< Green Chemistry >

Introduction to Green Chemistry techniques

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IAMC Toolkit

Innovative approaches for the Sound Management of Chemicals
and Chemical Waste

Introduction to Green Chemistry Techniques

The design of chemical products poses numerous challenges in chemistry such as non-ideal conversion, competing reactions, hazardous chemicals, raw material impurities, etc.

This presentation provides an overview of Green Chemistry techniques to improve material efficiency, reduce pollution intensity, and also produce safer products and processes.

The presentation provides an overview of Green Chemistry & Green Engineering design principles as well as guidelines for Green Chemistry metrics, material selection and reaction conditions.

Since Green Chemistry & Green Engineering are often applied together, common design principles are also shown.

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2. Green Chemistry & Green Engineering design principles
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    - Green chemistry metrics
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Green Chemistry & Green Engineering Examples

- Green Chemistry & Green Engineering examples
- Green Chemistry & Green Engineering design principles
- Overview of Green Chemistry techniques
  - *Green Chemistry metrics*
  - *Material selection*
  - *Reaction conditions*

Green Chemistry Example: Biocatalytic Process to Manufacture Simvastatin*

The traditional multistep synthesis of simvastatin, a leading drug for treating high cholesterol, is wasteful (yield <70%) and uses hazardous and toxic reagents, requiring significant amounts of solvents.

Codexis and UCLA developed a cost-effective synthesis process to manufacture simvastatin using an engineered biocatalyst to improve the reaction yield and reduce hazards and wastes.

Environmental, health and safety benefits:

- Catalyst manufactured from renewable feedstocks
- Simvastatin yields of 97% possible (compared to <70% for traditional routes)

- Reduced use of toxic and hazardous substances like tert-butyl dimethyl silane chloride, methyliodide, n-butyl lithium
- Reduced energy intensity since the reaction is operated at ambient temperature and near atmospheric pressure

- Aqueous reaction conditions reduce quantity of solvents used
- Bi-product (methyl 3-mercaptopropionic acid) is recycled in the process
- Primary waste streams are handled in standard wastewater treatment facilities

Economic benefits:

- Biocatalytically manufactured, simvastatin meets customer requirements
- Operating costs decreased since amounts of feedstock materials and solvents as well as energy and water were reduced

* Source: ACS Green Chemistry Case Study, 2012

Green Engineering Example: Production of Methyl Acetate with Reactive Distillation

Synthesis and purification of some chemicals can involve reactors and multiple distillation columns to increase the overall product yield, separate by-products and meet product purity requirements.

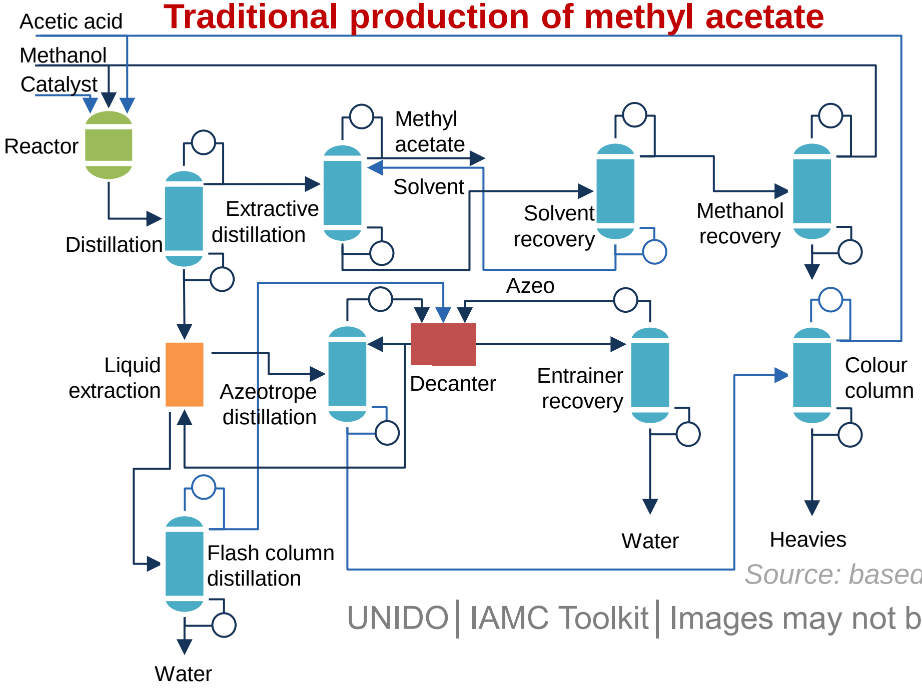
Reactive distillation is a chemical processing Improvement technology that combines chemical reaction and distillation in one equipment, in which the conversion is increased by continuously removing reaction products from the reaction zone by distillation.

Reactive distillation is especially useful for preventing equilibrium-limited reactions like esterification.

Benefits:

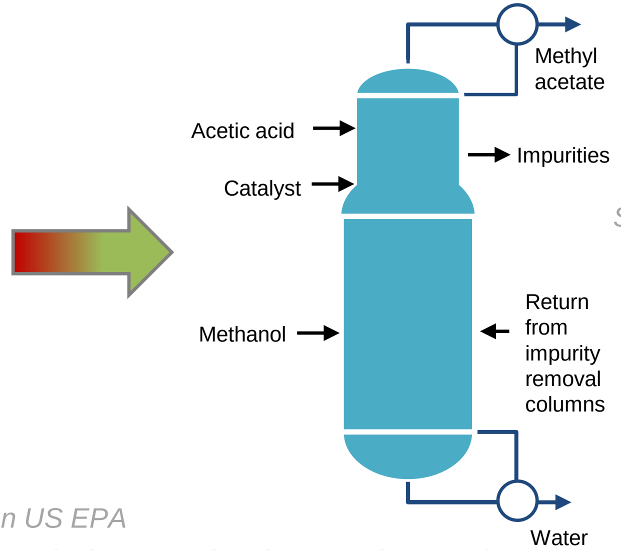
- Increase conversion, raw material productivity and selectivity
- Avoid/reduce separating reactants and solvents, reduce by-products and pollution intensity
- Reduce number of separation columns (capital investment)
- Decrease energy intensity

Traditional production of methyl acetate



Source: based on US EPA

Reactive distillation for methyl acetate production



Source: based on Huss et al., 2009

Green Chemistry & Green Chemistry Design Principles

- Green Chemistry & Green Engineering examples
- Green Chemistry & Green Engineering design principles
- Overview of Green Chemistry techniques
  - *Green Chemistry metrics*
  - *Material selection*
  - *Reaction conditions*

Definitions

Green Chemistry[1] is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green Chemistry applies across the life cycle of a chemical product, including its design, manufacture, use and ultimate disposal. Green Chemistry is also known as sustainable chemistry.

Green Engineering[1] is the design, commercialization and use of processes and products in a way that minimizes pollution, promotes sustainability and protects human health without sacrificing economic viability and efficiency.

Chemical process improvement is a component of green engineering focusing on improving process resource efficiency and reducing waste.

Green Chemistry and Green Engineering[2] are tools and principles applied across the life cycle so that chemical products and their production are resource-efficient with minimum pollution and safe for human health and the environment.

The 12 principles of Green Chemistry and 12 principles of Green Engineering can be used to guide their application in the design and commercialization of chemical products and processes (see following slides).

Sources: [1] United States Environmental Protection Agency; Anastas and Warner, 1998 [2] based on Jimenez-Gonzalez and Constable, 2011

12 Principles of Green Chemistry

1. **Prevention:** It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom economy:** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. **Less hazardous chemical syntheses:** Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing safer chemicals:** Chemical products should be designed to effect their desired function while minimizing their toxicity.
5. **Safer solvents and auxiliaries:** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used
6. **Design for energy efficiency:** Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of renewable feedstocks:** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable
8. **Reduce derivatives:** Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis:** Catalytic reagents (as selective as possible are superior to stoichiometric reagents.
10. **Design for degradation:** Chemical products should be designed so that at the end of their function the break down into innocuous degradation products and do not persist in the environment.
11. **Real-time analysis for pollution prevention:** Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently safer chemistry for accident prevention:** Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Source: Anastas and Warner, 1998

12 Principles of Green Engineering

1. **Inherent rather than circumstantial:** Designers need to strive to ensure that all materials and energy inputs and outputs are as inherently non hazardous as possible.
2. **Prevention instead of treatment:** It is better to prevent waste than to treat or clean up waste after it is formed.
3. **Design for separation:** Separation and purification operations should be designed to minimize energy consumption and materials use.
4. **Maximize efficiency:** Products, processes, and systems should be designed to maximize mass, energy, space, and time efficiency.
5. **Output-pulled versus input-pushed:** Products, processes and systems should be "output pulled" rather than "input pushed" through the use of energy and materials.
6. **Conserve complexity:** Embedded entropy and complexity must be viewed as an investment when making design choices on recycle, reuse, or beneficial disposition.
7. **Durability rather than immortality:** Targeted durability, not immortality, should be a design goal.
8. **Meet need, minimize excess:** Design for unnecessary capacity or capability (e.g., „one size fits all") solutions should be considered a design flaw.
9. **Minimize material diversity:** Material diversity in multicomponent products should be minimized to promote disassembly and value retention.
10. **Integrate material and energy flows:** Design of products, processes, and systems must include integration and interconnectivity with available energy and materials flows.
11. **Design for commercial „afterlife":** Product, processes, and systems should be designed for performance in a commercial „afterlife"
12. **Renewable rather than depleting:** Material and energy inputs should be renewable rather than depleting.

Source: Anastas and Warner, 1998

Green Chemistry and Green Engineering Design Principles

In practice, it is helpful to treat Green Chemistry and Green Engineering as a common approach to improve the sustainability of products and processes.

The many principles of Green Chemistry and Green Engineering can be organized into three guiding design principles*:

- Design systems holistically and use life cycle thinking through design (e.g. consider impacts of chemical products over its life cycle including consumer use and end of life) and being sustainable (e.g. use renewable feedstocks)
- Eliminate and minimize hazards and pollution through design (e.g. avoid persistence of products, safer production), measurement (e.g. real-time analysis, waste) and being sustainable (conserve ecosystems and protect human health and well-being)
- Maximize resource efficiency through design (e.g. use catalysis, reduce derivatives), measurement (e.g. mass balances, quantify by-products), efficiency (e.g. minimize energy requirements, optimize efficiency) and being sustainable (e.g. minimize depletion of natural resources)

**Adapted from the American Chemical Society*

Design Systems Holistically and Use Life Cycle Thinking

🟩 **Green Chemistry** 🟦 **Green Engineering**

Source: based on the American Chemical Society

Design

Minimize chemistry impacts
Consider the effect of the overall process and life cycle on the choice of chemistry.

Holistic approach
Engineer processes and products holistically, use systems analysis and integrate environmental impact assessment tools.

Use life cycle thinking
Use life cycle thinking in all engineering and chemistry activities.

End of use
Products, processes and systems should be designed for performance in a commercial "afterlife".

Durability
Targeted durability, not immortality, should be a design goal.

Conserve complexity
Embedded entropy and complexity must be viewed as an investment when making design choices on recycling, reuse or beneficial disposition.

Collaborate with engineers
Consult a chemical or process engineer.

Consider incompatibilities
Recognize where safety and waste minimization are incompatible.

Minimize material diversity
Material diversity in multicomponent products should be minimized to promote disassembly and value retention.

Being sustainable

Use renewables
A raw material feedstock should be renewable rather than depleting whenever technically and economically practical.

Material and energy inputs should be renewable rather than depleting.

Innovate to achieve
Create engineering solutions beyond current or dominant technologies. Improve, innovate and invent (technologies) to achieve sustainability.

Think locally
Develop and apply engineering solutions while being aware of local geography, aspirations and cultures.

Engage
Actively engage communities and stakeholders in the development of engineering solutions.

Apply measures
Help develop and apply sustainability measures.

Eliminate and Minimize Hazards and Pollution

🟩 **Green Chemistry** 🟦 **Green Engineering** *Source: based on the American Chemical Society*

Design	Measure	Being sustainable
Avoid persistence Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products. **Inherently non-hazardous** Designers need to strive to ensure that all material and energy inputs and outputs are as inherently non-hazardous as possible. **Synthetic methods** Wherever practical, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment. **Safer processes** Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires. **Prevention** It is better to prevent waste than to treat or clean up waste after it has been formed.	**Real-time analysis** Analytical methodologies need to be developed further to allow for real-time in-process monitoring and control prior to the formation of hazardous substances. **Losses** Measure catalyst and solvent losses in aqueous effluent. **Thermochemistry** Investigate basic thermochemistry. **Incompatibilities** Recognize where safety and waste minimization are incompatible. **Waste** Monitor, report and minimize laboratory waste emitted.	**Conserve and improve** Conserve and improve natural ecosystems while protecting human health and well-being.

Maximize Resource Efficiency

🟩 **Green Chemistry** 🟦 **Green Engineering**

Source: based on the American Chemical Society

Design	Measure	Being efficient	Being sustainable
Output-pulled vs. input-pushed Products, processes and systems should be “output pulled” rather than “input pushed” through the use of energy and materials. **Atom economy** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product. **Find alternatives** The use of auxiliary substances (e.g., solvents, separation agents) should be made unnecessary whenever possible and innocuous when used. **Reduce derivatives** Unnecessary derivatization (blocking group, protection-deprotection and temporary modification of physical / chemical processes) should be avoided whenever possible. **Use catalysis** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.	**Mass balances** Establish full mass balances for a process. **Heat and mass transfer** Anticipate heat and mass transfer limitations. **Conversion** Report conversions, selectivities and productivities. **By-product formation** Identify and quantify by-products. **Utilities** Quantify and minimize the use of utilities.	**Reduce** Separation and purification operations should be designed to minimize energy consumption and materials use. **Minimize** Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure. **Optimize** Products, processes and systems should be designed to maximize mass, energy, space and time efficiency. **Integrate** Design of products, processes and systems must include integration and interconnectivity with available energy and material flows. **Prevent** Strive to prevent waste.	**Minimize** Minimize depletion of natural resources. **Conserve and improve** Conserve and improve natural ecosystems while protecting human health and well-being.

Overview of Green Chemistry Techniques

- Green Chemistry & Green Engineering examples
- Green Chemistry & Green Engineering design principles
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  - *Green Chemistry metrics*
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Introduction to Green Chemistry Metrics

Metrics can be used to measure the greenness of a chemistry, process or product.

Consider the following when using metrics to measure the greenness:

- Where to draw the boundary to best capture the impact of the process or product
- Metrics should be easily understood and promote continuous improvement
- A system of metrics help provide a fuller picture
- All metrics should contribute to achieving Green Chemistry goals

Examples of Green Chemistry Metrics (I)

In addition to traditional chemistry metrics such as yield, selectivity; one can use the following metrics to measure the greenness of the chemistry:

Atom economy

$$\text{AE} = \frac{molecular\ weight\ of\ product}{total\ molecular\ weight\ of\ reactants} \times 100$$

Reaction mass efficiency

$$\text{RME} = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

Optimum efficiency

$$\text{OE} = \frac{RME}{AE} \times 100$$

(Process) Mass intensity

$$\text{PMI} = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

Examples of Green Chemistry Metrics (II)

In addition to traditional chemistry metrics such as yield, selectivity; one can use the following metrics to measure the greenness of the chemistry:

$$\text{Renewables intensity} = RI = \frac{mass\ of\ all\ renewably\ derivable\ materials\ used}{mass\ of\ product}$$

$$\text{Renewables percentage} = \frac{RI}{PMI} \times 100$$

$$\text{Waste intensity} = WI = \frac{total\ waste\ produced}{total\ mass\ input}$$

$$\text{Waste percentage} = \frac{WI}{PMI} \times 100$$

Green Chemistry Metrics: Example

Benzyl alcohol ($C_6H_5CH_2OH$) (10.81g, 0.10mol, 108.1g/mol) reacts with p-toluene sulfonylchloride ($CH_3C_6H_4SO_2Cl$) (21.9g, 0.115mol, 190.65g/mol) in toluene (500g) and triethylamine (15g) to give the sulfonate ester ($CH_3C_6H_4SO_2OC_6H_5CH_2$) (262.29g/mol) isolated in 90% yield (0.09mol, 23.6 g). Calculate the following parameters:

atom economy $= \frac{molecular\ weight\ of\ product}{total\ molecular\ weight\ of\ reactants} \times 100$

reaction mass efficiency $= \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$

mass intensity $= \frac{total\ mass\ in\ a\ process\ of\ process\ step}{mass\ of\ product}$

mass productivity $= \frac{1}{mass\ intensity} \times 100$

Source: Gonzalez and Constable

Green Chemistry Metrics: Example

Benzyl alcohol ($C_6H_5CH_2OH$) (10.81g, 0.10mol, 108.1g/mol) reacts with p-toluene sulfonylchloride ($CH_3C_6H_4SO_2Cl$) (21.9g, 0.115mol, 190.65g/mol) in toluene (500g) and triethylamine (15g) to give the sulfonate ester ($CH_3C_6H_4SO_2OC_6H_5CH_2$) (262.29g/mol) isolated in 90% yield (0.09mol, 23.6 g). Calculate the following parameters:

atom economy $= \frac{262.29}{108.1 + 190.65} \times 100 = 87.8\%$

reaction mass efficiency $= \frac{23.6}{10.81 + 21.9} \times 100 = 70.9\%$

mass intensity $= \frac{10.81 + 21.9 + 500 + 15}{23.6} = 23.2\frac{g}{g} = 23.2\frac{kg}{kg}$

mass productivity $= \frac{1}{mass\ intensity} \times 100 = 4.3\%$

Source: Gonzalez and Constable

Comparison of Metrics for Different Chemistries (I)

	Stoichiometry of B mole (%)	Yield (22%)	Atom economy (%)	Reaction mass efficiency (%)	Mass intensity excluding water (kg/kg)	Mass productivity (%)
Acid salt	135	83	100	83	16.0	6.3
Base salt	273	90	100	80	20.4	4.9
Hydrogenation	192	89	84	74	18.6	5.4
Sulfonation	142	89	89	69	16.3	6.1
Decarboxylation	131	85	77	68	19.9	5.0
Esterification	247	90	91	67	11.4	8.8
Knoevenagel	179	91	89	66	6.1	16.4
Cyanation	122	88	77	65	13.1	7.6
Bromination	214	90	84	63	13.9	7.2
N-acylation	257	86	86	62	18.8	5.3
S-alkylation	231	85	84	61	10.0	10.0
C-alkylation	151	79	88	61	14.0	7.1
N-alkylation	120	87	73	60	19.5	5.1
O-arylation	223	84	85	58	11.5	8.7

Source: Gonzalez and Constable

Comparison of Metrics for Different Chemistries (II)

	Stoichiometry of B mole (%)	Yield (22%)	Atom economy (%)	Reaction mass efficiency (%)	Mass intensity excluding water (kg/kg)	Mass productivity (%)
Epoxidation	142	78	83	58	17.0	5.9
Borohydride	211	88	75	58	17.8	5.6
Iodination	223	96	89	56	6.5	15.4
Cyclization	157	79	77	56	21.0	4.8
Amination	430	82	87	54	11.2	8.9
Lithal	231	79	76	52	21.5	4.7
Base hydrolysis	878[a]	88	81	52	26.3	3.8
C-acylation	375	86	81	51	15.1	6.6
Acid hydrolysis	478	92	76	50	10.7	9.3
Chlorination	314	86	74	46	10.5	9.5
Elimination	279	81	72	45	33.8	3.0
Grignard	180	71	76	42	30.0	3.3
Resolution	139	36	99	31	40.1	2.5
N-dealkylation	2650[a]	92	64	27	10.1	9.9

[a] Inflated by use of solvent as reactant

Source: Gonzalez and Constable

Chem21 Metrics Toolkit

The CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries) developed a Green Chemistry toolkit for the pharmaceutical industries which can be applied to all chemical processing industries.

The bench-scale toolkit involves a ‘zero pass’ and ‘first pass’ screening process.

- Zero pass: use at the discovery phase where large numbers of screening reactions are carried out on a small scale with the most promising reactions selected fro the ‘first pass’. This stage looks at metrics yield, conversion, selectivity, AE, RME, restricted solvents and health & safety
- First pass: more in-depth investigation of a reaction’s greenness including comparing different routes to the same target compound. Additional metrics include MI, critical elements, energy, chemicals of concern, and more detailed analysis

An excel tool can be downloaded here: http://pubs.rsc.org/en/Content/ArticleLanding/2015/GC/c5gc00340g#!divAbstract

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Improving Reaction Conditions: Material Selection – Solvents

Solvents are used in many industries for processing (e.g. distillation, equipment cleaning), synthesis (reactant) and formulation of products (carrier).

Solvents typically have serious health and environmental hazards including waste management issues, so:

- Avoid materials not integrated in the product (e.g. solvents) where possible
- If solvents are necessary, use ones with less health and environmental impacts, and minimize their use while optimize effectiveness

Improving Reaction Conditions: Material Selection – Solvent Properties & Selection (I)

Solvent properties are an essential criteria when selecting solvents for a process. Select solvents according to Green Chemistry principles (satisfy solubility requirements while minimizing health, safety and environmental impacts).

The 'CHEM21 solvent selection guide' can be used to evaluate existing and new solvents according to health, safety and environmental factors and classify them as:

- Recommended
- Problematic
- Hazardous

The background paper and an excel tool can be found here:

http://pubs.rsc.org/en/content/articlelanding/gc/2016/c5gc01008j#!divAbstract

Improving Reaction Conditions: Material Selection – Solvent Properties & Selection (II)

Once the solvents have been evaluated for health, safety and environmental impacts, the final selection as made based on functional performance and costs.

The following can be used to select solvents based on their properties:

- Property databases: e.g. search for water-miscible solvents with a boiling point between 70-95°C (e.g. CRC handbook)
- Principal components analysis: can be used to identify a system of EHS-friendly solvents to replace a single component hazardous solvent according to desired properties such as boiling point, melting point, dipole moment, solubility parameters. An practical way to address solubility challenges is to use the Hansen solubility parameters of mixtures to replace the functionality of a single component. For more information:

http://hansen-solubility.com/

Improving Reaction Conditions: Material Selection - Catalysts

Catalysts lower the reaction's activation energy and speeds up the rate of reaction and can result in increased reaction efficiency.

Example: BASF developed a new process to manufacture ibuprofen, replacing a technology with six stoichiometric steps and less than 40% atom utilization with a technology with three steps and 80% atom utilization, and large amounts of aqueous waste was eliminated.

Possible benefits of catalysis:

- Productivity: increased yield, selectivity, and reactor volume efficiency; reduced cycle time and variability
- Environmental: increased resource efficiency; reduction of undesired by-products; elimination or reduction of solvents;
- Safety: can reduce the use of hazardous chemicals

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Reaction Conditions

Reactions conditions are an important way to improve the greenness of the chemistry and process.

The most common reaction conditions which can be modified by the manufacturer include:

- Stoichiometry
- Temperature
- Order and rate of reagent addition
- Mixing

Design of experiments can be used to optimize reaction conditions using a minimum number of experiments. See more in ‘Introduction to Operational Excellence’. E11_1_Intro to OE

Common Activities in Batch Processing and Impacts on Green Chemistry

Many activities in the batch chemical processing impacts Green Chemistry. Common activities, the problems they cause and possible options to solve the problem are found in the reference document ‘Green Chemistry impacts in batch chemical processing’. ▶ C11_2_Chem processing GC impacts

The batch chemical processing activities include:

- Acid and base washes
- pH adjustment
- Salt washes
- Use of desiccants
- Chromatographic clean-ups
- Carbon cleanup
- Use of filter aids
- Put and take distillations
- Distillations
- Isolation steps / crystallization

Improving Reaction Conditions: Stoichiometry

Basic chemistry places importance on balancing equations for reactions. There is a balance between mass efficiency (reducing waste) and having excess reagent to drive reactions to completion. General principles for improving stoichiometry impacts include aiming:

- For reactions which need equimolar (or close to) quantities of reactants to reduce excess waste
- To minimize stoichiometric excesses of catalysts (e.g. reduce excess strong Lewis acids used as a catalyst in the nitrification of aromatics)
- To use bound catalysts which can be regenerated (e.g. Lewis solid acid (zeolite-based) which can be regenerated and avoid large quantities of waste)

Improving Reaction Conditions: Temperature

General Green Chemistry on selecting chemistries and temperature:

- Use reactions which can be run as close to ambient temperature (and to a lesser degree, pressure) as possible and avoid running reactions at very cold temperatures (< -20°C) since this is energetically very unfavourable.
- Balance temperature with reactions rates to optimize reaction kinetics while avoiding conditions which could cause an accident
- Estimate heat of reaction (endothermic or exothermic) before validating with experiments
- Be careful with exothermic reactions:
  - It is important to characterize impacts of reaction temperature, reaction rate, order of addition, mixing, pressure and heat evolution/removal.
  - Avoid run-away reaction conditions (heat evolution increases exponentially while heat removal is linear). Note: using the Arrhenius relationship, a 10°C increase in temperature can result in a 2-3 times increase of reaction rate and likewise heat release.

Improving Reaction Conditions: Mixing

Mixing is an important Green Chemistry issue in chemical processing and up-scaling. Mixing helps to overcome heat transfer and mass transfer limitations in chemical processing. Proper mixing:

- Avoids temperature and reagent concentration gradients (in reactors of all shapes and sizes) so that reactants are consumed and form product in equimolar amounts at the desired temperature thereby maximizing yield and reducing waste
- Prevents localized temperature hotspots and localized runaway reactions which could cause accidents (for exothermic reactions)
- Can control the rate of reaction if the kinetic rate is very high and the reaction is mass-transfer limited (e.g. simple acid or base neutralization reaction in which kinetic rate ~ 10^8 m^3/mol-s)

General tips:

- Solid-liquid: ensure solids or uniformly distributed in liquid
- Gas-liquid or liquid-liquid: ensure phases are uniformly mixed and interfacial area is optimized for desired reaction. Improper mixing in 2-phase systems can lead to problems with filtration, decrease product yield, increase processing time and lead to increased costs
- Improve mass transfer, increase product yield and decrease waste by considering alternative solvents (e.g. ionic liquids, supercritical fluids), phase transfer catalysts, or alternative reactors (e.g. vortex mixers, microreactors)

Improving Reaction Conditions: Order and Rate of Reagent Addition

The order and rate of reagent addition can have significant impacts on the process and final product, in particular:

- Optimization can lead to significant reductions in reaction time, energy consumption and waste
- Make reactions more controllable and safe. E.g. for exothermic or endothermic reactions, by adding reagents in a certain order, excessive temperatures (exothermic) or uncontrolled precipitation (endothermic) can be avoided

Order and rate of addition can be used:

- In micro or minireactors to achieve optimal reaction rate and temperature
- To control kinetic rate and possibly reduce undesired by-products, impurities and maximize yield
- To control temperature by heating or cooling reagents before addition
- In multiphase systems to prevent emulsion, control rate and timing of phase formation

Note: order and rate of addition should always be optimized together with mixing

Key Messages

Key Messages (1)

The design of chemical products pose numerous challenges in chemistry such as non-ideal conversion, competing reactions, hazardous chemicals, raw material impurities, etc. and Green Chemistry techniques can improve material efficiency, reduce pollution intensity, and also produce safer products and processes.

Green Chemistry and green engineering should be integrated to make green products using green processes. All design principles can be grouped in three guiding design principles:

- Design systems holistically and use life cycle thinking
- Eliminate and minimize hazards and pollution
- Maximize resource efficiency

Key Messages (2)

Green Chemistry can be applied in a practical way using the following parameters:

- Green Chemistry metrics: Quantifiable and verifiable metrics can be used to measure the greenness of reactions, processes or products. Often a system of metrics (with different boundaries) are required to understand the full impacts.
- Material selection:
  - Solvents are often the source of EHS impacts. Alternative, safer solvents can typically be found by comparing properties or using a solvent system mixture with similar single component prosperities (e.g. using Hansen solubility parameters)
- Reactions conditions are an important way to improve the greenness of the chemistry and process. The most common reaction conditions which can be modified by the manufacturer include:
  - Stoichiometry
  - Temperature
  - Order and rate of reagent addition
  - Mixing

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