Green Metrics in a Pharmaceutical Scenario- A Review

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Abstract

Various metrics are employed in pharmaceutical sector to define a system-wide, cycle-based perspective so as to deduce an accurate measure of ‘greenness’ of chemical processes and products. Green metrics cover areas of resources, materials, processing, cleaning, life cycle assessment and renewability. This review describes commonly used metrics to measure greenness of chemical reactions and processes for deriving meaningful correlations between them. A note on current and future endeavors in green metrics in a pharmaceutical scenario is also presented.

INTRODUCTION

Today, a vigorous endeavour in synthetic chemistry is to invent efficient and environment-friendly chemical reactions and processes. Scientists and engineers are making claims that their methods and technologies are ‘greener’ or ‘cleaner’ as against conventional existing models. Popularly termed as ‘green chemistry’, there is a pressing need to measure and rank “green” performance of chemical reactions quantitatively. Quantification of ‘greenness’ of chemical reactions and its processes is performed by using green chemistry metrics. It is now widely accepted that quantification of sustainable practices such as measuring ‘greenness’ of different chemical processes is essential to achieve real progress. Earlier attempts to identify green metrics focused significantly on quantifying waste generated from chemical processes. However, now scientists and green chemists are working on current green metrics that can incorporate more of the 12 principles of green chemistry as laid by Anastas and Warner [1].

As many scientists include greener approaches in their analysis of new processes [2], it is essential to accurately label the chemical processes and products as ‘green.’ Apart from waste, green metrics should focus on the following pointers, viz,

- Resource Efficiency- Mass, energy, waste.
- Environmental, health, safety profile of materials used and the chemical process.
- Overall life cycle assessment considerations such as, use of renewable feedstock, occupation hazard-risk and inherent safety using real-time analysis.

Pharmaceutical industry is devoted to inventing medicines that allow patients to live longer, healthier, and is committed to bringing key medicines to the patient with minimal environmental impact. Concepts of green chemistry and green engineering are not new in the pharmaceutical industry. In recent years, significant effort has been invested to improve efficiency, reduce waste, and enhance quality and control in research, development and manufacturing. This is driven by the desire not only to reduce costs but also to increase sustainability of manufacturing processes.
In this pursuit, American Chemical Society (ACS), Green Chemistry Institute (GCI), and several global pharmaceutical corporations founded the ACS GCI Pharmaceutical Roundtable (ACS GCIPR) [3]. It comprises of sixteen members, now: Abbott Laboratories, Amgen, Astra Zeneca, Boehringer-Ingelheim, Codexis, Dr. Reddy’s, DSM Pharmaceutical Products, GlaxoSmith-Kline, Johnson & Johnson, Eli Lilly and Company, Lonza, Merck & Company, Novartis, Pfizer, and Roche. These industry competitors work collaboratively to address the environmental impact of pharmaceutical industry [4,5]. The activities of the Pharmaceutical Roundtable reflect the joint belief that the pursuit of green chemistry and engineering is imperative for making more sustainable and environment-friendly business of drug discovery, development, and production.

NEED FOR GREEN METRICS

The consumer interest in ‘green products’ has encountered the disenabling practice of misleading claims. This also includes various publications claiming newer methods as ‘being green.’ Unethical practice of manufacturers to overstate or misquote green claims is identified as ‘greenwashing.’ Greenwashing is defined as ‘the act of misleading consumers regarding the environmental practices of a company or the environmental benefits of a product or service’ [6]. This can result in trivialization of the concept behind the terms like, sustainable, renewable and green. Resource reduction, pollution prevention and waste minimization have become a focal point to evaluate ‘greenness’ of chemical process. Hence, there is need for accurate measure to estimate ‘greenness’ of an organic reaction, related processes and products.

In this article, various green metrics employed in pharmaceutical sector with a note on current and future approaches needed for green metrics practice are described.

MEASURING PROCESS AND REACTION EFFICIENCY

Let us discuss the most common green metrics employed to estimate the greenness of a synthetic reaction.

1. Reaction Yield: It is one of the most generic metric for an organic reaction. Yield is the universally accepted metric in chemistry for measuring efficiency of a chemical synthesis. It provides simple and understandable way of measuring success of a synthetic route and comparing it to other reactions. Theoretical yield is initially calculated based on the amount of the reagent used in a reaction and percentage yield is the actual yield calculated after the synthesis. For any given chemical reaction, A+B \rightarrow C,

\[ \text{Theoretical yield} = \text{Stoichiometric ratio} \times \frac{\text{MW of desired product}}{\text{MW of limiting reagent}} \times \text{wt of limiting reagent} \]

where, MW is molecular weight.

and, Percentage yield = (actual yield/theoretical yield) x 100

Let us examine the formation of n-propyl bromide from n-propyl alcohol (0.6g)

\[ \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-OH} + \text{NaBr + H}_2\text{SO}_4 \rightarrow \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-Br} + \text{NaHSO}_4 + \text{H}_2\text{O} \]

MW (60) (103) (98) (123) (120) (18)

One mole of n-propyl alcohol gives one mole of n-propyl bromide,

\[ \text{Theoretical yield} = \text{Stoichiometric ratio} \times \frac{\text{MW of C}_3\text{H}_7\text{Br/MW of C}_3\text{H}_7\text{OH}}{\text{X wt of limiting reagent}} \]

\[ = \frac{(1/1) \times (123/60) \times 0.6}{1.23 \text{ g}} \]

Percentage yield will always be less than the theoretical yield due to formation of side products, incomplete conversion, loss during work up of reaction mixture and loss during isolation and purification of the desired product. In the above reaction, let us assume that the actual yield was found to be 0.98 g, then, % yield = (actual yield/theoretical yield) x 100

\[ = \frac{0.98}{1.23} \times 100 = 79.6 \% \]

Higher yields in a reaction are desirable from economic point of view, but it is not enough. It fails to account for reagents consumed, solvents and catalysts that will not be fully recovered, and, most importantly, resource- and energy-consuming separation stages such as water quenches, solvent separations, and distillations.

2. Atom Economy (AE): This metric addresses Green Chemistry Principle # 2 (atom economy) and # 8 (reduce derivatives). Atom economy is the most fundamental concept applied to estimate greenness of an organic reaction. Atom economy helps in designing reactions so that the atoms present in the starting materials end up in the product rather than in the waste-
of minimizing waste to the molecular level [7]. Atom economy answers the basic question, ‘How much of what you put into your pot ends up in your product?’ [8]. Barry Trost published the concept of atom economy [9] and was bestowed the Presidential Green Chemistry Challenge Award for his work [10]. Atom economy is the measure of how efficiently atoms of the reactants in any reaction are incorporated into the desired product.

\[
\text{% AE} = \left( \frac{\text{Formula weight of atoms in desired product}}{\text{Formula weight of reactants}} \right) \times 100
\]

The process of calculating atom economy may be simplified by only considering the key reactants and desired products. If applied to the same example as above.

\[
\text{% AE} = \left( \frac{123 \times 100}{60 + 103 + 98} \right) = 47.1\%.
\]

Only less than half of the reactant atoms are incorporated into the product and rest are waste products. Organic reactions can have either a higher atom economy or lower atom economy. This came to be known as ‘inherent atom economy.’ Higher the atom economy, greener is the route of chemical reaction in question. However, this metric does not account the actual yield or stoichiometry of reactants used in a system, or for solvents and other reagents, so there is scope for misrepresentation of the efficiencies of a real system.

3. **E-factor:** It was proposed by Roger and Sheldon [11] and is defined as follows:

\[
\text{E-Factor} = \frac{\text{Total waste (kg)}}{\text{Total weight of desired product (kg)}}
\]

4. **Mass Intensity (MI):** Total mass used in the process or process step (kg)/Mass of product (kg) is called mass intensity [12]. This metric takes into account the yield, stoichiometry, solvent, and reagent used in the reaction mixture, and expresses this on a weight/weight basis rather than a percentage. Total mass includes everything that is used in a process or process step with the exception of water; i.e., reactants, reagents, solvents, catalysts, etc. Total mass also includes all mass used in acid, base, salt and organic solvent washes, and organic solvents used for extractions or crystallization. Water has been excluded from mass calculations since, it skews mass data in many processes and does not constitute a significant environmental impact. It is expressed as:

\[
\text{E-Factor} = \frac{1}{\text{MI}} - 1
\]

5. **Mass Productivity:** By expressing mass intensity as its reciprocal and making it a percentage, it is in a form similar to effective mass yield and atom economy. This metric will be called mass productivity.

\[
\text{Mass Productivity} = \left( \frac{1}{\text{MI}} \right) \times 100
\]

Though the above metrics have been known for some time, they have been presented as separate and unrelated quantities. Moreover there is still ongoing debate as to what metric is best to measure “greenness”. Several other metrics related to atom economy have been developed and explored at GlaxoSmithKline. These are known as carbon efficiency (CE) and reaction mass efficiency (RME). Other metrics reported so far are atom utilization (AU) [13], environmental or elegance quotient (EQ) [14], and mass efficiency [15].

6. **Carbon efficiency:** It is defined as the percentage of carbon in the reactants that remain in the final product. When calculating carbon efficiency, yield and stoichiometry of reactants and products are included.

For a generic reaction \( A + B \rightarrow C \),

\[
\text{% CE} = \left( \frac{\text{Amount of carbon in product}}{\text{total carbon present in reactants}} \right) \times 100
\]

If the reaction is, \( A + B \rightarrow \text{Product} + \text{co-product} \)

\[
\text{% CE} = \left( \frac{\text{[(number of moles of product x number of carbons in product)/moles of A carbons of A) + (moles of B x carbons in B)]}}{100} \right)
\]

7. **Reaction mass efficiency (RME):** When calculating reaction mass efficiency, atom economy (AE), yield and the stoichiometry of reactants are included. RME is the percentage of the mass of reactants that remain in the product. For a generic reaction, \( A + B \rightarrow C \),

\[
\text{% RME} = \left( \frac{\text{mass of product C/mass of A + mass of B}}{100} \right)
\]

**GREEN METRICS IN PHARMACEUTICAL INDUSTRY**

Many small-tier pharmaceutical and biopharmaceutical companies generally do not keep track of green metrics unless the metric is required to demonstrate compliance with environmental regulations. Generic drug industry is largely untouched by the
green metric system; however, a notable exception is the Dr. Reddys, which has been active in green chemistry applications to pharmaceutical processes within metrics [16]. Most commonly used metrics by drug manufacturers are mass intensity (MI) or process mass intensity (PMI) and E-factor (E).

E-Factor, as a green metric is relatively simple and easy to understand that draws attention to the quantity of waste produced for a given mass of product. It also expresses the relative wastefulness of different parts of the chemical processing industries. However, it is difficult for pharmaceutical industries to routinely use this metric in its operations due to lack of clarity on waste management. This is due to the fact that ‘total waste’ in the numerator of the formula lacks clarity. These include, a) Is the waste that passes over the fence the only waste considered? b) Is waste that is produced as a result of emissions treatment (e.g., gas scrubbing, pH adjustment in wastewater treatment plants, etc.) included? c) Is waste that is produced as a result of energy use (heating-cooling reactions, abatement technology, etc) included? From an operational perspective, these types of questions complicate routine use of this metric for chemists whose primary concern is to get new products on to the market in a short period of time. Different variations on E-factor have been proposed and used in the pharmaceutical industry, such as mass intensity, mass productivity and process mass intensity as discussed in the earlier section.

These green metrics have the aim of greening processes by highlighting the amount of materials used in the process while developing new syntheses and products in R&D or evaluating manufacturing processes for commercial routes to produce active ingredient (API). While designing a reaction, one is primarily concerned about their implications on sustainability, environmental degradation, and the cost of waste disposal. In this context, efficiency metrics such as mass intensity or mass efficiency have advantage over waste metrics like E-factor for communicating and framing sustainability of a chemical process design.

While defining various green metrics, water used in the reactions was not included, since it was believed that it can surmount to higher E-factors and comparisons of reaction processes will be difficult. Further, water was not integral to the chemical reaction but was used during work-up operations such as, phase separations or effect pH changes. Many also believed that water was cheap and did not represent an environmental impact. Pharmaceutical Roundtable has decided to define Process Mass Intensity including water, and now routinely uses this metric for benchmarking purposes [17]. Pharmaceutical industry uses ultra-purewater and there are life cycle impacts related to the chemicals and equipment used to purify water. Through careful assessment of many pharmaceutical batch reactions conducted over many years, GSK reported that solvents are the biggest mass contributor to its processes [18] hence, some additional metric equations are denoted as follows,

Solvent intensity = (mass of all solvent used excluding water/mass of product) kg/kg of product.

Thus, % Solvent intensity = (mass of all solvent/ mass intensity) kg/kg of product.

Water intensity = (mass of all water used/mass of product) kg/kg of product.

This led to the development of methodologies for measuring the relative greenness of common solvents used in the pharmaceutical industry to aid chemists in their understanding of the environment, health and safety issues associated with choosing any particular solvent [19,20].

**Life Cycle Metrics:** Incorporating a life cycle approach forms the central idea in green pharmaceutical chemistry. Life cycle approach evaluates ‘greenness’ of a product or a process not only by the amount of waste generated and harmful materials released during the manufacturing process, but also the consumption of energy, depleting raw materials and fate of chemical products in the environment [21,22]. The main focus of LCA methodology is to collect and evaluate the data on the emissions and their environmental impact at every step in the process of production of a given product starting from resource consumption like - acquiring raw materials (including energy, extraction), production, transportation, distribution, pollutant emissions and subsequent fate of the product in the environment. This is known as ‘cradle-to-grave’ assessment approach where, cradle-to-gate involves comparison of two different synthetic routes to obtain the same API and gate-to-grave is comparison of solvent treatment processes. LCA methodology provides a framework of directly applicable green metrics for the life cycle impacts. These metrics are reported as direct inventory data, for example life cycle energy, life cycle mass, life cycle emissions; measures of individual potential impacts such as global warming. Analysis of environmental impacts of products and processes from cradle-to-grave aims to avoid the false impression of the ‘environmental friendliness’ of processes which can arise on inspecting only a part of the product/process cycle. The various green metrics that are employed in LCA methodology are described below.
Energy Metrics: These metrics include not only the processing energy, but also energy required to produce raw materials, recycle of materials and waste treatment. Some of the energy metrics include,

Energy intensity = total process energy (MJ)/mass of final product (kg)

Life cycle energy = life cycle energy requirements (MJ)/mass of final product (kg)

= \sum \text{process, material manufacturing, recovery, treatment/mass of final product (kg)}

Waste treatment energy = waste treatment energy requirements (MJ)/mass of final product (kg)

Solvent recovery energy = solvent recovery energy requirements (MJ)/mass of final product (kg)

Solvent energy ratio = total energy for solvent use and recovery/total energy input

Waste energy ratio = total waste produced/total energy input

Renewability metrics: This particular metric is focusing on Green Chemistry Principle # 7, i.e, using renewable feedstock [23]. Renewable materials come from natural resources that can be replenished at a rate equal to or faster than they are consumed. Renewable sources include water, wind, the sun, and certain agricultural and marine feedstock. The use of renewably resourced material is a desirable goal superficially; there is more complexity when one considers the energy required to produce them. It is adjudged that there are the environmental life cycle impacts associated with growing, harvesting, competing use of land, processing and purifying renewable materials. Hence there is a need to take a life cycle standpoint in this case. One way to look at the renewability of a chemical is to use a Renewability Index based on life cycle data. In GSK, this has led to the concept of a renewability index, where a score is given, say between 1 (no renewables) and 10 (most renewables), to account for the proportion of renewable resources in any given supply chain. The use of this type of index will require one to consider whether to assign more weight to renewable feedstock or to renewable energy.

For calculating Renewables Intensity (RI) metric based on the mass of the total product [24],

Renewables Intensity = mass of all renewably derived materials used (kg)/mass of product (kg)

To account for the energy, a Renewability Index (RI) including process energy can be written based on the life cycle Carbon mass intensity, as,

Renewability Index = [Carbon from renewable materials (kg)/total cradle mass carbon mass intensity] + [Carbon from renewable energy (kg)/total energy mass carbon mass intensity]

The first term in the equation encompasses life cycle carbon mass intensity per kg of material as the proportion of the life cycle carbon mass from renewable materials. The latter term include energy derived from oil, coal, natural gas and renewable sources and all energy is converted to kg carbon. Since RI is the fraction of carbon from renewable materials out of the total life cycle carbon, this number may be a small percentage, given the amount of chemicals necessary to purify and isolate final product. Renewability Index is hence scored for a given set of materials by ranking the materials from 1 to 10 having highest renewability fraction.

Solvent Metrics: This covers the Green Chemistry Principle # 5 (Use of Safer solvents). On careful assessment of various pharmaceutical processes, GSK revealed solvents are the biggest mass contributor to its processes [25]. It is observed that pharmaceutical industry has the highest waste generation and the highest amount of organic solvents used per mass of product produced for any commercial sector. The solvent use rates can range from 10–800 kg/kg API depending on the type of pharmaceutical and stage of development [26]. Generation of solvent waste is due to poor solvent selection and processing inefficiencies, resulting in increased concerns about environmental and human safety. Ionic liquids, water, supercritical fluids, fluorous solvents and molecular solvents from renewable sources are desirable green solvents. However, it is not always possible to employ them as their use must be balanced with process efficiency, operation-capacity and cost. Various metrics have been developed for accurate selection of solvents and recycling-reuse approaches given in Table 1.

Recyclability metrics: Generally process recycling include in-process and post-process recycle methods, but in pharmaceutical operations, post-recycle is feasible and a cost-effective method. In recycle metrics one can sum the masses of potentially recyclable chemicals, solvents, water and miscellaneous reagents.

Degradation potential metric: Concerning Green Chemistry Principle # 10 (design for degradation) the challenge for pharmaceutical industry is to design drugs that will survive in harsh environments inside the human body for long enough to reach target receptors and then provide an effective dose. This means that API’s are designed to have certain level of inherent
resistance to biodegradability, which has led to concerns regarding the level of risk from pharmaceuticals in the environment. It is important to carefully evaluate distribution and degradation mechanisms that will directly affect the potential for exposure from any given chemical. Further research is ongoing to evaluate long-term impact of pharmaceuticals [36, 37].

Table 1. Computer-aided Solvent selection tools and its primary features

<table>
<thead>
<tr>
<th>Solvent Selection Tool</th>
<th>Features</th>
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</thead>
<tbody>
<tr>
<td>GSK-Solvent Selection Guide (Expanded)</td>
<td>Proprietary visual, web-based solvent-selection tool for selecting “greener” solvents for various reactions common in pharmaceutical synthesis. Expanded view recently incorporated sustainability measure while selecting solvents. [27]</td>
</tr>
<tr>
<td>BMS Process Greenness Scorecard</td>
<td>A computer tool to rate relative greenness of solvents based various green chemistry process parameters. [28]</td>
</tr>
<tr>
<td>Solvent Predictor</td>
<td>Solvents are ranked by theoretical yield and number of criteria (limiting reactants, products) met for a reaction.[29]</td>
</tr>
<tr>
<td>ProCAMD (ProPred, PDS, Solu-Calc, CAPEC-Database); SMSwin</td>
<td>Hybrid computer-aided technique for solvent selection; applies to wide range of industrial applications.[30]</td>
</tr>
<tr>
<td>NRTL-SAC and eNRTL-SAC</td>
<td>Method uses chemical thermodynamic parameters like activity coefficient applicable for solvents like electrolytes. [31]</td>
</tr>
<tr>
<td>COSMO-RS, COSMO-SAC</td>
<td>A physical property predictive modelling method for solvent fluid phase thermodynamics.[32]</td>
</tr>
<tr>
<td>ISSDS</td>
<td>Method permits alternative solvent selection from multiple databases though one “Integrated Solvent Substitution Data System.”[32]</td>
</tr>
<tr>
<td>SAGE</td>
<td>Logic-tree program that evaluates a user-defined scenario and suggests alternative solvents and processes based on EHS, economic, regulatory, and operational criteria. [33]</td>
</tr>
<tr>
<td>PARIS II (Program for Assisting the Replacement of Industrial Solvents)</td>
<td>Suggest alternative solvents by searching for solvents that have similar physical and chemical properties in current use but which carry lower environmental impacts. [34]</td>
</tr>
<tr>
<td>SMART (Solvent Measurement, Assessment, and Revampment Tool)</td>
<td>Integrated software program that contains EHS and regulatory information for over 320 commonly used industrial solvents. Depending on the design objective and operating parameters, SMART searches its database to compile a list of possible solvent choices. [35]</td>
</tr>
</tbody>
</table>

**Process safety metrics**: This metric focuses on Green Chemistry Principle # 12 (Inherently safer chemistry for accident prevention) which involves cost-effective measures to avoid or eliminate materials that are inherently unsafe- reactive, radioactive, unstable in nature. Several indices have been developed as metrics for estimating and ranking the safety of a given process or chemical reaction, such as the DOW fire and explosion index [38], Stoessel index [39] for hazard assessment and classification of chemical reactions, the Inherent Safety Index, the Prototype Index for Inherent Safety, amongst others [40,41].

**CURRENT AND FUTURE PRACTICES OF GREEN METRICS**

Pharmaceutical industry has always been accused in the past of being ‘ungreen.’ Today industry implements technologies that eliminate hazardous substances from their products and processes and adopt cleaner technologies because of favorable economics: material, compliance, and clean-up costs are lowered. Improvements are being made at both the process and consumer level. Today, pharmaceutical industry have placed a series of green chemistry metrics of different categories (mass, energy, safety, ecotoxicity, etc.) in order to evaluate efficiency and potential environmental impact of various chemical processes. Mass metrics such as PMI or its inverse, mass efficiency, are an indispensable intermediate step to estimate LCAs and footprints. In addition, mass metrics are found to be reliable; high-level metrics are easy to generate and compare, can
easily and directly be measured by chemists and engineers in laboratory settings, are easy to communicate and benchmark, and can be used to quickly obtain an estimation of the greenness of a chemical route. Considering the possibility that no green metric can evaluate ‘greenness’ of a synthetic route in isolation, unification of metrics came into picture. Stoichoimetric factor (SF) was developed that allows taking into account reactions run under nonstoichoimetric conditions. Based on four competing factors (reaction yield, atom economy, stoichoimetric factor and a factor accounting for reaction and post-reaction solvent and/or catalyst recovery), a general algorithm for reaction mass efficiency has been proposed. This has been followed by the introduction of minimum atom economy (AE)min and maximum environmental impact factor Emax that have been applied to over 400 named reactions [42]. EcoScale is a newer metric tool for the evaluation of the effectiveness of a synthesis reaction [43]. It evaluates quality of the organic preparation based on yield, cost, safety, conditions and ease of purification. It uses a scale from 0 to 100 with 100 representing the ideal reaction. EcoScale score is then calculated by lowering the maximum value of 100 by any applicable penalty points, which take into account both the advantages and disadvantages of specific reagents, set-ups and technologies. By calculating the EcoScale score, a quick assessment of the "greenness" of reaction protocol is obtained, and the areas that need further attention are clearly indicated, which finally can lead to the improvement of reaction conditions.

CONCLUSION

Today, many green metrics have been identified and implemented to meet varied demands of pharmaceutical industry. Generally, green chemistry metrics are an oversimplification and do not allow to know some environmentally important properties, such as toxicity, biodegradability, bioaccumulation and the fate of chemicals used. However, these factors are often used by chemical and pharmaceutical industries because they are easy to use and provide information that allows the comparison between different processes. It is also evident that no single metric, in isolation can judge the ‘greenness’ of a process. Rather than compartmentalizing, metrics should be interrelated for better evaluation of greenness of pharmaceutical processes. Even with unification approaches to green metrics, as described require continuous evaluation, validation for its applicability, extrapolation, reliability and integrity of the data obtained to wide variety of organic reactions.

Application of LCA metrics is still at initial stages in the pharmaceutical industry and scientists face challenges whilst its application. One of the challenges is large amount of data required from a variety of sources. Other main challenge is the absence of data for many raw materials needed in the production of most typical APIs. These challenges have driven companies and academics to use more limited approaches to life cycle in an attempt to improve the decision-making process. Green metrics are context-dependent—one kind or one set of metric does not fit all situations. Industries and organizations have already worked out their own green metrics to evaluate their chemical processes like GSK and Bristol-Myers, which is also open in the public domain.

REFERENCES