticides which are specific to target organisms, for instance, they are toxic only to target organisms and decompose into environmentally harmless substances. An additional example is the use of highly toxic organic tin-based organic compounds (Sn), earlier coated on the outside to prevent the capture of seaweed and plankton. These organic compounds have been replaced by a non-toxic product called Sea-Nine. Another example is the production of polymers of polyphenylene sulfone (PPSU), which is nowadays widely used for indoor airplanes, it is also introduced in underground trains where it is a significant to use non-flammable materials. It is a new engineering plastic characterised by a novel combination of useful environmental, mechanical, and flame-resistant properties.

5. Use safer solvents and reaction conditions

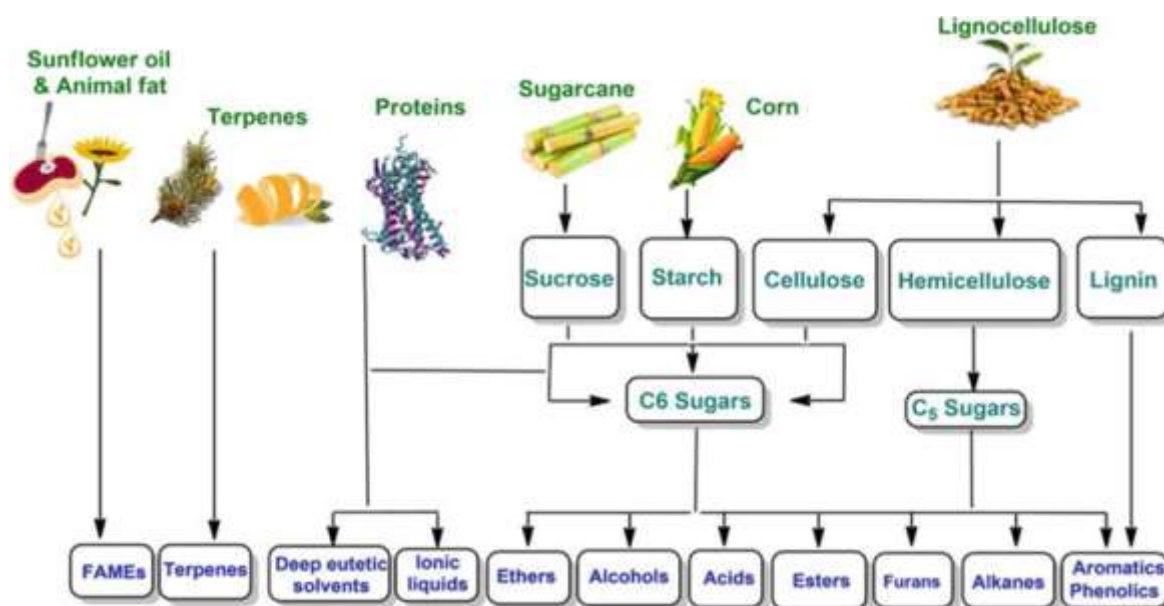
The fifth principle of green chemistry aims to avoid using solvents, separation agents, or other auxiliary chemicals. Solvents are possibly the most active area of green chemistry research. They characterize as an important challenge for green chemistry as they often account for the vast majority of mass wasted in synthesis and processes. It accounts for 50 – 80 percent of the mass in a standard batch chemical operation. Solvents and mass separation agents also drive most of the energy consumption in a process as it is alternately heated, distilled, cooled, pumped, mixed, filtered, etc. Also, solvents are the major contributors to the overall toxicity profile. On the other hand, they contribute to the greatest concern for process safety issues because they are flammable and volatile, or under the right conditions, explosive such as alcohol, benzene (known carcinogenic), CCl_4 , CHCl_3 , perchloroethylene, CH_2Cl_2 . They generally drive workers to do personal protective equipment of one kind or another.

To address all those shortcomings, chemists started a search for safer and solvent-free fewer systems that utilize bio-based solvent, water, ionic liquid, and supercritical fluids (SCF) which are some of the examples of those new “green” answers. Green solvents have been distinguished for their low toxicity, low miscibility in water, easy biodegradability under environmental conditions, high boiling point, not easily evaporating, low offensive smell, health problems to workers and ease to recycle after use.



One of the green solvents is supercritical carbon dioxide (scCO₂). As a reaction medium, the attractive physical and toxicological inertness properties of supercritical carbon dioxide (scCO₂) have made it superior to conventional organic solvents. First, scCO₂ has liquid-like density and gas-like viscosity and consequently leads to high solubility and rapid mass transfer velocity. Secondly, a slight change of pressure, especially near the critical point of scCO₂ enables the solvent properties such as density, viscosity, diffusivity and polarity to change constantly from approximate gaseous to a similar liquid state. Thirdly, separating scCO₂ from the reaction mixture is energy-efficient and a product can be obtained by simple treatment. More importantly, scCO₂ is inexpensive, nonflammable, nontoxic, environmentally friendly and one of the reaction media, which is favored for green chemistry research. At present, scCO₂ has been used as a medium in the following chemical reactions: enzyme-catalyzed reactions, polymerization, radical reactions, cyclo-addition reactions, transition metal-catalyzed reactions and so on.

Making use of renewable resources in producing solvents is a promising and important strategy to move towards sustainable chemical processing and replace organic solvents derived from fossil raw materials. In the end, bio-based feedstock such as carbohydrates, carbohydrate polymers, proteins, alkaloids, plant oils and animal fats have been used to produce bio-based solvents. This often requires prior processing of the raw materials to give familiar solvents or to provide completely new and innovative solvent entries, such as essential oils extracted from citrus peels (which are rich in terpenes), that are used directly. The main processing methods include biochemical and thermochemical conversion. Using one or a combination of these processing techniques, several classes of bio-based solvents (including alcohols, esters, ethers, alkanes, aromatics and neoterics) can be manufactured.



Ionic liquids (ILs) are a group of interesting compounds that have been known for more than a century, attracting major attention within the last two decades. ILs are normally defined as compounds with a melting point determined to be below 100°C. They are composed of ions and, thus, each IL possesses unique properties that are the effect of a cation and an anion's nature. However, in general, ILs are characterized by a low melting point, high thermal and chemical stability, non-flammability and negligible vapor pressure. Density and viscosity, as well as many other properties, can easily be tuned as they are dependent on the chemical structure of the ILs.



6. Increase energy efficiency

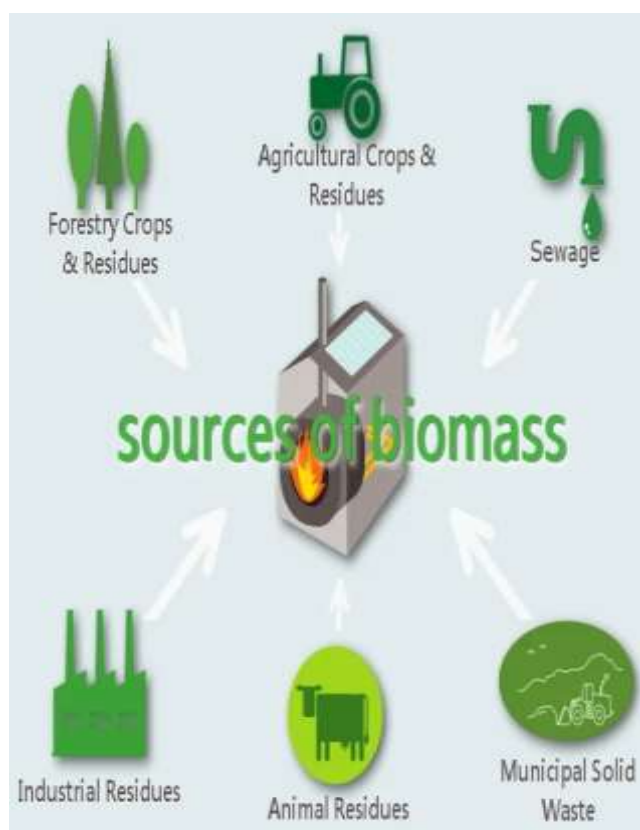
The sixth principle of green chemistry aims to conduct chemical reactions at room temperature and pressure whenever possible. The design of chemical reactions that do not involve intensive energy use is highly desirable. Dropping the energy barrier of a chemical reaction or choosing suitable reactants so that the transformation may proceed at room temperature is one example of what chemists can do in order to reduce energetic requirements, with all the direct and indirect benefits accompanying it. Energy is a key issue in the 21st century. A majority of the energy that is produced is based on and will continue to be based on fossil fuels. Therefore, alternative energies are wanted. Several of those renewable energies have been recognised in biofuel production, including solar power (thermal and photovoltaic), wind power, geothermal energy, hydropower, and hydrogen fuel cells. Green chemists have a significant role to play in this new challenge as they can design both energy-efficient transformations and chemical systems that can be used to harvest some of those renewable natural energies.



Solar energy is considered the primary sustainable energy source on earth and is considered an alternative to petroleum. Considerable efforts have been dedicated to design chemical systems to convert solar radiation into voltaic energy. Also, organic, inorganic, and hybrid solar cells have paid attention due to their higher efficiency. The main principle of those cells depends on the ability of the material used to absorb photonic energy from solar radiation. The absorption causes the formation of excited states which can be relayed and generate electronic current. In the same word, building materials that can efficiently transform light into current remains a challenge and are key to the achievement of this approach.

7. Use renewable feedstocks

The seventh principle of green chemistry advocates the use of starting materials (also known as feedstocks) such as agricultural products or the wastes of other processes that are renewable rather than depletable feedstocks (petroleum, natural gas, or coal) or mining operations. In the past 10 years, significant advances have been made in the development of fuels, chemicals and materials from renewable feedstocks. These for example, have included biodiesel from plant oils and algae, bioethanol and butanol from sugars and lignocellulose, plastics, foams and thermosets from lignin and plant oils, and even electronic materials from chicken feathers. Also, Coca-Cola, a worldwide company, for the time being, makes bottles made of 30% polyethylene (PE) blends, however, American company Nature Works uses bottles made from lactic acid polymers made from lactic acid, obtained by fermentation of dextrose obtained from starch, most commonly corn.



8. Avoid or reduce chemical derivatives

The eighth principle of green chemistry focuses on avoiding or reducing unnecessary derivatization such as blocking groups, protection/deprotection, and temporary modification of physical/chemical processes because such steps require additional reagents and can generate waste. One of the best ways of doing this is the use of enzymes. Enzymes are so specific that they can often react with one side of the molecule and leave the rest of the molecule alone hence protecting groups are often not required. A typical example is the production of antibiotics based on penicillin or the replacement of classical chemical enzymatic processes whereby the 6-aminopenicillic acid is obtained by reacting with the catalyzed immobilized enzyme penicillin amide. This resulted in several chemical steps being replaced by an enzymatic reaction, and no longer required a low temperature (-60°C), organic solvents, and completely unsuitable conditions that increased and complicated production in the case of chemical synthesis.

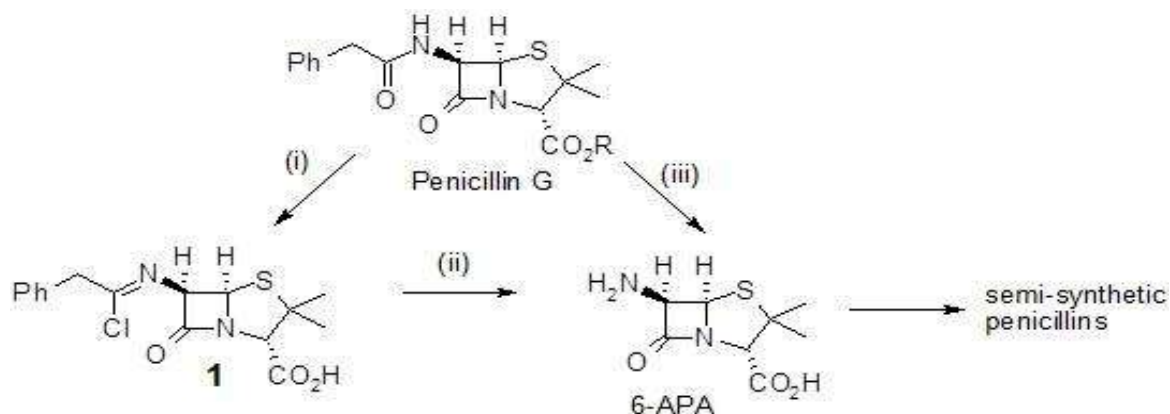


Figure 5. Synthesis of 6-aminopenicillic acid catalyzed by immobilized penicillin G amide.

9. Use catalysts, not stoichiometric reagents

The ninth principle of green chemistry intends to minimize waste by using catalytic reactions. Catalysis offers numerous green chemistry advantages including lower energy necessities, catalytic against stoichiometric quantity of materials, enhanced selectivity, decreased use of processing and separation agents, and permit

the use of less hazardous materials. Catalysts are effective in small amounts and can carry out a single reaction many times. For example, the reduction of a ketone to the corresponding secondary alcohol using sodium borohydride or molecular hydrogen as the reductant. Reduction with the former has an atom economy of 81% while reduction with the latter is 100% atom economic that is everything ends up in the product and, in principle, there is no waste. Unfortunately, hydrogen does not react with ketones to any extent under normal conditions. For this, we need a catalyst such as palladium-on-charcoal. A catalyst is defined as *“a substance that changes the velocity of a reaction without itself being changed in the process”*. It lowers the activation energy of the reaction but in so doing it is not consumed. This means that in principle at least, it can be used in small amounts and be recycled indefinitely, and it doesn't generate any waste. Moreover, molecular hydrogen is also the least expensive reductant and, for this reason, catalytic hydrogenations are widely applied in the petrochemical industry, where the use of other reductants is generally not economically viable.

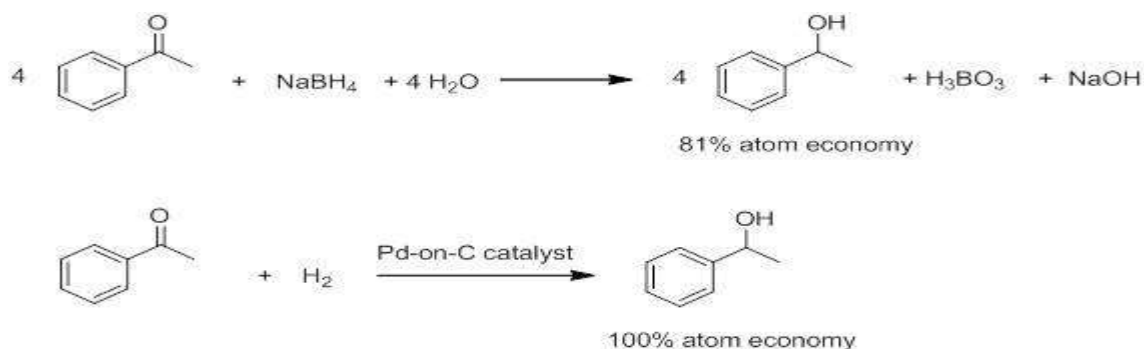


Figure 6. Atom Economy Reaction with Catalyst.

10. Design chemicals and products to degrade after use

The tenth principle of green chemistry targets the design of chemical products to break down into innocuous substances after use so that they do not accumulate or persist in the environment. Biodegradation, hydrolysis, and photolysis can be used to design chemical products. In the same way that mechanistic toxicology knowledge is essential to identify and design molecular features that are the basis for hazards, an understanding of the mechanisms of degradation and persistence is required to design chemical features that promote degradation and eliminate features that promote persistence. Branched chains, halogenated moieties, quaternary carbons, tertiary

amines, and certain heterocycles are some chemical structures examples of persistent compounds.

Many of the synthetic polymer chemicals that are used on a daily basis such as those found in plastics, rubber, soap /detergents and electronic products (including batteries) are not environmentally friendly because they don't degrade easily after they're used. Therefore, Chemist aimed to use alternative feedstocks or polymers to fulfil the purpose of green chemistry such as the use of biodegradable plastics including starch-based plastics, Soy-based plastics, Cellulose-based plastics, and Lignin-based plastics that are made from polymers derived from naturally-occurring materials like cellulose, starch, and collagen that degrade into non-toxic components.



12. Minimize the potential for accidents

The twelfth principle of green chemistry which is known as the "Safety Principle" purpose is to design chemicals and their physical forms (solid, liquid, or gas) used in a chemical process to minimize the potential for chemical accidents including explosions, fires, and releases to the environment. Safety can be defined as the controlling of known hazards via achieving an acceptable level of risk and is achieved at some levels of the lowest use of personal protective equipment.

The graphic shows that the most effective means of increasing safety is eliminating the hazard component, which results in safer conditions for workers. The manufacturing or laboratory worker is often the first in-line person to benefit from hazard reductions, a safer environment for the general public, and a safer planet for us all.

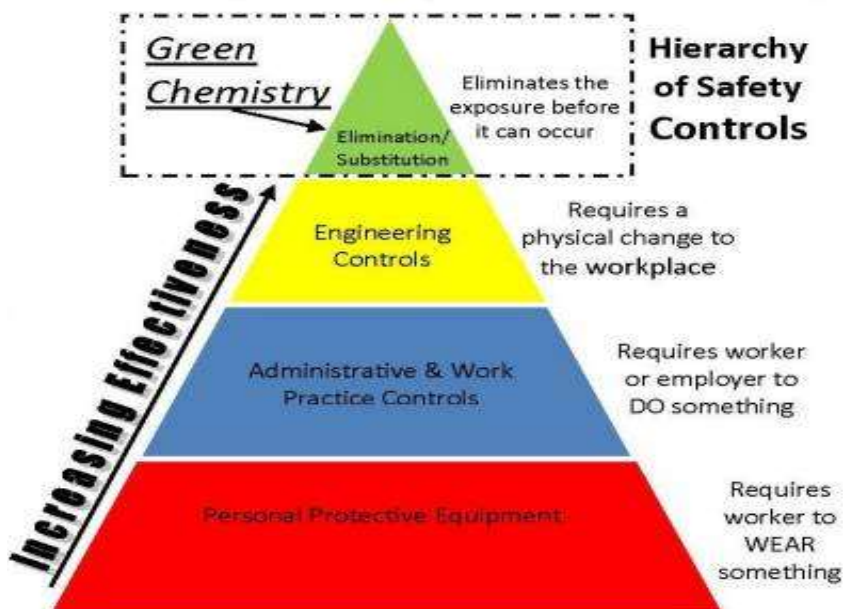


Figure 7. Hierarchy of security control.

11. Analyze in real time to prevent pollution

The eleventh principle of green chemistry emphasizes the need for analytical methodologies to fulfil the requirements for a real-time, in-process monitoring and control prior to the formation of hazardous substances. Green analytical chemistry can be defined as the use of analytical procedures that produce lesser waste and are safer for the environment and human health. This definition includes both parts of live monitoring of a chemical transformation and the environmental shortcomings accompanying traditional analysis. Traditional analytical chemistry implies large amounts of samples for analysis and abundant use of solvents and energy but with the development of new methods and precision mobile instruments, it is possible that the analysis works with a small sample size at the sampling site and with much less solvent can be done. The principle of real-time analysis was applicable by the use of

new platforms so-called microfluidic analytical platforms where laboratory functions can be scaled down into a miniaturized system whilst maintaining the accuracy and precision observed in the larger-scaled experiments.



Figure 8. Microfluidic analytical platforms concepts.

Green Analytical Chemistry

Green analytical chemistry (GAC) introduces many methods to make the practice in analytical laboratories more environmentally friendly, safer to the analyst and less energy demanding. This is done by finding alternative solvents, reagents, and auxiliaries or avoiding certain procedural steps such as sample preparation. As a result, green analytical chemistry introduces the idea of reduction of analytical activities' impact on the environment. The principles of green chemistry, suggested by Anastas and Warner, are directly related to analytical chemistry as well, the most important of them being; the prevention of waste generation; safer solvents and auxiliaries; design for energy efficiency; real-time monitoring and safer chemistry to minimize the potential of chemical accidents. In this way, analytical chemistry

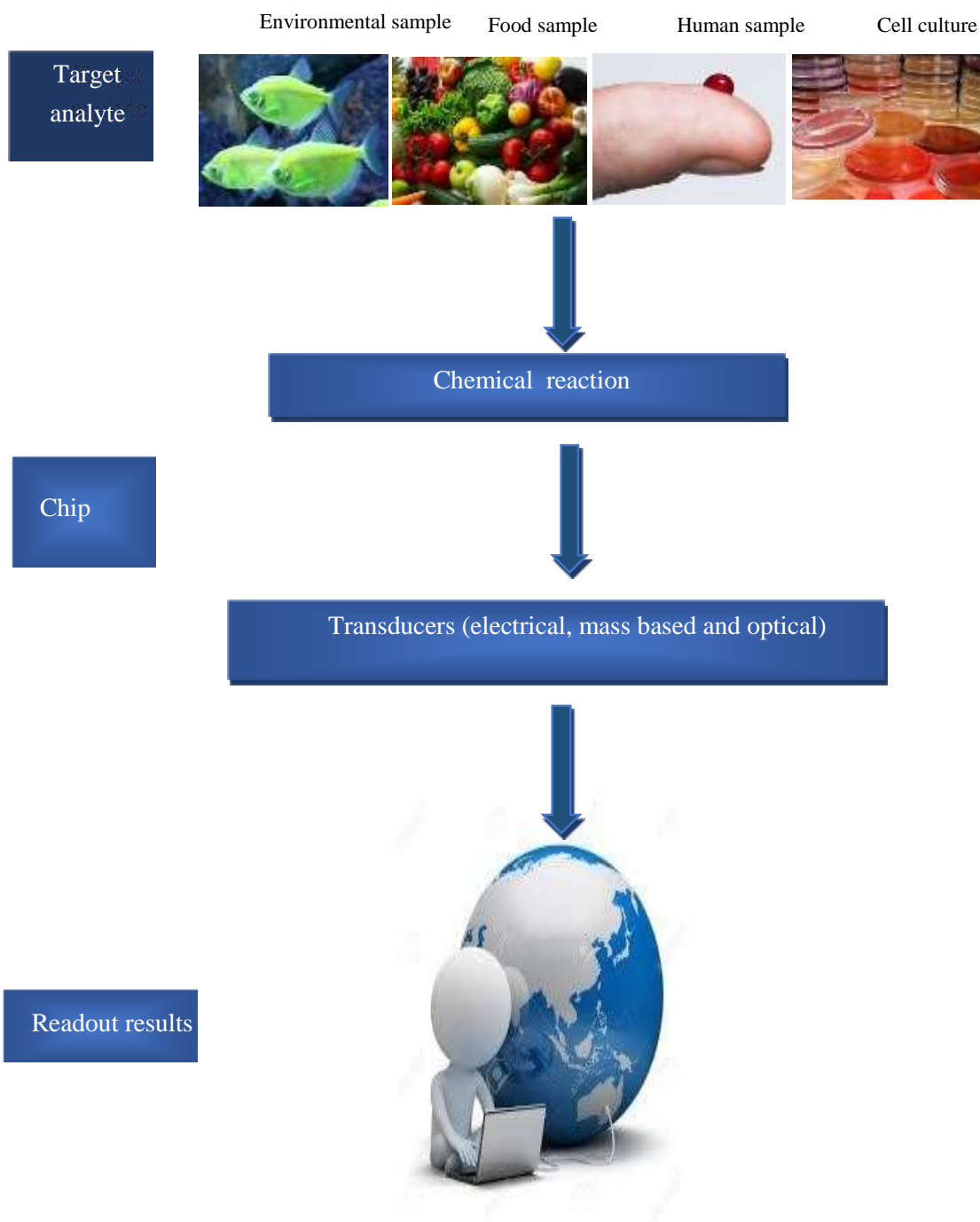
becomes an object of application of the principles of green chemistry and can be the target of a green chemistry approach.

Analytical chemistry is considered to be a small-scale activity, but this is not always true in the case of controlling and monitoring laboratories whose number of runs performed is high. This makes an analytical laboratory comparable with the fine chemicals or pharmaceuticals industry. The use of instrumental methods instead of wet chemistry, automation, and minimization is a new trend in analytical chemistry, making this branch of chemistry more sustainable. Recently, miniaturized systems so called micro analytical systems have replaced traditional analysis methods. The ability to perform laboratory operations on small scales using miniaturized devices provides numerous benefits including reduced quantities of reagents, very short reaction time could be achieved due to extremely fast reaction mixing which is impossible to be achieved in conventional reactors. Additionally, microfluidics offered higher reaction selectivity due to good control thus suppressing unnecessary waste generation. Due to rapid mixing velocity, the organic reaction is possible to be performed in mild conditions at ambient temperature thus cryogenic conditions and usage of protecting groups could be avoided. The miniaturized device makes this technology feasible to be used as a portable system thus reducing the energy for chemical distribution. It means that microfluidics served as an ideal reaction platform owing to high atom and step-economical straightforward synthesis.

Micro analytical chemistry

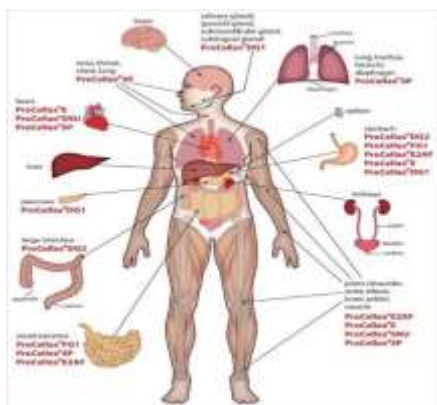
Micro analytical chemistry is a branch of science in which laboratory functions can be scaled down into a miniaturized system whilst maintaining the accuracy and precision observed in the larger scaled experiments. The development of micro analytical chemistry allows a new technology to be taken outside of the laboratory setting and away from the use of more costly conventional methods, it is time saving, more efficient and integrated several processes into one device. As a result, there is a need for construction of a portable, disposable, automated and miniaturized systems, such as lab-on-a-chip (LOC) devices , point -of -care (POC) systems, micro total analysis system (μ TAS), and drug delivery system (DDS), etc., which can provide valuable information. Due to the minimization of the device the in/out fluid must be

minimized to microfluidic size. The microfluidic system should compile of generic components such as the introduction of a sample, movement of a sample, mixing/washing stages and a detection system. The design and approach for these components can vary greatly within research groups but with each sharing an end goal, to produce a device which can function easier and just as well as the conventional methods currently available.



History of micro analytical chemistry

System miniaturization using Micro analytical chemistry include the use of microfluidics which can be best defined as "the science and technology of systems that process or manipulate small (10^{-9} to 10^{-18} liters) amount of fluid, using channels with dimensions of tens to hundreds of micrometers". This method can be used to control the concentration of molecules in space and time. Microfluidics concepts go back to 1950s, originating in the inkjet printer manufacturing. In 1970 a miniaturized gas chromatograph system was demonstrated and this has been followed by a huge rise in the number of publications in this field. Microfluidic systems have been successfully overcome the inherited problems related with traditional analysis as can be seen from below image. This encouraged researches to apply it in the diverse area including chemistry, medicine, engineering, forensics and bioanalytical researches, for example for DNA separation and analysis, cell separation and manipulation, enzyme kinetic studies, drug discovery, and immunoassay, etc.



Sampling



Chemical reaction



Transport



Detection

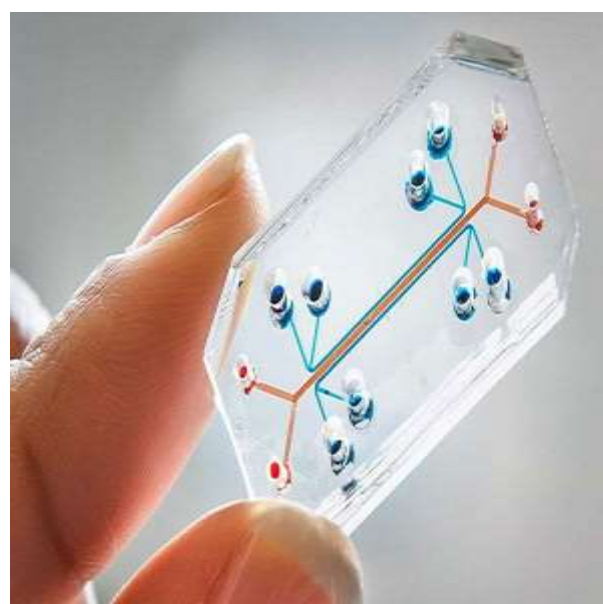
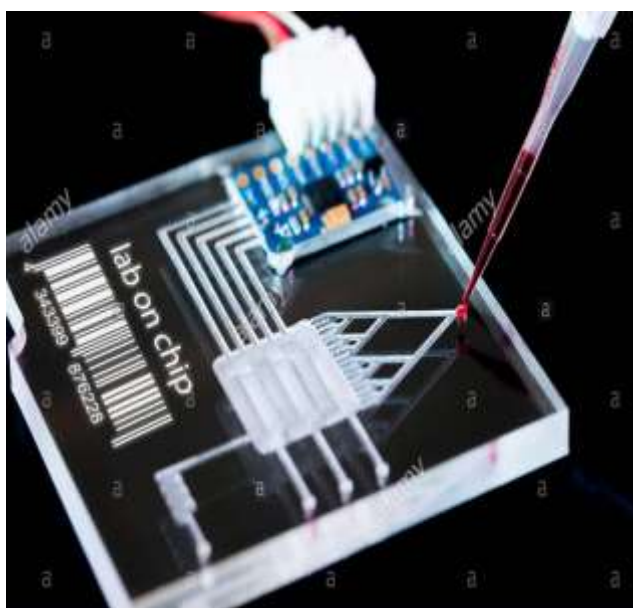


Pretreatments



Data analysis

This diversity is related to major advantages of microfluidic systems: (i) the use of small sample and reagent volumes alongside the easier integration of multiple processes on a single device (ii) reduction of chemical waste and contamination (iii) construction of microfluidic device is relatively inexpensive and (v) improvement in sensitivity and resolution, such characteristics make this microfluidic system appropriate for dealing with limited or degraded samples. Finally, it can be said that due to its miniaturized design, microfluidic systems can be considered to be portable, compact and easy to use.



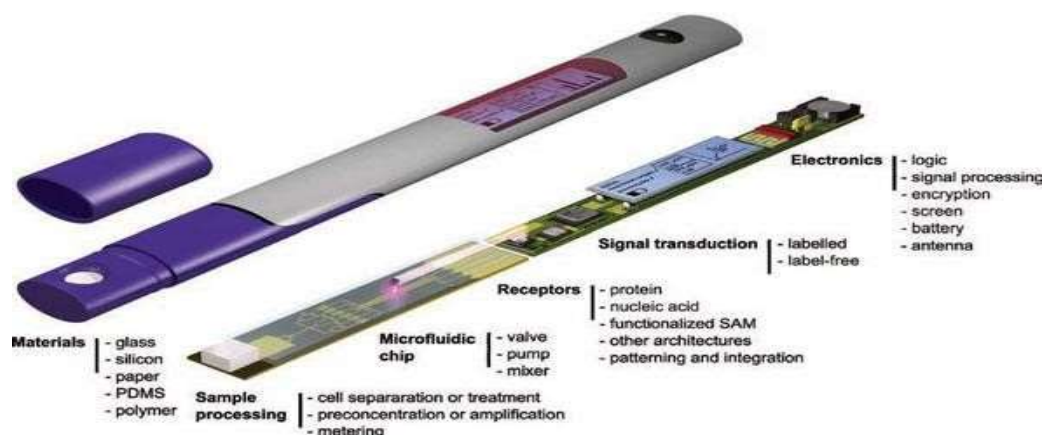
Micro analytical systems:**1. Lab-on-a-chip**

A lab-on-a-chip (LOC) or so called "micro total analysis systems" (μ TAS) is a device that integrates one or several laboratory functions on a single integrated circuit (commonly called a "chip") of only millimeters to a few square centimeters to achieve automation and high-throughput screening. LOCs can handle extremely small fluid volumes down to less than pico-liters. "lab-on-a-chip" indicates generally the scaling of single or multiple lab processes down to chip-format, whereas " μ TAS" is dedicated to the integration of the total sequence of lab processes to perform chemical analysis.

**2. Point of care**

Point of care testing is a medical device or system which can be brought to the patient's bedside or home rather than in a hospital or doctor's surgery and the results received by the patient either immediately after the test or a short time afterwards, as opposed to a few days. A POC device must also be small to allow for portability and in-expensive to manufacture. The features of microfluidics create a perfect platform for POC, the small consumption of reagents and sample allow for a fast turnaround in analysis, and the key idea is that rapid testing will lead to a rapid intervention improving the prognosis for the patient. One of the earliest POC system was used to detect glucose through a tablet, after which came the dipstick assays for pregnancy testing and human immunodeficiency virus (HIV) which only require the addition of a sample. Therefore most research has been aimed at producing a device for a POC

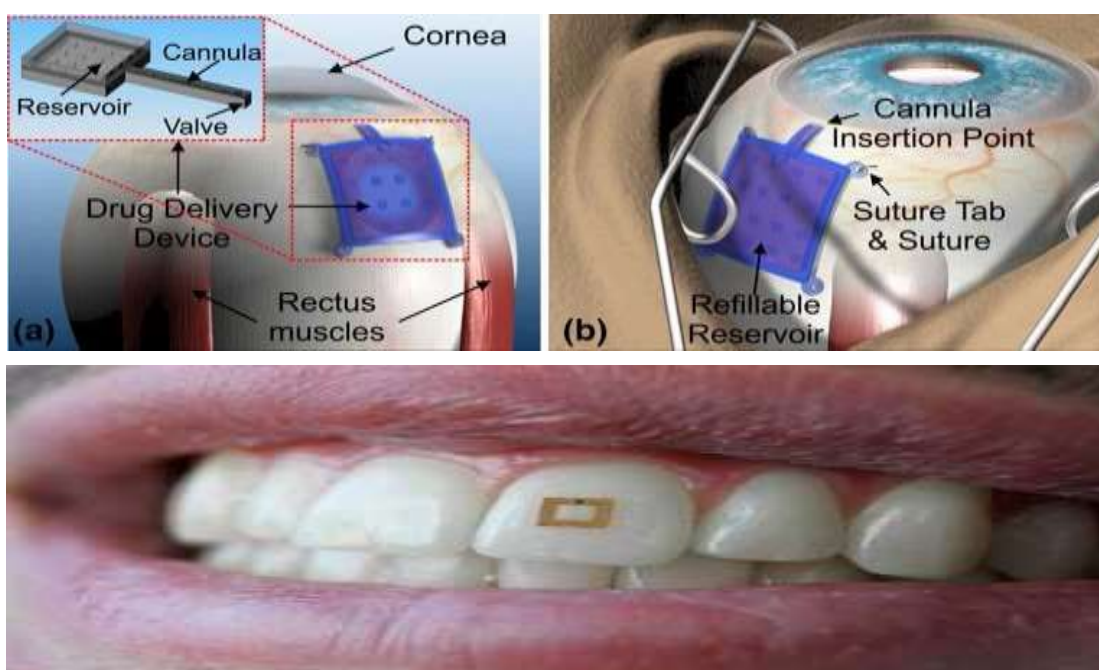
system that is simple to use which in turn requires minimal equipment and an easy analysis.



3. Drug delivery system

A drug delivery system is a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time and place of release of drugs in the body.

In the area of drug delivery science, microfluidics offers advantages, such as precise dosage, ideal delivery, target-precise delivery, sustainable and controlled release, multiple dosing, and slight side effects. These advantages bring significant assets to the drug delivery systems. Microfluidic technology has been progressively used for fabrication of drug carriers, direct drug delivery systems, high-throughput screening, and formulation and immobilization of drugs.



The prospects of microfluidic device

To fulfil the important criteria of a simple, cheap, automated, and selective system; researchers seek for an analytical improvement, resulting in the automated and miniaturized microfluidic platform. Therefore, the basic requirements and principles of this promising technology was studied as follow:

1. Materials

A key factor in microfluidic chip fabrication is the material substrate that is used. Various substrate materials have been reported, such as silicon, glass, and polymers. Silicon is the most common surface due to extensive surface chemistry studies plus its high temperature resistance and good thermal conductivity. However, silicon suffers from some disadvantages such as it is not optically transparent, electrically conductive and it is expensive compared to other materials. On the other hand, glass has good optical transparency, and is not electrically conductive and is chemically resistant, which makes glass substrate good for practical application in a microfluidic chip construction. Nonetheless, handling with glass is slightly complicated due to the fact that glass is fragile which add extra attention and it is less expensive than silicon but more expensive than other materials. Polymers are popular for bioanalysis with desirable characteristics such as simple fabrication, biocompatibility and reduced cost. Suitable polymers include polymethylmethacrylate (PMMA), polydimethylsulfoxide (PDMS) and polystyrene(PS), etc. Nevertheless, polymers have some disadvantages such as limited temperature range, and lower optical transparency compared to glass. Recently different modified electrodes have been used, including glassy carbon, gold (Au), carbon paste, screen-printed electrode and where they act as a support material for reagent immobilization, miniaturizing the microfluidic device components.

2. Sample/ Reagent transport

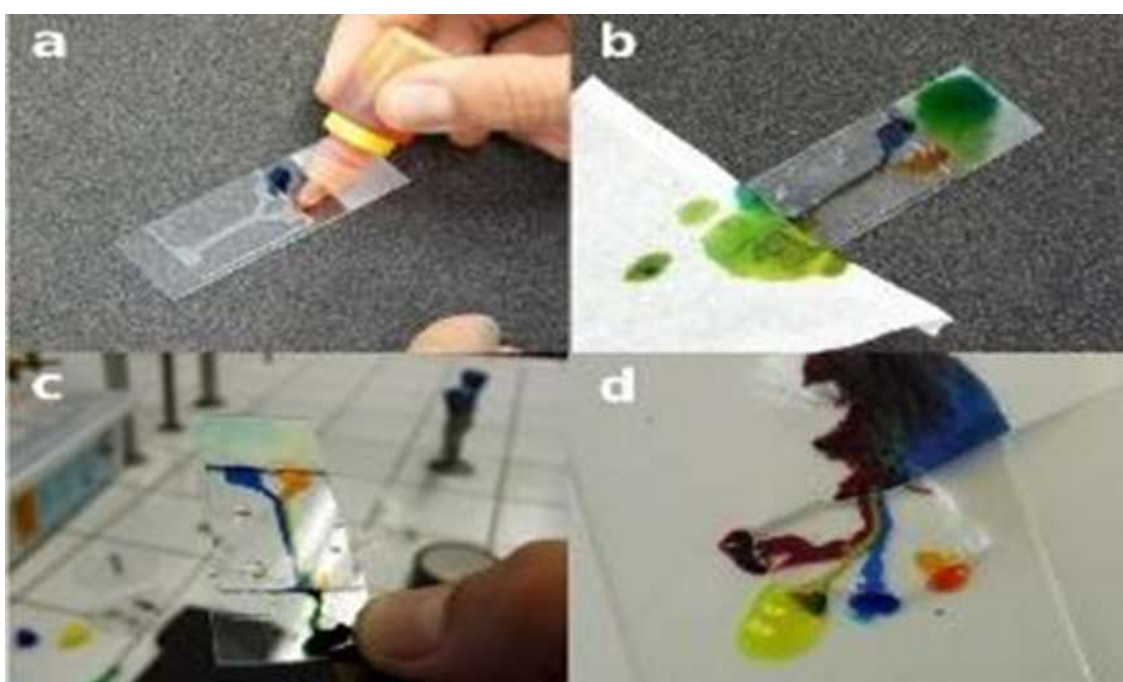
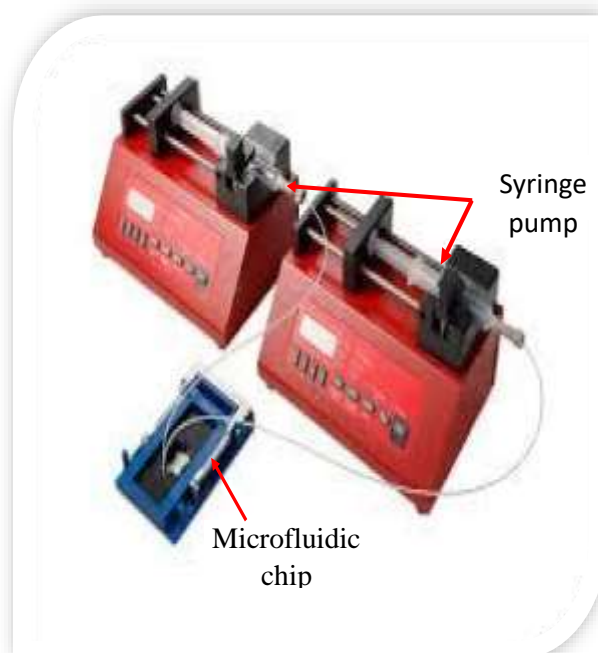
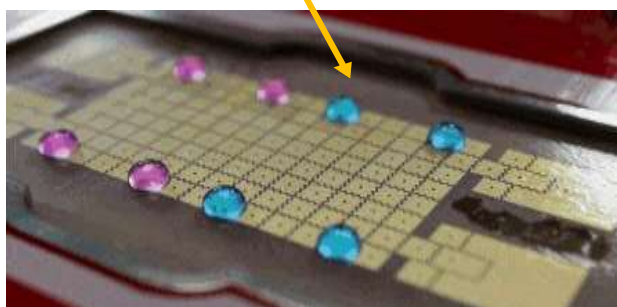
Microfluidic chips are directly affected by the performance of the fluid transport system. Therefore the fluid transfer plays an important role inside a microchannel. This can be categorized into three main fluid handling forces:

1. Electric forces where the fluid transport system depends on flow generated by the electrophoretic and electroosmotic interaction of ionic species with the applied

electrical field, whereas electrowetting force depends on the manipulation of the fluid drop in the presence of program voltage applied to an electrode array.

2. pressure-driven flow, this can be achieved by the aid of a syringe pump or by applying vacuum at the outlet of the channel in order that the reagents can be delivered inside the microfluidic system.

3. Passive forces, this force does not need an external power source that transport fluid. Mainly gravity and capillary forces have been employed to drive fluid within microchannel.

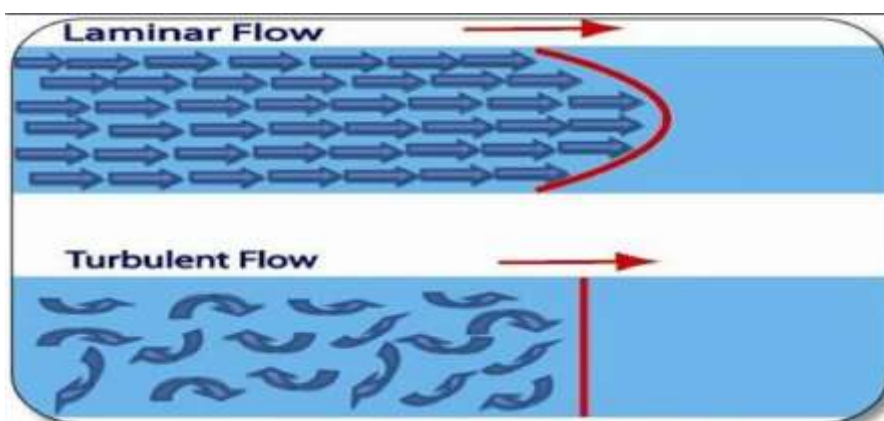


3. Reagents mixing

In microfluidic channels, the fluid flow through the channel must be considered. The flow of a fluid through a microfluidic channel is characterized by the Reynolds number (Re), defined as:

$$Re = \rho V L / \mu$$

Where ρ is the density of the fluid (kg m^{-3}), V is the velocity of the flow (m s^{-1}), L is the diameter of channel (m), and μ is the viscosity (Ns m^{-2}). Where there is a Reynolds number of < 2000 the flow is seen as laminar where mixing then only occurs via viscous forces of the two fluid, if the Reynolds number is greater than 3000 then the flow is seen as turbulent flow where mixing relies on diffusion of the reagent across the channel, if the Reynolds number is between 2000 and 3000 it is termed to be a transition from laminar to turbulent flow.



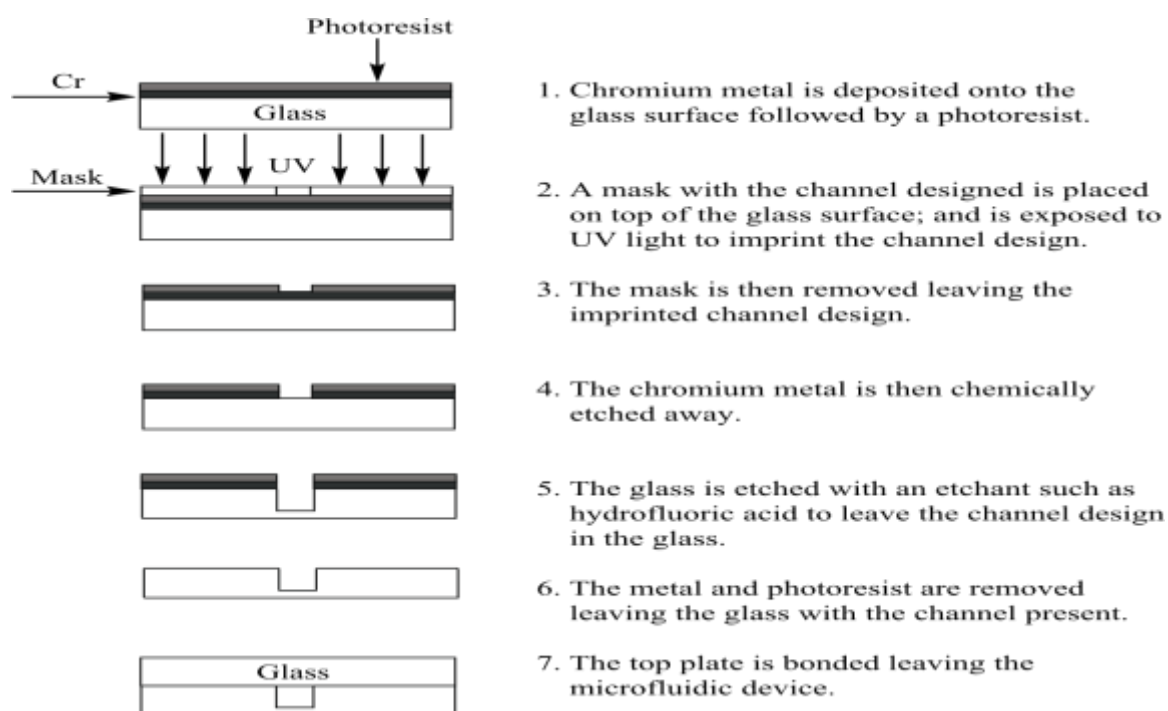
3. Detection

Coupling a detector to the microfluidic system is a crucial step, where most clinical diagnostic and environment monitoring require low power consumption, automation, high sensitivity and specificity of the target analyte. These include electrochemical detectors which include current (amperometric) and potential (potentiometric). The second category is optical detectors which consist of surface plasmon resonance (SPR), thermal lens microscope (TLM), wavelength-interrogated optical sensing (WIOS), absorbance, fluorescence, radioactive and chemiluminescence.

Classification

1. Closed microfluidics

Over the past two-decades, the closed microfluidic concept has been growing due to minimization and integration of chemical and physical processes such as fluid transport, mixing, valving, separation, and detection. In order to perform the previous process, the closed microfluidic device consists of microfluidic unit operations including valves, pumps, actuators, switches, sensors, dispensers, mixers, filters, separators, heaters, etc. A closed microfluidic system composed mainly from glass and silicon which are the most substrate use for fabrication the microfluidic device, where the method based on the photolithography with wet etching is widely applied with this substrate. The procedure of this technique depends on using a chromium metallic layer that a photoresist is a spin coated to covering the glass or silicon with over, and final step put a mask which contains the design of the channels. The channel design firstly imprints onto the surface of the device rely on the UV light which penetrates the photoresist. After the channels are etched into the substrate surface, the chromium layer is then removed using a metal etch (typically hydrofluoric acid). The spin coating layer of sodium silicate used as adhesive to bond the cover plate onto the chip with heating the chip to complete the chip bonding. The fabrication process can be seen in figure below:



Despite the advantages offered by the closed microfluidic system, the device development is hindered by the need of mechanical components which add complexity to the device. In addition, the fabrication process using a material such as silicon and glass requires a complex process such as chemical etching and thermal bonding which takes time and cost, while the polymer fabrication using hot embossing suffer from the bubbles trapped between the stamp and the substrate which requires a specialized vacuum and this can reduce the reproducibility. Air bubble impacts significantly on the fluid flow behaviour within the microfluidic system which poses a challenge for the microfluidic platform operation. Handling biological samples such as blood through the microfluidic system adds more complexity to the system compared to pure water handling due to blockage issues. For these reasons closed microfluidic devices are not favoured from a commercial manufacturing perspective.

2. Open microfluidics

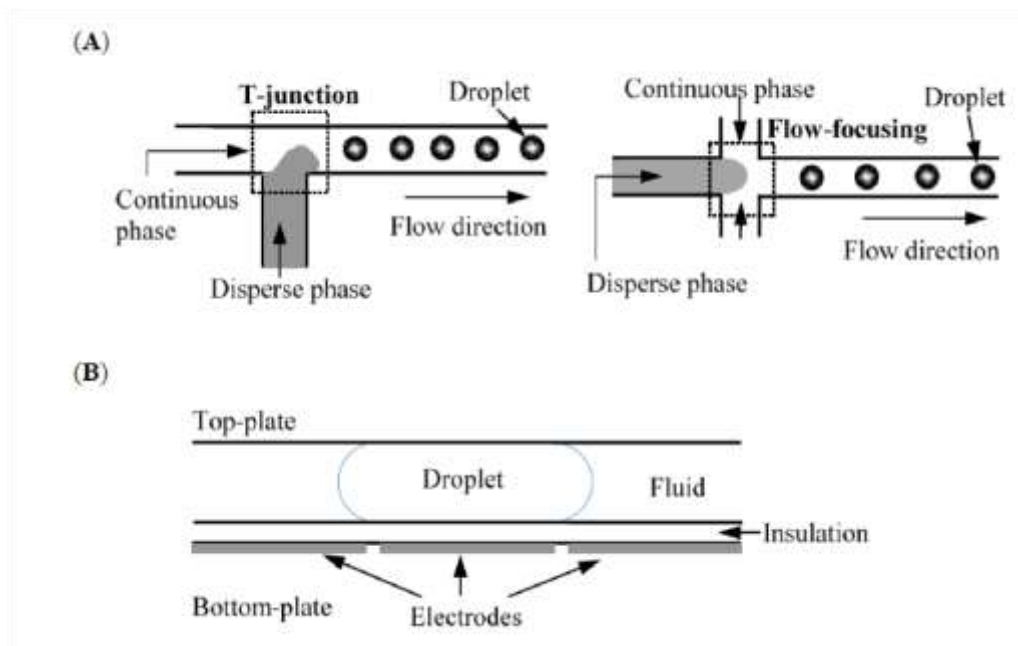
Since closed microfluidic systems were developed research into a related but distinct technology, open microfluidic systems have been carried out, primarily to overcome the inherited problems related to the closed microfluidic system. Open microfluidic systems, have open boundaries where the biological, environmental, forensic samples, etc. should be able to interact with microfluidics in the open space. The fluid moves mainly due to capillary forces.

The advantage of this system lies in the simplicity of open microfluidic chip architecture design, resulting in lower fabrication costs, and this approach overcomes bubble trapping. Also, the easy accessibility of reagents and samples addition and optical observations are facilitated. All these aspects have emerged open microfluidic system as a versatile approach for the development of an integrated microfluidic device for the lab-on-chip application. Open microfluidic include droplet, and continuous open microfluidic systems that will be explained in the following section:

- ***Droplet microfluidics***

Droplet microfluidic system includes both electrowetting-based droplet (well known as a digital droplet or discrete droplet) and continuous-flow emulsion-based droplet microfluidics. In digital microfluidics, the discrete droplet for both reagents and sample are manipulated by applying an electrical potential to an array of the electrode on an

open surface. This technique is driven by surface tension or so-called electrowetting or electrowetting-on-dielectric (EWOD). While for the other technique droplet is formed as a result of an emulsion created using two immiscible liquids including gas/liquid and liquid/liquid systems. For the droplet generation control, various techniques are used such as dielectrophoresis and channel geometry (T-junction).



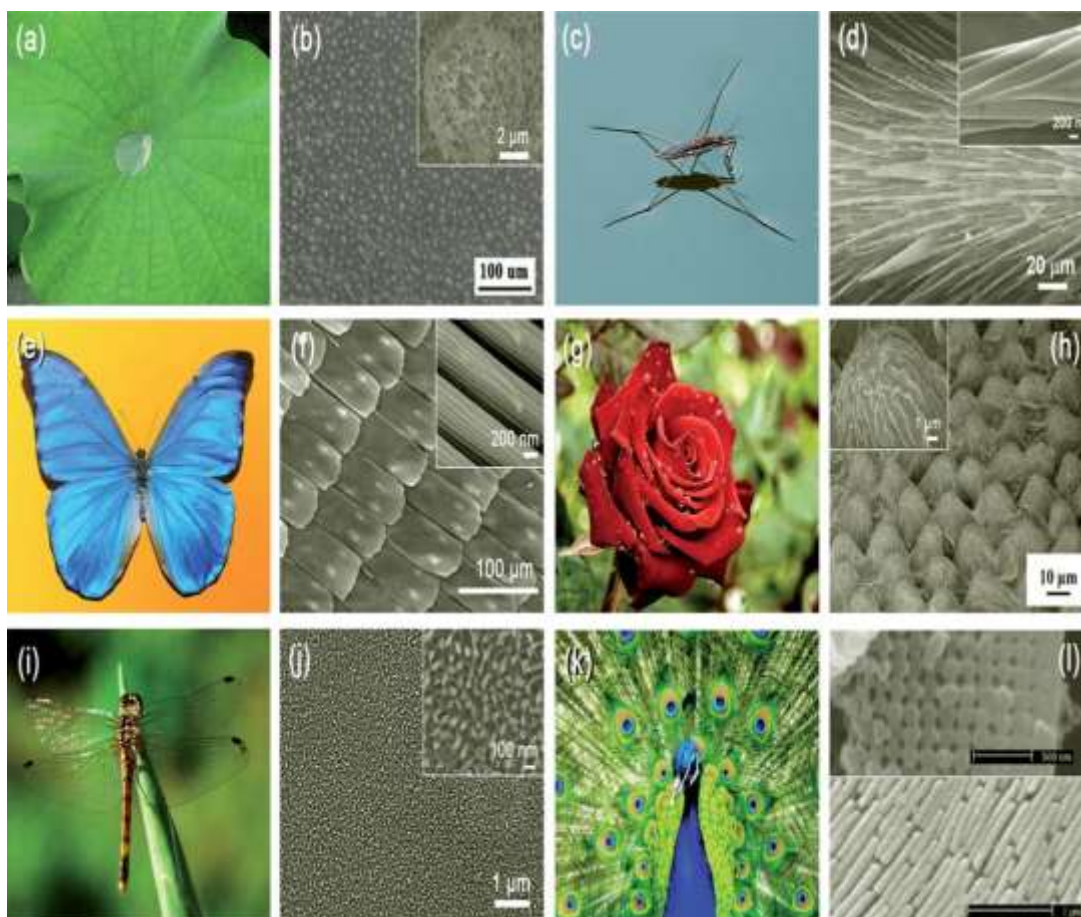
The figure above shows two droplet open microfluidic configurations (A) continuous flow emulsion-based droplet (from T-junction and flow focusing) (B) electrowettingbased droplet.

- **Continuous flow open microfluidics**

A new promising generation of microfluidics has recently been investigated. The continuous open microfluidic technique includes devices that are designed using wettability pattern consisting of hydrophilic patterns on a hydrophobic substrate or conversely, by applying a hydrophobic pattern on a hydrophilic substrate. Once the surface is patterned, the aqueous sample flow will be along the hydrophilic channel fabricated on a hydrophobic substrate by capillary forces, provided the pressure is maintained below a critical value (thus this is called surface-directed fluid flow), since the fluid (aqueous solution) will only wet the hydrophilic patterns as the hydrophobic region acts as “curbs” .

Hydrophobic surfaces have numerous profitable applications as these surfaces can be transferred to commercial products because of their self-cleaning, anti-sticking

and anticontamination properties. This remarkable phenomenon was first observed from natural plants self-cleaning after a simple rain shower as the natural environment get contaminated or polluted, also it is a self-defense against pathogenic organisms. A famous example of natural hydrophobic surfaces is lotus leaf which has a water contact angle of $161 \pm 2.7^\circ$, this is attributed to epicuticular wax secreted by the lotus leaf itself forming a hierarchical micro- and nano-structure, the combination of roughness and wax contributed to the superhydrophobicity of this surface. In addition to a lotus leaf, there are various natural surfaces that present the hydrophobic surfaces from the plant kingdom including red rose petal, scallion, and garlic, etc.. Examples of hydrophobic surfaces are presented also in animals such as water strider legs, cicada orin's wings and butterflies wings which are water repellent where water droplet roll-off their surfaces. The knowledge from biomimetic (learning from nature) inspired researchers to mimic hydrophobic surfaces by producing artificial surfaces taking in consideration the principle connections related to water repellency and surface roughness using different techniques including lithography, etching, plasma treatment, electro-spinning, templating, layer by layer deposition, chemical vapour deposition and use of nanoparticles.



One of the most famous examples of hydrophobic/hydrophilic surfaces used for building the microfluidic device is paper as so-called “paper-based microfluidic” or “lab on paper”. The fundamental principle that paper microfluidics lies on is the paper basic material which is cellulose, it is considered naturally hydrophilic and allows penetration of fluid within its fiber matrix. Patterns are fabricated on the paper sheet aiming to create micron-scale capillary channels on paper which enable fluid to be confined inside the patterns and therefore fluid flow can be guided in a controlled manner.

The ubiquitous and cheap material of paper, comparability with a wide range of chemical/medical/biochemical applications and the omitting of external forces to enable fluid flow and depending on capillary forces, made paper becomes an attractive substrate for building microfluidic devices. Other surfaces include glass, polymer, electrodes, etc. which can transfer into hydrophobic surfaces after coating using dip coating or spin coating methods using for an example saline derivative.

Applications

One of the most important applications of microfluidic systems is the integration of these systems with sensors. Sensors can be defined as devices that consist of an active detecting element incorporated with a signal transducer. These two components in the sensors can play a major role in transmitting either electrical, mass-based or optical signals to a digital signal for selective compound analysis. Sensors can be classified into two categories: chemical sensors and biosensors. According to the international union of pure and applied chemistry (IUPAC), “a chemical sensor transforms chemical information ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal”. On the other hand, biosensors are composed of a biological sensing material well known as a bioreceptor and a physical transducer.

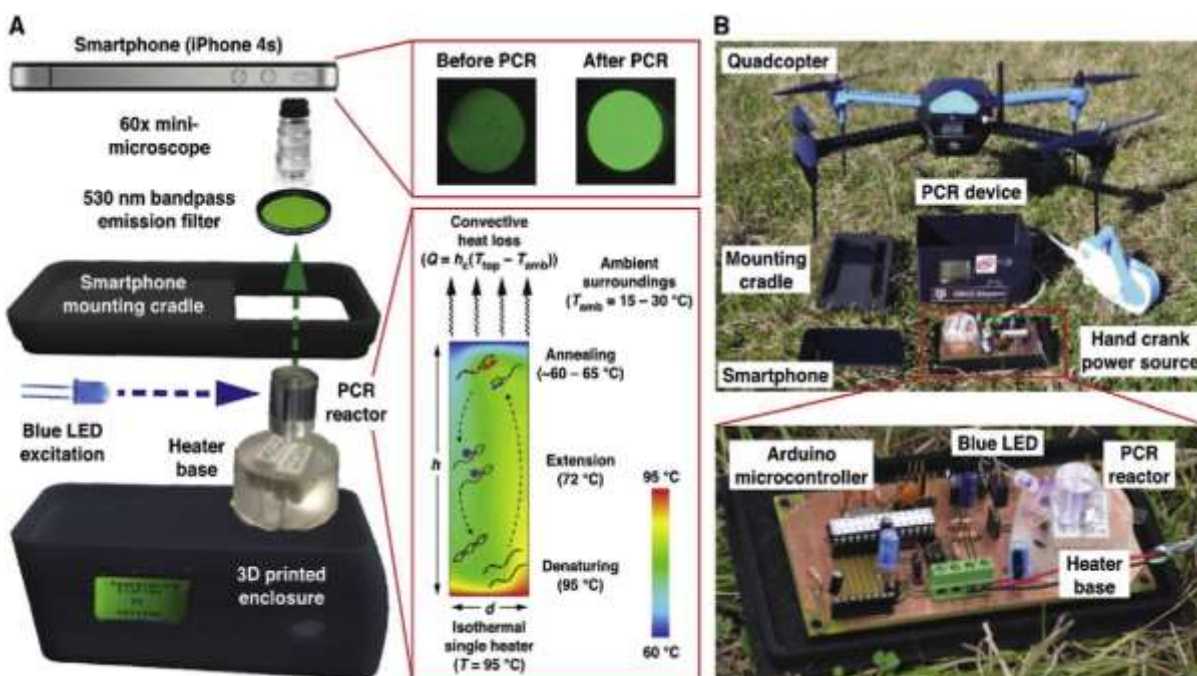
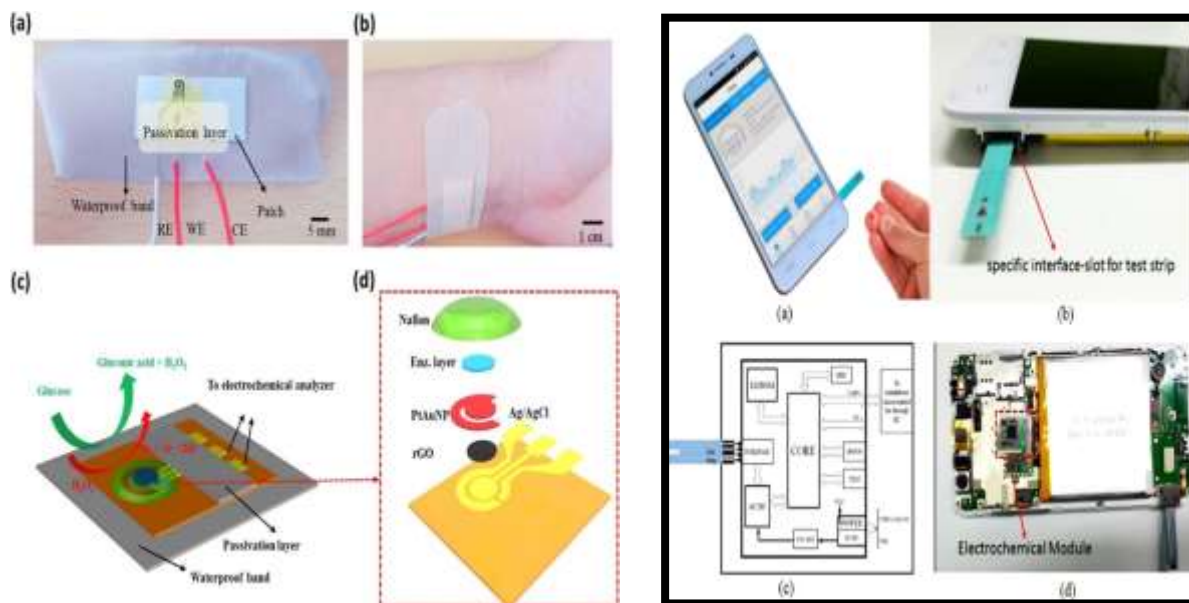
Combining a biosensor’s ability to interact with an analyte at an extremely low concentration with extremely high selectivity, enables their application in a variety of applications using lab-on-a-chip (LOC), drug delivery system (DDS) and point-of-care systems (POC). Biosensors devices can be divided into bioreceptor which is

aptamers, protein receptors, DNA, enzyme, tissue, and antibodies; which transform biochemical information (substrate) into a form of energy to provide readable data.

The second part is the transducers convert the biological response to a detectable analytical signal. Depending on the output signal, transducers can classify into electrochemical transducers (amperometric, potentiometric, impedimetric, and conductometric), mass-based transducers (piezoelectric, surface acoustic wave and magnetoelastic) and optical transducers (absorbance, luminescence, fluorescence, and reflective index).

The analogue signal is correlated to the concentration unit and is transferred to a digital signal via a microprocessor and displayed on a computer or mobile phone screen for analysis. The combination of a biosensor, transducer, microprocessor and display screen has given rise to the construction of industrial, forensics, environmental, healthcare and medical biosensors platforms. Traditional biosensor systems are relatively expensive, bulky and hard-to-handle, which largely limits their use in sample analysis. The problems mentioned above are successfully addressed with the popularization of smartphones and the development of microfluidic technology for their applications of biosensors, which integrates smartphones, microfluidic components and sensory elements together, paving the way for wide application of smartphone-based microfluidic biomedical sensory systems.

Smartphones are now similar to miniature computers with operating systems, internal memory, and high-quality camera lenses. They are, however, potentially more accessible and cheaper than portable analytical laboratory devices. These portable, low-cost devices could be used to run routine tests, which are currently performed by trained personnel using laboratory instrumentation such as microscopes and spectrophotometers. This would offer tremendous potential for improving the diagnosis and treatment of pathologies, particularly in low-resource countries. Below are examples of biosensors integrated with smartphone and microfluidic components.



Benefits of Green Chemistry

Human health

- Cleaner air: Less release of hazardous chemicals into the air leading to less damage to the lungs.
- Cleaner water: less release of hazardous chemical wastes into the water leading to cleaner drinking water.
- Cleaner food: elimination of persistent toxic chemicals that can enter the food chain.
- Increased safety for workers in the chemical industry; less use of toxic materials; less personal protective equipment required; less potential for accidents (e.g., fires or explosions).
- Safer consumer products of all types: new, safer products will become available for purchase; some products (e.g., drugs) will be made with less waste; some products (i.e., pesticides, cleaning products) will be replacements for less safe products.

Environment

- Many chemicals end up in the environment by intentional release during use (e.g., pesticides), unintended releases (including emissions during manufacturing), or disposal. Green chemicals either degrade into innocuous products or are recovered for further use.
- Plants and animals suffer less harm from toxic chemicals in the environment.

Economy and business

- Higher yields for chemical reactions, consuming smaller amounts of feedstock to obtain the same amount of product.
- Fewer synthetic steps, often allowing faster manufacturing of products, increasing plant capacity, and saving energy and water.
- Reduced waste, eliminating costly remediation, hazardous waste disposal, and end-of-the-pipe treatments.
- Allow replacement of a purchased feedstock by a waste product.
- Reduced use of petroleum products, slowing their depletion and avoiding their hazards and price fluctuations.

Application of green chemistry in daily life

1. Green Dry Cleaning of Clothes: Perchloroethylene (Perc.) is the solvent most commonly used in dry cleaning clothes. Perc. ($\text{Cl}_2\text{C} = \text{CCl}_2$) is suspected to be carcinogenic and it contaminates groundwater at its disposal. A new technology known as micell technology is developed by Joseph De Simons, Timothy Remark and James Mc clain in which liquid carbon dioxide can be used as a safer solvent along with a surfactant to dry clean clothes. This method is now being used commercially by some dry cleaners.

2. Green Bleaching Agents: Conventionally during the manufacturing of good quality white paper, lignin from the wood used for it is removed by placing small pieces of wood into a bath of sodium hydroxide and sodium sulphide followed by its reaction with chlorine. Chlorine during the process also reacts with aromatic rings of the lignin to form chlorinated dioxins and chlorinated furans. These compounds being carcinogens, cause health problems. Terrence Collins developed a green bleaching agent which involves the use of H_2O_2 as a bleaching agent in the presence of some activators such as tetraamido macrocyclic ligands (TAML[®]) which catalysis the fast conversion of H_2O_2 into hydroxyl radicals that cause bleaching. This bleaching agent breaks down lignin in a shorter time and at a much lower temperature. It can be used in laundry and results in lesser use of water.

3. Green Paint: Oil-based 'alkyd' paints give off a large amount of volatile organic compounds (VOCs) as it dries and cures and many have one or more environmental impacts. Procter & Gamble established a mixture of soya oil and sugar that replace fossil-fuel-derived paints resins and solvents which reduced the hazardous volatiles by 50%. Chempol[®] MPS paint formulation uses these bio-based Sefose[®] oils to replace petroleum-based solvents and create safer paint to use. Sherwin-William established water-based acrylic alkyd paints from recycled soda bottle plastic (PET), acrylics and soya bean oil. These paints give performance benefits of alkyds and the low VOC content of acrylics. In 2010, enough quantity of these paints was manufactured to eliminate 362,874Kgs of VOCs.

4. Green firefighting foams: The conventionally chemical firefighting foams used worldwide discharge toxic substances into the environment contaminating water and

depleting the ozone layer. A new foam called Pyrocool has now been invented to put out fires effectively without producing toxic substances as in other firefighting materials.

5. Green wastewater treatment: Conventionally, municipality and industrial wastewater are clarified by the use of aluminium sulfate (Alum) which was found to increase toxic ions in treated water which causes Alzheimer's disease. The tamarind seed kernel powder discarded as agricultural waste has been found an effective and economical agent to make municipal and industrial wastewater clear as with Alum. In addition, tamarind kernel powder is nonpoisonous, biodegradable and economic.

6. Green Biodegradable Plastics: Many companies have been working in this direction. A method has been discovered by the scientists at Nature Works in which microorganisms convert corn starch into a resin just as strong as the petroleum-based plastic presently used for making containers, water bottles etc. The company is trying to use raw materials from agricultural waste. In another example, Baden Aniline and Soda Factory (BASF) developed a biodegradable polyester film called Ecoflex®. This film is used along with cassava starch and calcium carbonate to make fully biodegradable bags called Ecovio. These bags are also found to be tear-resistant, puncture-resistant, waterproof, printable, and elastic so can be used in place of conventional plastic bags.

7. Green Computer Chips: Many chemicals, huge amounts of water, and energy are required to manufacture computer chips. At the Los Alamos National Laboratory, scientists have developed a method where supercritical carbon dioxide is used in one of the steps of chip preparation which appreciably decreases the amounts of chemicals, energy and water required to manufacture chips. At the University of Delaware, a method was established to make use of chicken feathers to manufacture computer chips. The protein keratin of the feathers was used to make a fiber form that is light but tough enough to withstand mechanical and thermal stresses.

8. Green Medicine: The pharmaceutical industry is working to develop medicines with less harmful side effects, by methods which produce less deadly waste. Merck and Codexis developed a second-generation green synthesis of sitagliptin which is an active ingredient in Januvia, a treatment used for type 2 diabetes. This resulted in an

enzymatic process that eliminates the need for a metal catalyst, reduces waste, and enhances yield and safety. The drug, Simvastatin, sold under the brand name Zocor, is used on a large scale for treating high cholesterol. The traditional method to make this medication employed a large number of steps, used a large quantity of harmful reagents and formed a large amount of toxic waste in the process. Professor Yi Tang used an engineered enzyme and a low-cost feedstock to synthesize it. Codexis, optimized both the enzyme and the chemical process which reduces hazard and waste to a great extent, is lucrative and meets the requirements of the consumers.

9. Green Solar Cell: The solar cell is the most important example of green technology. It directly converts the light energy into electrical energy through the process of photovoltaics. Solar photovoltaic technology has been found to be one of the few renewable, low-carbon producers with both the scalability and the technological development to congregate the ever-growing global demand for electricity. The use of solar photovoltaics has been rising at an average of 43% per year since 2000. Generation of electricity from solar energy results in less consumption of fossil fuels, and a reduction of pollution and greenhouse gas emissions.

10. Green build: The building makes use of a variety of environmentally friendly techniques in order to reduce their impact on the environment. The use of domesticated materials, reflexive solar design, natural ventilation and green roofing technology may allow builders to construct a building with a significantly smaller carbon footprint than normal construction. These techniques are beneficial for the environment as well as they can produce cost-effective buildings which are healthier for the occupants too. Green ventilation techniques reduce the need for traditional air conditioning by allowing natural airflow.

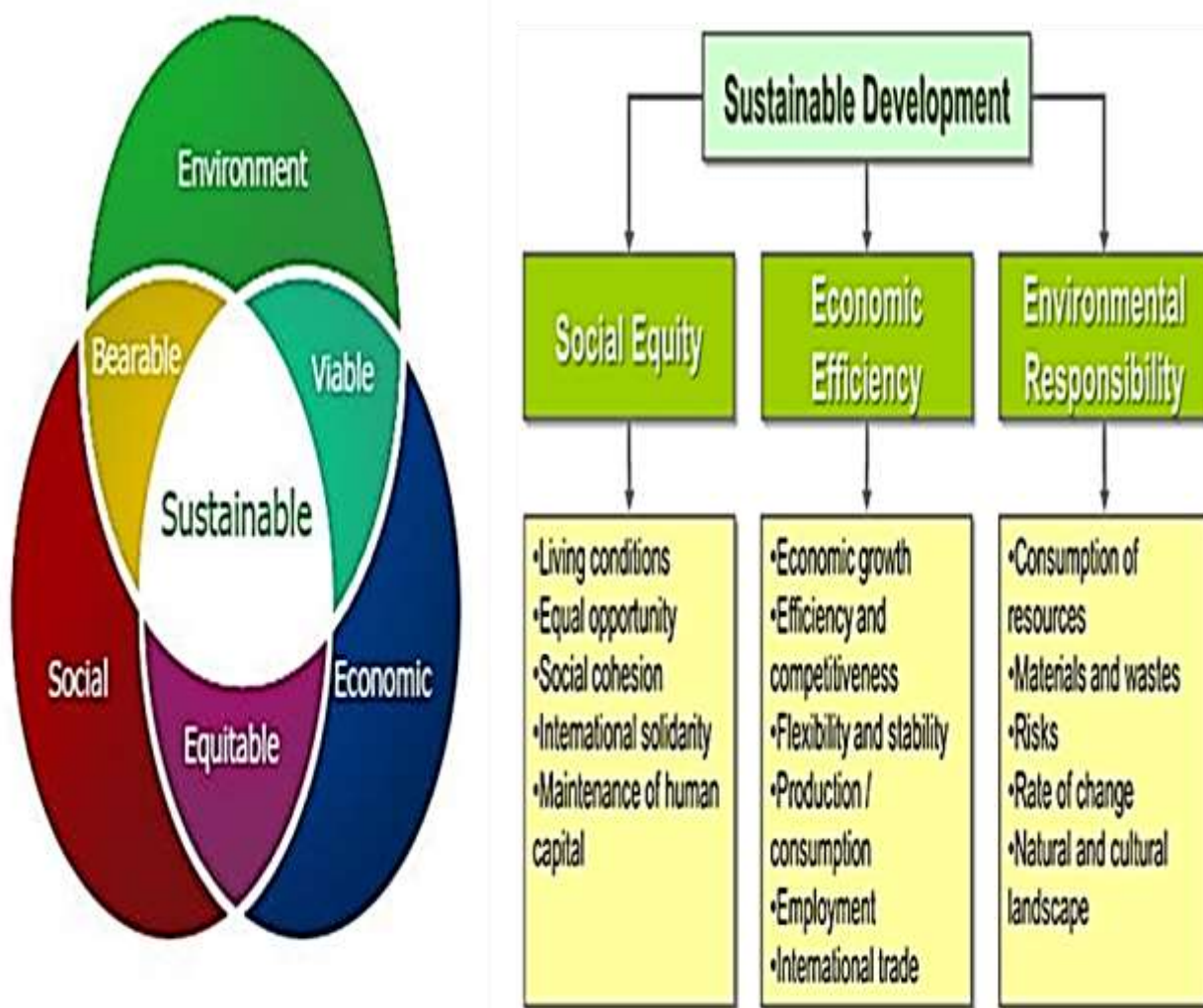
11. Green cement: Cement manufacture releases approximately 6% of carbon dioxide of its total release in the atmosphere. For every 1 tonne production of cement at 1500°C, 100 kg of fossil fuel is used and nearly 1 tonne of carbon dioxide is released in the environment. Silicates which are the primary constituents of cement are present in enormous amounts in some types of waste and low-value biomass. e.g. Rice hulls contain about 10% silicates in them. These silicates can be produced from them at 600° C and then further processed at 800° C. Rice hulls are produced in extreme amounts in the U.S.A., China and Brazil.

GREEN CHEMISTRY: A Framework for a Sustainable Future

The concept of sustainable development was first introduced in 1987 and is defined as "meeting the needs of the present generation without compromising the ability of future generations". Green chemistry focuses on how to achieve sustainability through science and technology. Sustainability is dependent on the rates of both resource utilization and waste generation. A sustainable technology needs to fulfil two conditions:

- (i) Natural resources should be used at rates that do not unacceptably deplete supplies over the long term.
- (ii) Residues should be generated at rates no higher than can be readily assimilated by the natural environment.

It is evident, for example, that non-renewable fossil resources - oil, coal and natural gas – are being used at a much higher rate than they are replaced by natural geological processes. Consequently, their use is unsustainable in the long term. By the same token, the extraction and use of fossil resources are generating carbon dioxide at rates that can't be assimilated by the natural environment. This is widely accepted to be a root cause of climate change. In order to preserve the planet's resources, to enable future generations to fulfil their own ambitions regarding living standards, the current rate of resource extraction has to be restrained. A balance needs to be found between economic development, environmental impact and societal equity. This is reflected in the three types of sustainability metrics or indicators: economic, ecological and societal, or the three Ps, profit, planet and people, represented by three overlapping circles in Scheme 1. Two-dimensional metrics - socio-economic, eco-efficiency, and socio-ecological – are obtained where two of the circles intersect and a fully sustainable technology where three circles overlap, corresponding to all three aspects of sustainability being fulfilled.



Scheme 1. Sustainability metrics Venn diagram

Mass efficiency metrics pertain to five of the twelve principles (numbers 1, 2, 5, 8 and 9) of Green Chemistry and are, therefore, at the heart of green process design. However, for a holistic analysis of the greenness of a chemical process, more aspects need to be delineated, namely the energy efficiency of the process (principle 6), the renewability of the raw materials (principle 7), health and hazard risks for workers involved (principles 3, 11 and 12), and the environmental impact of the chemicals used and the waste generated (principle 3). Moreover, in order to assess its overall sustainability the economic and societal metrics that is the socio-economic indicators, of the process need to be considered. In short, green chemistry is an integral part of sustainable, benign-by-design processes for chemicals manufacture.