Tools, technologies & solutions for the pharmaceuticals industry

The Green Chemistree Foundation (www.greenchemistree.co.in) organised a two-day conference on 'Advancing Implementation of Green Chemistry & Engineering in Indian Pharma Industry' at Hyderabad, on September 27-28, 2018. The conference was conducted in association with American Chemical Society's Green Chemistry Institute (ACS-GCI) – Pharmaceutical Roundtable and Telangana State Pollution Control Board.

The second day of the seminar included an event on 'Ready To Implement Tools, Technologies and Solutions in Green Chemistry/Engineering for Pharma Industry', and a 'Workshop on Essential Tools and Technologies for driving Green Chemistry in the Pharmaceutical Industry.'

A report on the two events follows.

One of the major goals of green and sustainable chemistry is to promote the design and development of more efficient chemistries and chemical synthetic processes. The aim is to develop processes that use less mass and energy per kg of the desired substance produced; create less waste; use inherently less hazardous reaction conditions and chemicals; and in general, move the chemical and allied industries towards more sustainable business practices.

In order to design more sustainable chemistries and synthetic routes, systematic, multivariate, and regular assessments of green chemistry (GC) performance need to be established throughout the development cycle of a new chemical or product. To do this, key GC measures must be agreed and tools to facilitate chemical, chemistry and process assessment must be developed. A set of agreed targets, with benchmarks for each development phase, accompanied by guidance and interpretation should be communicated directly to the development scientists responsible for optimising chemistries and processes. Life cycle environmental impacts should also be included as part of a continuing assessment of synthetic routes under development.

Solvents and reagents – making more sustainable choices

Solvents are widely used in the fine chemicals and pharmaceutical industries where they serve to facilitate reaction-based processes by, for example, dissolving reactants and/or bringing them together in concentrations that ensure optimal reaction conditions. However, the excessive consumption of solvents leads to the treatment, storage and disposal of millions of tonnes of solvents per year. While there are many tools available to assess environmental, safety and health impacts of chemicals, solvents, reagents and other process chemicals, there is not widespread knowledge amongst chemists about these tools, how to use them, or how to integrate them into their research practices.

Implementable GC tools and techniques

Dr. Rakeshwar Bandichhor, Director & CoE Chemistry Head – API R&D, Dr. Reddy's Laboratories Ltd., pointed out that application of green metrics and technologies during operations is a must for safer and economical outcomes.

He detailed various metrics used in GC including:

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- Yield & molar yield, which depends on selectivity and atom economy;
- Reaction mass intensity, which is the total mass of raw materials, including everything except water, to afford one kg of product; and
- Process mass intensity (PMI), which is the preferred metric, as it includes contribution from solvents and water.

The focus on PMI, he added, has led to several efforts at careful solvent selection, and development of alternatives for problematic solvents, such as use of toluene instead of carcinogenic benzene, etc.

He made several recommendations for implanting GC in pharmaceutical processes including:

- Right route selection to minimize PMI, increase atom economy, etc.;
- Use of Design of Experiments (DoE) during R&D;
- Switching to continuous flow processes to have good process control; and
- Greater emphasis on lifecycle assessment, carbon footprint and safety.

"The ideal API synthesis process is

simple, one-step, safe, environmentally acceptable, atom efficient, uses available materials and offers 100% yield without any wasted reagents. However, waste is generated in real processes and managing that waste is important. There are several guiding principles in GC that can help the pharmaceutical industry avoid generation of waste, rather than cleaning it up afterwards," he added.

Creating green solutions through lab informatics

Dr. (Ms.) Satya Lakshmi Oruganty, Director – Life Sciences – Enterprise Analytics and Intelligence, PerkinElmer (India) Pvt. Ltd., discussed how laboratory informatics solutions could help implement GC principles in the pharmaceutical industry.

Pharmaceutical production is often a complex interplay of several processes with data coming from several instruments. This data needs to be collected, collated and prepared before any insight or decision can be arrived at. Converting all the disparate data sources and data collection to digital platforms has several advantages:

1. Creates seamless data access and sharing paths between scientists, programme managers and executive management;
2. Reduces the intensity of manual recording, filing, archival and collation procedures, thereby creating a more productive workforce; and
3. Results in an improved, compliant environment, meeting regulatory standards.

Dr. Lakshmi provided some examples of the information flow to offer a glimpse of its complexity, pointing out that the real-life scenarios are even more complex. "Information overload may pose difficulties in decision making. Too less as well as too much information is bad," she opined.

An efficient laboratory, she noted, is a 'green laboratory'. PerkinElmer Informatics offers several solutions for such laboratories to integrate (ChemDraw, E-Notebook) and analyse (TIBC Spotfire), while increasing efficiency and productivity.

She presented a decision support example of synthesis of acetaminophen, which can be by five different routes. "The PerkinElmer solutions offer comparison of all routes based on their experimental data. Operational feasibility check, time taken for each route, as well as overall comparison of the routes can be carried out to select the best optimised route."

Homogenous hydrogenation – beyond chiral applications

Dr. V. Sivakumar, Technical Services Manager, Johnson Matthey India Ltd. (JMIL), discussed the utility of asymmetric hydrogenations by homogenous catalysts in the development and production of chiral APIs. However, he pointed out, the application of homogeneous hydrogenations for achiral transformations is not yet employed on large scale.

Dr. Sivakumar focused on the development, commercialisation and achiral applications of atom economical homogeneous hydrogenation catalysts for selective carbonyl reductions in the presence of other functional groups and ester hydrogenations.

According to him, there are several catalyst options for carbonyl hydrogenations, of which the Baratta catalyst is a multi-tasking catalyst that shows good activity and can carry out different reactions including transfer hydrogenation of aldehydes and nearly solvent-free aldehyde hydrogenation.

Dr. Sivakumar also discussed the homogeneous ester hydrogenation technology in detail. Typically, copper (Cu) or zinc (Zn) chromate or Raney nickel (Ni) are used as catalysts. The optimised homogeneous catalyst system from JMIL offers several advantages – safer reactions, milder conditions, increased chemo-selectivity, simpler work-up procedure, and reduced waste.

The Gusev technology for ester hydrogenation uses two catalyst systems, both of which are commercially available. These catalysts have wider substrate scope and can also be used for ketones.

Dr. Sivakumar presented a comparison of the Baratta, Gusev and triphos-Ruthenium catalysts. The Gusev catalysts show very high activity. He also compared the performance of these three catalysts for hydrogenations of furfural and cinnamaldehyde.

MBDS – A new approach to batch distillation design and simulation

The recent increase in the production of high value-added, low-volume specialty chemicals and biochemicals has generated renewed interest in batch processing technologies. Batch distillation is an important unit operation in the batch processing industry and is widely used. The flexibility of batch distillation, combined with the inherent unsteady nature of the process, poses challenging design and operational problems. The transient nature of batch distillation allows for configuring the column in a number of different ways. Considering the different kinds of batch distillation columns prevailing in the process industry, and the different

modes of operation, the number of possible column configurations tends to be very high.

According to Mr. Virendra Chouhan, General Manager, Equinox Software & Services Pvt. Ltd., Multi-BatchDS (MBDS) is a comprehensive software package for simulation, design and control of batch distillation, developed in association with Stochastic LLC, USA.

It is a stand-alone tool dedicated to distillation and helps in design of new columns and optimisation of recipes on daily basis. With a 64-bit integrated visual environment on PC or workstation running under Windows 10, MBDS can recalculate the output with any change of configuration, operating mode or any parameter. "MBDS can help increase productivity. It can minimise number of trials for new streams or feeds; avoid manual calculations for utilities and heat load in plants; minimise number of samples for QC; and is simple to operate," he noted.

Green and eco-friendly technologies of CSIR-IICT

Dr. (Ms.) Shailaja Donempudi, Senior Principal Scientist and Head – Research Management Division, CSIR – Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad, discussed various platform technologies developed by the laboratory pertaining to GC and the environment.

CSIR-IICT has been recognized by the Ministry of Environment, Forest & Climate Change as a nodal organisation for development of alternative technologies for high global warming potential hydrofluorocarbons. "Several pharmaceutical companies, pesticide manufacturers and fine chemical industries are beneficiaries of the technologies developed at IICT, in addition to global giants like DuPont, Dow, etc.," she noted.

The laboratory provides robust and sustainable solutions to the pharmaceutical industry through their synthetic organic chemistry expertise and green solutions utilising flow chemistry, parallel synthesis, as well as technologies for organo-fluorine chemistry, photochemical reactions, supercritical carbon dioxide extraction, and fluorinated surfactants.

She pointed to the development of a green process for the production of paracetamol, using acetic acid instead of acetic anhydride, via acylation of *para*-aminophenol.

CSIR-IICT is also assisting in development of new drug molecules for treating different diseases, for greater self-reliance. The project is to be ready by 2020. The lab also assists in impurity synthesis and profiling; and offers technologies for pharmaceutical excipients like copovidone, hydroxypropylcellulose, xylitol, extra-white starch, etc. Technologies for these products have been transferred to industry. The institute also offers technologies for liposome-based drug delivery, animal testing services through well-equipped animal house, high-value analytical services such as NMR, X-Ray, etc. It has also developed several waste utilisation technologies, membrane technologies for wastewater treatment, and solid waste management technologies.

Co-processing – sustainable & compliant waste management solution

Co-processing refers to the disposal or use of wastes as alternative fuels and raw materials (AFRs) in resource-intensive industries such as cement kilns, thermal power plants, steel plants, etc. The wastes can come from chemical, pharmaceutical, FMCG, automobile, petrochemical, refinery, foods & beverages, steel and other industries.

Cement kiln co-processing is globally accepted and widely practiced. It is approved by the Basel Convention for disposal of hazardous and other wastes, and by the Stockholm Convention for disposal of Persistent Organic Pollutants (POPs) in an environmentally sound manner. In India, several trials have been implemented for demonstrating the capability of cement kilns for the disposal of hazardous and non-hazardous wastes and deemed successful by the Central Pollution Control Board.

There are two appropriate feed points for co-processing in cement kilns: at the main burner, which is at more than 2000°C; and the calciner, which operates at 850-1000°C. In India, Ambuja Cement and ACC offer waste co-processing services at seven locations.

According to Mr. Pratas Baruah, National Sales Head, ACC – Geocycle, co-processing overcomes some of the problems of incineration: inefficient thermal destruction; need for disposal of the residue or ash left behind after incineration; and high investment for emission control. "Compared to incineration, co-processing offers efficient thermal destruction of waste in half the residence time; and no residue is left as it goes into the cement. Co-processing in cement kilns enables about 80% energy recovery, as compared to just 30% during incineration, and there is no release of carbon dioxide. It offers double valorisation of materials and energy," Mr. Baruah observed.

However, he added, cement plants need homogeneous material with consistent physical and chemical properties. Therefore, the waste needs to be first converted to a homogeneous mass before co-processing. The pre-processing requires additional equipment and investment and India is lacking in this.

Wastes available from pharmaceu-

tical industry include that from manufacturing processes, process rejections, expired medicines, market returns, etc. These wastes, at times, have high chlorine content and low flash point, due to high solvent content, and pose challenges for co-processing. Mr. Baruah urged technological interventions in pharma manufacturing to eliminate or reduce chlorine content as one way to increase co-processing of pharma wastes.

Process safety and process optimisation in pharmaceutical industry

Process safety and process optimisation is very important in the chemical and pharmaceutical industry. Investigating safety hazards of a process is very critical for robust and sustainable processes. To reduce the optimisation time and increase productivity, this is done using state-of-the-art instruments.

Mettler-Toledo AutoChem offers instruments such as reaction calorimeters for process optimisation from laboratory to plant. Their proprietary software, iCsafety, offers integrated data analysis and automatically converts data into safety parameters.

Dr. Prashant Waske, Senior Manager (Technology & Applications Scientist), Mettler Toledo India Pvt. Ltd., noted that chemical properties matter more when carrying out reactions in the laboratory, while physical characteristics matter more in a plant. While carrying out scale-up, the kinetics, mixing characteristics, mass transfer and heat transfer properties are all important. "For process safety, information such as specific heat, heat transfer characteristics, reaction enthalpy, rate of reaction, maximum heat output, etc. are important," he added.

Green ways for ZLD

Soil biotechnology (SBT) is a green engineering approach for waste management. The technology is based on bio-conversions where the fundamental reactions of nature, viz. respiration, photosynthesis and mineral weathering, bring about the desired purification. SBT is an oxygen-supplying biological engine and therefore the process can treat all types of wastes – domestic, municipal and industrial (pharmaceuticals, textiles, etc.).

According to Mr. Ankur Turakhia, Sugam Paryavaran Vikalp Pvt. Ltd. (SPVPL), Mumbai, the technology can handle recalcitrant wastes, does not produce any sludge, and does not have any moving parts in its installation. Furthermore, the COD-to-BOD ratio in the wastewater does not affect the performance of SBT.

"There is a huge diversity in biomedia (culture) that helps in successful waste treatment," he added.

SPVPL has constructed over 50 SBT installations for domestic as well as industrial applications. Some of its industrial clients include Ami Organics, Anupam Rasayan, Eytan Labs, GNFC, NOCIL, Saurav Chemicals, Symed Labs, USV Ltd., Yashasvi Rasayan and Zydus Cadila Healthcare.

Recycle solutions for API and pharma intermediate industry

The pharmaceutical industry has one of the highest E-factors (kg waste generated/kg final product) in the chemical industry. As the Indian pharma industry has emerged as a global manufacturing hub, huge volumes of intermediates and APIs are being produced here, generating enormous amount of liquid effluents. High COD and high TDS of these waste streams is a challenge.

The conventional approaches for pollution control by waste treatment include effluent treatment plants (ETPs), centralised effluent treatment plants (CETPs), zero liquid discharge (ZLD), etc. However, the GC approach is a pollution preventive approach, which is also a profit-centric and performance-oriented.

Ms. Megha Shanbhag, Business Development Manager, Newreka Green Synth Technologies Pvt. Ltd., discussed a solution readily available from the company, Recycle@Source, that involves treatment of acidic, neutral or alkaline effluent streams generated at each process step, with Newreka's proprietary catalytic formulation to remove impurities and recycle the stream into the same step as a reaction/extraction medium, thus reducing effluent load and improving process efficiency.

Using this technology, the sulphuric acid in a nitro to amine reduction reaction can be recycled. "The acidic effluent from the conventional diazotisation reaction is treated with R-Cat, a patented technology, and recycled up to 75 times, offering about 50% savings in sulphuric acid," she noted.

The Newreka reduction technology (NRT) is offered for several reactions including nitro to amine, dinitro to diamine, nitroso to amine, and oxime to amine.