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GREEN APPROACHES FOR THE INDUSTRIAL PRODUCTION OF ACTIVE PHARMACEUTICAL INGREDIENTS

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ABSTRACT

Approaches to improve the environmental profile of manufacturing processes and end products is an important goal in many industries, including pharmaceuticals. In the case of pharmaceutical manufacturing, these approaches can involve ways to increase reaction efficiency and yield in order to reduce waste, reduce solvents and reagents, or to improve reaction conditions when synthesizing active pharmaceutical ingredients, intermediates, or lead compounds. The worldwide demand for lower-priced drugs with proven benefits to human health poses an increasing challenge to process chemists to develop manufacturing routes that not only deliver maximum value, but also minimize waste generation. There are existing and emerging solutions to counter pollution. The design of green, efficient and cost competitive industrial process is the need of era. Green chemistry seeks to promote the adoption of safer more efficient chemicals, products and processes. In order to design inherently safer chemicals it is important to understand the basic principles that dictate toxicity. The production of organic chemicals as raw materials or reagents for other applications is a major sector of manufacturing polymers, pharmaceuticals, pesticides, paints, artificial fibers, food additives, etc. Organic synthesis on a large scale, compared to the laboratory scale, involves the use of energy, basic chemical ingredients from the petrochemical sector, catalysts and after the end of the reaction, separation, purification, storage, packaging, distribution etc. To educate future generations of engineers and decision makers in the importance of green engineering in pharmaceutical syntheses & greener designs for solvent recovery targeting the reduction

of the overall solvent consumption, the associated waste, and life cycle emissions from cradle to gate. Strategic greener techniques include reactions in alternative solvents, atom economic multicomponent reactions, microwave and ultrasonic reactions, solid-supported synthesis, fluorous and ionic liquid-based recycling techniques, flow reactors and green catalytic techniques including organocatalysis, supported catalysis, biocatalysis, fluorous catalysis, catalytic direct C-H bond activation reactions, Solid state grinding & Exergetic Life Cycle Analysis (ExLCA). It is imperative that we push the frontiers of science, technology and innovation to meet these demands. Catalysis is the key technology for the development of green processes for the industrial production of API. Enzymes are the ultimate green catalysts–they are renewable, biodegradable and are generally believed to provide a more sustainable means of synthesis than more traditional chemistry approaches.

KEYWORDS: API, Strategic Greener Techniques, Energetic Life cycle Analysis, Environmental Sustainability.

INTRODUCTION

The design, manufacture and application of safer products and manufacturing processes have been important goals over the last decade and will advance in the future under the umbrella of "Green Chemistry". There has been a paradigm shift in the use of innovative drugs to that of low-cost API drugs after the economic recession, thereby causing a positive impact on the overall growth of the API market. In order to keep abreast with this change, API manufacturers are applying various novel technologies to reduce the processing time in order to yield more production. Consistent rise in biotechnology and generic sectors will fuel the growth of the global active pharmaceutical ingredients (API) market. While the ongoing research and development of biosimilars and up-to-date innovations in biotechnology are likely to create a huge potential for the API market across the world, the expiry of patented drugs and shift towards the use of low cost API drugs due to economic recession will help to propel the growth of API market, The Development in the High Potency Active Pharmaceutical Ingredient (HPAPI) and Biogeneric drugs is boosting the growth of the Active Pharmaceutical Ingredient (API) market.[1]

Catalysis is the key technology for the development of green processes for the industrial production of active pharmaceutical ingredients. The design of green, efficient and cost competitive industrial process of API and medicinal drug shows the central role of catalysis. Biocatalysis likely to be one of the most important tools for Fine Chemicals & Pharmaforcost

effective & sustainable manufacturing. Green Chemistry would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the stages of the synthetic routes and minimize waste as far as practically possible. In this way, organic synthesis will be part of the effort for sustainable development.1-3 By changing the methodologies of organic synthesis health and safety will be advanced in the small scale laboratory level but also will be extended to the industrial large scale production processes through the new techniques.

Presents a series of new techniques, assessing the green chemistry aspects and limitations (i.e. cost, equipment, expertise). Techniques include reactions in alternative solvents, atom economic multicomponent reactions, microwave and ultrasonic reactions, solid-supported synthesis, fluorous and ionic liquid-based recycling techniques, flow reactors and green catalytic techniques including organocatalysis, supported catalysis, biocatalysis, fluorous catalysis, and catalytic direct C-H bond activation reactions. Advances in micellar catalysis, solid-state chemistry, catalytic asymmetric synthesis, and function-oriented synthesis for natural products represent noteworthy developments in green chemistry that can be applied to the synthesis of active pharmaceutical ingredients.[2]

WHEN SHOULD GREEN CHEMISTRY BE IMPLEMENTED?

The interface between discovery and development is closer and more transparent than ever before. With the acquisition of experimental drug candidates, the line practically disappears. As discussed previously, R&D budgets are getting smaller, and there is a need to do more with less. The chemistry used in the first synthesis of a compound can have a disproportionately large influence over the chemistry of an ongoing project and the subsequent chemistry of compounds in development.[3] To realize the greatest benefits, green chemistry principles should be integrated into the drug development process at its earliest stages, in drug discovery, and every phase thereafter. Green chemistry is a continuous endeavor to innovate. As many companies do, Pfizer recognizes this continuum is critical to advancing scientific innovation, and commits to integrating environmental and health and safety considerations throughout the research, discovery, development, and manufacture of their products.[4]

“Right first time” is commonly associated with emphasis on quality, but the same mantra could be said for designing sustainability in from the onset. With discovery organizations designing the first synthetic route, the direction put forth at this earliest stage can have a significant long-term impact on the environmental profile of the product, as well as cost,

scalability, and efficiency. In the pharmaceutical industry, second or third generation processes are filed for any number of reasons. A recent study evaluated the regulatory approval times for process changes and found a disparity among approval times from regulatory agencies resulting in the potential need to carry inventory for both first and second generation processes for months to several years until all regulatory agencies granted approval. Thus, the environmental and economic benefits of a green chemistry process change may not be realized for a significant period of time following the original product being introduced to the market.

Johnson & Johnson (J&J), among other companies, recognize that waiting to incorporate green chemistry into a second or third generation process not only delays the ecological impact, but it is also time-consuming and significantly more expensive. J&J's focus is to design a sustainable chemical process the first time. Abiraterone acetate, the active ingredient in ZYTIGA™, a treatment for prostate cancer, was recognized with an internal company award for reducing the number of solvents from eight to two, utilizing 64% less raw material and 78% less water.[5]

To summarize, the time to implement green chemistry is now. There is no perfect application of the 12 principles; however, intentionally applying them to the design of materials at their earliest phase of development, in discovery, will optimize the impact of the decisions. Second generation processes may be further improvements, but the regulatory approvals further delay implementation and realization of the benefits.

GREEN CHEMISTRY BARRIERS IN PHARMACEUTICAL INDUSTRY

As all stakeholders of chemical industry are taking steps towards implementing green chemistry, there are various barriers being encountered. To accelerate the implementation of green chemistry, it is important to first distinguish and confront these barriers. Once there barriers are distinguished, some new possibilities could be created to breakthrough these barriers/roadblocks.

As a green chemistry solution provider, while we engaged with the industry to develop, scale-up and commercialise green chemistry based technologies or solutions, we have had a first-hand experience of some of these barriers. Given below are some of the key barriers to implementation & industrialisation of green chemistry.

While much progress has been made, there are still barriers to overcome. Perhaps the biggest roadblock is cost. Existing chemical feedstocks can take advantage of huge economies of scale. Massive refineries, crackers, and plastics plants are able to generate material at relatively low cost. The first bridge that green chemistry has to cross, therefore, is sufficient research funding to design promising new products in order to demonstrate potential viability. Once achieved, these products must then show a track record of demand to support capital investment on the order of tens of millions of dollars, and in many cases billions, to build the plants required to enable green chemicals to overcome traditional feedstocks. Bottom line: As well as finding the right products, the green chemical sector also has to find the right cost basis. Yet the collapse of oil prices earlier in 2015 has increased the competitiveness of oil-based products. When oil was well over $100 a barrel, chemical producers had incentive to find renewable alternatives that might reduce their costs over the long term. But with trading at around $60 a barrel, they are less motivated to pour funds into green chemistry. Clearly, then, we are still at the early stages of the green chemistry movement. Much research is needed to create new compounds to replace petrochemical derivatives and meet the goals of renewability. The volume of this research is expected to grow rapidly over the coming decade. Pike Research forecasts that this will bring about direct cost savings as well as enabling chemical producers to avoid liability for environmental and social impacts brought about through the continued usage of traditional chemicals. At the end of the day, therefore, green chemistry is all about developing new substances that drive environmental change and improve our everyday lives.[6]

- Availability of green technologies
- Scale-up and commercialisation
- Connecting green chemistry solution providers to industry
- Understanding of basics of green principles
- Short Development cycle
- Limited patent life
- Product quality
- Regulatory requirement
- Lack of unified metrics
- High cost of development
- High Project attrition

Technical Barriers: no ecosystem for knowledge-based entrepreneurship

- Seed capital & funding barriers:
- IP Barriers: protecting IP
- Market Barriers: awareness, business model
- Human Barriers: Inertia to change, culture, language
- Scale-up Barriers: same result in lab as in plant, availability of plant, risk
- Barriers created by "Old Nexus"
- Regulatory Barriers: changes in DMF
- Financial Barriers: working capital for growth

GREENER TECHNIQUES/TOOLS USED FOR API PRODUCTION

Sr. No.	Name of Technique/Matrix/Tool/Model	Benefits/Use/Advantages
1	**Green matrix**	
	PMI(Process mass intensity) & E-factor(Environmental factor)	Calculate mass of waste per mass of API, Decrease amount of material used to make a drug
	ELNs(Electronic Lab Notebook)	For selection of greener solvent, chemical& reagents
	Atom economy	Measure of the amount of starting materials that become useful products. Inefficient, wasteful processes
	Life Cycle Analysis	LCA is a technique to assess the environmental aspects and potential impacts associated with a product, process, or service.
	Green solvent selection guide	Encourage greenest possible solvent selection.
	Reagent guide	For green chemical selection
	Solvent recovered and recycled	Minimize cost of production
2	**Greener (Sustainable)Technology**	
	Biotechnology Competence Fermentation & Enzymology Catalysis & Competence Chemo-Catalysis & Bio-Catalysis	Greener, Economical, fast, selective & specific mfg. process.
	Combining Biocatalysis and Homogenous Catalysis	Shortcuts synthesis of a pharma intermediate
	Microwave-assisted organic synthesis	Fast synthesis & minimum energy
	Integrated approach of chemistry, biology and process technology	Reduces number of chemical steps to final API
	Solid Phase Synthesis	Synthesis of multiple non-oligomeric organic molecules at same time
	Multicomponent/Convergent synthesis	
	Hydrogenation Technology	keep the molecule flat as long as possible, Homo and hetero both offer sustainable solutions
	Flow chemistry (Micro reactor technology Process Technology Integrated Process - Low Energy and Energy Integration)	Successful multi-ton application with a higher selectivity and less waste**,** Process Intensification towards sustainable manufacturing, Improved

	Intrinsic safety High productivity High selectivity GMP production	selectivity of Ritter synthesis, Less consumption of raw material and energy (purification), Reduced DSP efforts, Modular small units enable switch from batch to continuous processing, Avoiding cryogenic cooling (energy), high heat and mass transfer
	Micro process technology	Learning from nature, Enhanced transfer by increased transfer area, Enhanced transfer by decreased transfer distance
3	**Toolkits**	
	Eco-Design Toolkit	For green process
	Life cycle analysis	Old complex chemical route vs. white biotech route
	"LCA light" tool for pharma intermediates	For green ICT
4	**Proactive management**	Telescoping, solvent recycling, Encourage innovation while integrating green chemistry and engineering into drug discovery, development and manufacturing, Define and deliver tools for innovation,

A] Solid Phase Synthesis: Solid phase synthesis is a methodology whereby one of the reactant undergoing a chemical transformation is attached to an insoluble solid support and after the completion of the transformation; it is cleaved to release the product. This methodology was first developed in 1963 for the synthesis of a tetrapeptide which was later extrapolated for the synthesis of polynucleotides and oligosaccharides. Recently, application of combinatorial chemistry strategies in solid phase synthesis has allowed the extension of strategy for synthesis of multiple non-oligomeric organic molecules at same time. An advantage with this chemistry is that a number of reactions can be performed in a mixture simultaneously by linking the reactant to a resin and easy purification or isolation of products by simple filtration technique. Solid phase Freidel Crafts reaction was employed in the synthesis of 2,3-benzodiazepines with good yields and purities. A specific example is the solid-phase synthesis of 1-aryl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones, which are potentially useful for the treatment of epilepsy comprising friedel-crafts acylation of resin-bound 3,4-dimethoxyphenylacetate using various acyl chlorides yielding resin bound ketones as products which are ultimately converted into the corresponding 2,3-benzodiazepines. Also the technique has been combined with microwave conditions to synthesize molecules having pharmaceutical applications. A successful application of solid phase technique in microbial transformation of Cortexolone, an anti-dementia drug, is another example broadening the scope of synthesis from synthetic laboratory to biochemicals.[7]

B] Co-crystal Synthesis

Cocrystals can be synthesized by various techniques including dry grinding or neat grinding, solvent-drop grinding (also called liquid-assisted grinding), mixing, milling, reaction crystallization, slurring, sonic slurring and solution crystallization techniques designed to grow single crystals including slow evaporation from solution, vapor diffusion, and layering for liquid diffusion. The oldest cocrystallization technique is perhaps dry grinding as it was performed as early as the 1800's. It was only since 2002 that solvent-drop grinding has been implemented for the synthesis of cocrystals. Grinding and milling are beneficial over traditional solution techniques as they are a "greener" approach requiring much less solvent and cocrystal formation tends to occur at a faster rate with higher yields.Solvent-drop grinding with multiple solvents has also proven to be a reliable method to generate polymorphs of a particular cocrystal.

C] Multicomponent/Convergent synthesis: is an approach which aims at improving yields. In linear synthesis, the overall yield of the product is reduced at every step. Hence this method involves synthesis of building blocks and coupling of all the fragments thus minimizing the sequential isolation and purification processes and improving the yields. Most advantageously, the methodology can be extended to solid phase synthesis, microwave synthesis or other green synthetic techniques. The situation can be exemplified by an illustration of synthetic scheme for the synthesis of: **Dendrimers:** These are typically branched molecules with 3D symmetric morphology. Applications of dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radioligands, imaging agents, or pharmaceutically active compounds. Proteins (Polypeptides) are again polymers of amino acids. Many amino acids/peptides are polymerized together in a convergent synthesis to yield a polypeptide or a protein. An example of its use in total synthesis is the final step (photochemical [2+2]cycloaddition) towards the compound *Biyouyanagin A*, an inhibitor of HIV replication. The convergent synthesis involves two cascade sequences and a remarkably selective [2+2] cycloaddition reaction to forge the cyclobutane ring of the target molecule in the ultimate step.

D] New "Green" Methods in Synthetic Organic Sonochemistry

Ultrasound-assisted organic synthesis is another "green" methodology which is applied in many organic synthetic routes with great advantages for high efficiency, low waste, low

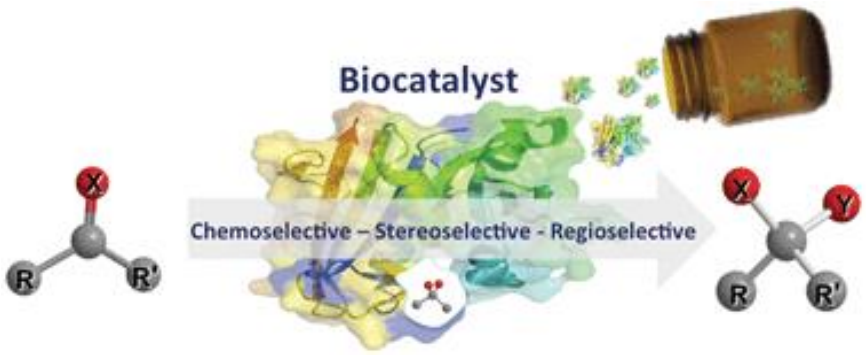
energy requirements. Sonochemistry (in the region of 20 kHz to 1 MHz) has many applications due to its high energy and the ability to disperse reagent in small particles and accelerate reactions. Irradiation with high intensity sound or ultrasound, acoustic cavitation usually occurs (growth, and implosive collapse of bubbles irradiated with sound). Experimental results have shown that these bubbles have temperatures around 5000 K, pressures of roughly 1000 atm. These cavitations can create extreme physical and chemical conditions in otherwise cold liquids. Also, Sonochemical engineering is a new field involving the application of sonic and ultrasonic waves to chemical processing. Sonochemistry enhances or promotes chemical reactions and mass transfer. It offers the potential for shorter reaction cycles, cheaper reagents, and less extreme physical conditions. Existing literature on sonochemical reacting systems is chemistry-intensive, and applications of this novel means of reaction in environmental remediation and pollution prevention seem almost unlimited and is rapidly growing area.38.

D] Biocatalysis and Biotechnology

Advances in biocatalysis of the past 5 years illustrate the breadth of applications for these powerful and selective catalysts in conducting key reaction steps. Asymmetric synthesis of value-added targets and other reaction types are covered, with an emphasis on pharmaceuticalintermediates and bulk chemicals. Resources of interest for the non-initiated are provided, including specialized websites and service providers to facilitate identification of suitable biocatalysts, as well as references to recent volumes and reviews for more detailed biocatalytic procedures. Challenges related to the application of biocatalysts are discussed, including how ‘green’ a biocatalytic reaction may be, and trends in biocatalyst improvement through enzymeengineering are presented.

Biocatalysis and biotechnology are impacting the whole spectrum of chemicals manufacture from pharmaceuticals and fine chemicals through to flavours and fragrances, consumer products and bulk chemicals such as monomers and polymers. Of the top 200 pharmaceuticals, 72% of drugs are chiral and this number is probably increasing. Many chiral building blocks are routinely accessible by biocatalysis, such as non-proteinogenic amino acids, carboxylic acids, amines or alcohols. Today, chiral building blocks can be synthesized with enzymatic biotransformations on the multi-hectogram scale within useful drug discovery timelines, thus, biocatalysis can be seen as a pivotal technology across the pharmaceutical development pipeline from discovery chemistry, drug metabolism and pharmacokinetics

(DMPK) and manufacturing. The spectacular advances in bioinformatics, gene sequencing and synthesis, ready access to enzyme structures, high throughput screening and genetic manipulation have led to an exponential growth in the number of enzyme catalysts available for potential industrial use. Today, any negative attributes of an enzyme with respect to synthetic organic processing can be rapidly engineered out. Driven by emerging technologies such as enzyme engineering and rational design, a number of routes to pharmaceuticals are now being swapped from purely chemo- and metal catalysis to biocatalysisbased routes—examples are syntheses of Montelukast (Singulair) by using alcohol dehydrogenase,[5] Perindopril by using phenylalanine ammonia lyase, and the hepatitis viral protease inhibitors Telaprevir and Boceprevir by using monoamine oxidases. The efficient synthesis of chiral amines is of strategic importance for the chemical industry. Over the past few years, there have been many advances in this area. The asymmetric biocatalytic toolbox for amines contains transaminases, aminodehydrogenases, amino oxidases and ammonia lyases, with imine reductases as an important emerging class of biocatalyst for C-N bond formation. For the future, C-C bond forming enzyme classes such as iminases and pictet–spenglerases are expected to be important. Cytochrome P450 enzymes are another important class of biocatalyst for preparative-scale syntheses of drug metabolites and natural product derivatives. Biotransformations can be used with classical chemical synthesis approaches for natural product modification, for example towards derivatives of cyclomarin A, and thus can be a source of metabolites and new lead molecules for pharmaceutical research. Increasingly, the flavours and fragrance industry is looking towards biocatalysis and biotechnology for sustainable production because many structurally complex molecules are not efficiently accessible by chemistry. The manipulation of enzymes such as cyclases and synthases used in processing complex terpenes is starting to provide alternative, more sustainable routes and, increasingly, synthetic biology is being applied to establish pathways from fragile natural organisms into industrial producer strains such as Escherichia coli and yeasts. Engineered biosynthetic pathways will lead to lower costs, higher purities and more sustainable and reliable supply chains.[5]



E] Flow Chemistry[8-13]

The implementation of continuous flow processing as a key enabling technology has transformed the way we conduct chemistry and has expanded our synthetic capabilities. As a result many new preparative routes have been designed towards commercially relevant drug compounds achieving more efficient and reproducible manufacture. Batch processes are perceived to provide flexibility since, in principle, a single vessel can allow multiple operations to be performed. However, this is not necessarily true. A sustainable production method, that is yet to demonstrate its full potential in the scale-up of APIs, is the incorporation of continuous manufacturing processes. Flow chemistry can minimise the amount of waste generated, with increased productivity and decreased capital at the large scale, when compared to batch processes. The reason for these advantages is their superior reaction mechanics and better rates of heat and mass transfer, leading to safe and economic processes. While conventional batch processes require the chemistry to be modified for the plant equipment, flow chemistry allows the design of a reactor based on the reaction.

a. ***New flow heating approaches***

One of the main advantages of flow chemistry is the safety and ease with which reactions can be performed continuously at elevated temperatures. With the exception of flow microwave constructs all other reactor types rely on convective heat transfer. Although this is rapid for small reactor dimensions as the scale of the device increases the efficacy of the heating rapidly falls.

b. ***Gaseous reagents in flow***

Another example in which flow chemical synthesis was used as the key step in an industrial setting was reported by scientists from Eli Lilly (USA) in 2012. An asymmetric highpressure hydrogenation towards LY500307 was demonstrated (Scheme 14). As this campaign aimed to produce the key intermediate 83 at pilot-scale, a flow-based asymmetric hydrogenation

was chosen as an economically more viable option compared to establishing a high-pressure batch process.

c. *Flow manufacturing*

Whereas the previous applications have demonstrated how flow chemistry can enable the rapid preparation of several pharmaceuticals by focusing on the synthetic effort, the final examples in this review showcase how flow synthesis can be linked to in-line assaying of new molecules as well as the continuous manufacture and formulation of drug compounds.

d. *Solution delivery*

As the previous examples have demonstrated, the development of an efficient flow process is often the result of designing and implementing a new concept or piece of equipment that is better suited to performing an otherwise challenging task. One aspect of continuous flow synthesis for which little progress was made for a long time concerned the way in which reagents streams were delivered into the reactors.

F] Parallel Screening

Molecules in the API business are typically NCEs or novel intermediates and reported procedures do not always work as expected. As a consequence, existing conditions may have to be modified to make them practical. Reaction scouting to find new conditions may be necessary, requiring significant experimentation. Parallel reaction screening saves a substantial amount of time and enables timely activities during process research, provided it is planned and utilised well. With the aid of high throughput screening, and automation in activities such as weighing, quenching and analysis, it is possible to conduct hundreds of reactions in parallel for a given transformation during the feasibility stage of route scouting.[14]

G] Solvent less Synthesis Approach:

Although the use of solvent is linked deeply and inseparably in a chemical reaction, use of extensive solvents is one of the major reasons for low sustainability of the reactions. The various methods developed by the synthetic chemists to develop sustainable chemistry in practice include developing solventless reactions, using water as solvent, or using green substitutes like ionic liquids and supercritical fluids as the reaction media.

H] Synthetic routes to natural products

Paul Wender, professor of chemistry at Stanford University in Palo Alto, California, has developed an approach called function-oriented synthesis (FOS), which involves step economy in the organic synthesis of biologically active compound, including compounds from natural products. Although natural products are a good source for potential drug targets, there are often challenges in the developing green & cost-effective synthetic routes to these complex molecules. FOS addresses this problem by seeking to refine or enhance the biologically active lead structure using simpler scaffolds that are more readily synthesized[15-17] Wender has applied the FOS approach to several natural product lead compounds. These compounds include: arenes that modulate protein kinase C and mimic the more complex phorbols; simplified enediyne compounds for cancer treatment; simplified bryostatin analogs, also used as potential anticancer agents; laulimalide analogs with simplified structures that remove the inherent functional instability of natural laulimalide; the design, synthesis, and optimization of polyarginine drug transporters used to improve potency and circumvent multidrug resistance pathways in cancer cells; and a process to convert the natural product, phorbol, into prostratin, an HIV drug adjuvant.

I] Recycling Technology

Artimesinin is a known antimalarial and an anticancer drug, the synthetic method for the production of which is very complicated. Artemisinic acid is a substance produced as a byproduct from the isolation of artemisinin from sweet wormwood, which is produced in volumes ten times greater than the active ingredient itself. Moreover, artemisinic acid can easily be produced in genetically modified yeast as it has a much simpler structure. Chemical researchers have developed a process to convert the artemisinic acid into artemisinin in a single step and a simple apparatus for this process, which enables the production of large volumes of the substance under very controlled conditions. The antimalarial activity and other effect of the molecule to treat other infections and even breast cancer is due to an endoperoxide group which is a very reactive chemical group formed by two neighboring oxygen atoms. Photochemistry is used to incorporate this structural element into the artemisinic acid by converting oxygen into a form that can react with molecules to form peroxides. The example illustrating the recycling technology concentrates on the economy of the reaction sequence to develop the pharmaceuticals by utilizing the waste products into useful entities.[10]

J] Multicomponent/Convergent synthesis

Multicomponent/Convergent synthesis is an approach which aims at improving yields. In linear synthesis, the overall yield of the product is reduced at every step. Hence this method involves synthesis of building blocks and coupling of all the fragments thus minimizing the sequential isolation and purification processes and improving the yields. Most advantageously, the methodology can be extended to solid phase synthesis, microwave synthesis or other green synthetic techniques.[18]

K] Solvent Selection Guide

ACS GCIPR introduced its solvent selection guide recently, based upon safety, health, and environmental parameters. "Because effectiveness of a solvent for a particular reaction or work-up step depends upon the chemistry and conditions used, the effectiveness of the solvent was not included in the scope of this work," Hargreaves said. The PDF version of the guide is available at www.acs.org/gcipharmaroundtable, and as an iPhone app. The guide may be used to "compare solvents scored in the Roundtable guide to those of their own corporate guides, and to raise awareness and provide a resource." "By switching to green solvents, a company can expect equivalent functional and performance with minimized environmental impact." Green chemistry also may lower waste disposal costs for harmful solvents, reduce the need for expensive emissions abatement equipment, and lower the costs of virgin solvent when solvents can be recycled. Other speakers added greater efficiency and reduced energy use to green chemistry's attributes.

L] Quantification

Many innovative companies are embracing green chemistry, citing environmental sustainability, increased efficiency, and lowered costs, as they develop the tools and measurements that inform the choices of solvents and reagents throughout a compound's development and manufacturing, "The ACS GCIPR has defined and implemented a process mass intensity metric for measuring material resource efficiency of manufacturing routes to active pharmaceutical ingredients," because "the total volume of solvent used is also an important measure," noted Caireen Hargreaves, senior environmental specialist, AstraZeneca. As Quirinus B. Broxterman, Ph.D., corporate scientist for route scouting and selection at DSM recalled, "When Roundtable members reported their PMIs in 2008, more than half was solvent use, and nearly one-third was water. Most of that occurs in the preclinical phase, as

chemists do everything possible to make the compound." PMI decreases significantly once the compound is in clinical development.

PMI and E-factor are the two leading mass-based quantitative options, but PMI is a better indicator of sustainability than the E-factor equation, as per the opinion of Dr. Broxterman, PMI relates to kilograms of product we make and, therefore, easily captures the interest of the nonscientific aspects of a company. The use of PMI also allows the easy transition to carbon footprint measurement.

The Roundtable is rolling out a simple PMI calculator with calculations embedded in a spreadsheet, so users only need enter the quantities of reagents, solvents, and water. "To facilitate more sustainable manufacturing, we need to quantify relevant sustainability parameters. PMI is a first-generation parameter and is a good (starting point) to drive toward a carbon footprint, an ecofootprint, or something to be defined.

IMPLEMENTATION OF ADVANCES IN GREEN CHEMISTRY IN PHARMACEUTICAL INDUSTRY[19-23]

The pharmaceutical majors deploy green-chemistry strategies to improve the synthesis of active pharmaceutical ingredients and intermediates. Lured by improved process conditions and economics, incorporating green chemistry into the synthesis of active pharmaceutical ingredients (APIs) and intermediates is of ongoing importance to the pharmaceutical industry. Solvent reduction and replacement and biocatalysis are some of the tools used to optimize select API syntheses.

Each year, the Environmental Protection Agency's Presidential Green Challenges Awards recognize advances in green chemistry or environmentally favored approaches in all fields of chemistry. A review of entries for the 2008 awards, which were announced earlier this year, shows several large pharmaceutical companies among the contenders.

Eli Lilly optimizes production of neurokinin 1 antagonist by green-chemistry approach

Eli Lilly and Company (Indianapolis, IN) developed a green-chemistry approach for the commercial production of an investigational new drug candidate, "LY686017," an antagonist of the neurokinin 1 subtype of the tachykinin receptor. The drug, (2-[1-(3,5-bis-trifluoromethylbenzyl)-5-pyridin-4-yl-1H-[1,2,3]-triazol-4-yl]-pyridin-3-yl}-(2-chlorophenyl) -methanone, is in Phase II clinical trials. Lilly demonstrated the commercial route on a pilot-

plant scale in 2006 at its facilities in Indianapolis, Indiana. Two prior synthetic routes were executed at the pilot-plant scale at the company's Indianapolis and Mount Saint Guibert, Belgium, facilities. Eli Lilly used a metric similar to but not identical to Sheldon's E-factor, which measures kilograms of waste to kilograms of product (2). Lilly's e-factor measures the total mass of all raw materials, including water, which are used to produce each kilogram of API. The new route for LY686017 has a net e-factor of 146 kg/kg of API, which is an 84% reduction compared with the original route of the drug. Key technology in the new route include a chemoselective nucleophilic aromatic substitution, which produced the drug in high entaniomeric excess (> 99%) despite the complexity of the structure and potential for positional isomers for all five aromatic rings.

Codexis develops biocatalytic route for montelukast intermediate

Codexis (Redwood City, CA) developed an improved route to (S,E)-2-(3-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3- hydroxypropyl)-benzoate (MLK-III), a chiral intermediate used in the synthesis of the anti-asthma drug "Singulair" (montelukast sodium) using biocatalysis. In the traditional approach, the ketone reduction to this chiral alcohol requires at least 1.8 equivalents of the reductant (–)-β-chlorodiisopinocampheylborane ((–)-DIP-Cl) in tetrahydrofuran at −20 to −25 °C. After quenching, an extraction removes spent borate salt waste. The reduction produces the S-alcohol in 97% ee and requires crystallization to give 99.5% ee in 87% yield.

Using another approach, Codexis developed a biocatalytic reduction for MLK-III using a ketoreductase biocatalyst evolved to reduce MLK-II. Codexis evolved the ketoreductase to increase its activity and stability by more than 2000-fold, replacing one-third of the amino acids in its active site in the process and under improved reaction conditions: 100 g/L in isopropanol–water–toluene at 45 °C. Isopropanol is the reductant, which the ketoreductase uses to regenerate its catalytic cofactor, NADPH, producing acetone as the coproduct. The process runs as a slurry-to-slurry conversion with product precipitation driving the reaction to completion. The precipitated chiral alcohol is of high chemical purity and stereopurity. Codexis has scaled up the manufacture of MLK-III using this biocatalytic reduction and has provided samples of MLK-IV to manufacturers of generic montelukast. The company is planning commercial-scale manufacture on a multiton scale in 2008

GSK develops green chemistry toolkit

GlaxoSmithKline (GSK, London) developed the "Eco-Design Toolkit" as a way to provide bench-level chemists and engineers with access to green-chemistry information and tools for process research and development and manufacturing. The toolkit has five modules: a green chemistry and technology guide; a materials guide on solvents and bases with related environmental, health, and safety data; a fast life-cycle assessment for synthetic chemistry for streamlining evaluations of the environmental life cycle and measuring green metrics, including mass efficiency; a green packaging guide; and a chemicals legislation guide that identifies legislation phasing out hazardous substances. Using the toolkit, GSK reported that in 2006, the mass percent of chemicals of concern for all new products decreased nine-fold, and the estimated average life-cycle impacts were reduced four-fold as compounds moved to the last stage of development.

J&J improves route to darunavir

Johnson & Johnson (J&J, New Brunswick, NJ) used green-chemistry techniques to improve the synthesis of darunavir, the API in its protease inhibitor, "Prezista." The improved process reduced waste and raw materials by 46 tons, reduced hydrogen gas by 4800 cubic meters and eliminated 96 tons of methylene chloride in 2006, the year in which the drug was approved.

The key gains in the route were: reduced solvent use; separation of the acidification and quenching steps to eliminate the formation of hydrogen gas and the replacement of hydrochloric acid with methane sulfonic acid and addition of acetone to react with excess hydride to form isopropanol; and replacement of a solvent system containing methylene chloride and triethylamine with a system containing acetonitrile and pyridine.

Merck develops greener process for raltegravir

Merck & Co. (Whitehouse Station, NJ) developed a greener process for producing raltegravir, the API in "Isentress." Isentress was approved in 2007 to treat HIV. An important part of the process involves replacing the reagent methyl iodide with trimethylsulfoxonium iodide. With this change and other improvements, the E-factor for the process was reduced from 388 for the original process to 121. The new process also improved yield by 35%.

Roche betters route for pyridinylimadazole-based drug

Roche developed an improved route for a pyridinylimadazole-based drug that functions as a p38(4) mitogen-activated protein kinase inhibitor. One of the fragments involved in the original synthetic route is 3-aminopentane-1,5-diol. This aminodiol intermediate is highly

water-soluble, making it difficult to isolate from an aqueous reaction mixture. Extraction from the aqueous system required a very large volume of the organic solvent, dichloromethane. Purification of the resulting viscous liquid is either by distillation or via crystalline salt, but requires multiple operational steps. This process was sufficient to produce the API for Phase I and Phase II, but an improved route was needed for commercial manufacture. In the new process, 3-aminopentane-1,5-diol is synthesized in two isolated steps and four chemical reactions starting from readily available and inexpensive dimethyl acetone-1,3-dicarboxylate. The company optimized the process through significant streamlining, resulting in the use of a single solvent, which is easily recovered and recycled. The key improvements involve: sodium borohydride reduction of dimethyl 3-N-tert-butoxycarbonylaminoglutarate, an one-pot deprotection, and purification of the 3-aminopentane-1,5-diol using an acidic resin under non-aqueous conditions. The overall yield of the new synthesis is 89% and the API purity is 99.5%.

FUTURE PROSPECTIVES

According to the recent Pike report, Asia will have one third of the $100 billion green chemistry & engineering market by 2020, making it $ 30-40 billion industry. India, being one of the largest Asian markets, is rapidly adopting green chemistry & engineering practices due to the current changing realities such as: enforcement from regulatory bodies, societal awareness, industry realising the potential, government recognising its role, and so on. This shift in existing dynamics, opens up huge opportunities (of more than $ 5 billion) in the coming 5-10 years for entering the emerging green chemistry & engineering market in India.

CONCLUSION

Organic synthesis is the branch of science which focuses on generating compounds in laboratory and this science is extended for biologically active small molecules in pharmaceutical industry. A practical compilation of the chemical sciences with the life sciences discoveries like that of the target molecule and the disease mechanisms is the basis of rational drug discovery of small molecule therapeutics. Apart from the application of principles of rational drug discovery and other approaches like natural products based or diversity based drug discovery, modern concepts like green chemistry and applications like microwave chemistry help in developing an economic and more potential process to generate new therapeutic scaffolds. It is also evident from the literature that more often a combination of one or more of these strategies can help abridging the ‘valley of death’. The examples,

presented here, although not exhaustive, may help the pharmaceutical society in presenting an outlook to appreciate the new trends and techniques.

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