LCA approach to the analysis of solvent waste issues in the pharmaceutical industry

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Life cycle assessment offers a unique opportunity to analyze emission reductions across all manufacturing sectors. However, few efforts have been made to apply this method to the pharmaceutical industry. Typically, between 80 and 90% of the total mass used in the production of an active pharmaceutical ingredient (API) may be attributed to solvent use. Manufacture of virgin solvent and solvent waste management contribute significantly more life cycle emissions than comparable processes for commodity chemicals, with the majority of this waste consisting of CO_2 and other green house gas emissions. Three case studies from Pfizer, Bristol-Myers Squibb, and Novartis are examined. In these cases, solvent recovery and reduction techniques are integrated into API syntheses. It is shown that the actual extent of the environmental footprint reduction can only be realized with a full life cycle analysis.

Introduction and background

Life cycle assessment

Life cycle assessment (LCA) is a systematic method for analyzing the environmental impact of a product, process, or service through a cradle-to-grave approach. A cradle-to-grave approach assesses the environmental impact of the manufacture, use, and disposal of a material. This approach considers all effects from the point at which materials are gathered from the earth until these materials are returned to the earth.[1] This allows for a comprehensive understanding of the overall environmental effects of a process, allowing the analyst to recognize problems and solutions that a single-issue approach does not readily identify.[2] Through this comprehensive view, LCA avoids shifting environmental issues from one source to another.[1] The International Standards Organization (ISO) has issued a methodology for LCA development and interpretation, including ISO documents ISO-14040, ISO-14044, and ISO-14047.[3] Software packages with extensive process and environmental data, such as SimaPro 7.1® (PRé Consultants, Amersfoort, Netherlands), are also available to aid in the development and analysis of an LCA.

The methodology for developing an LCA includes the following steps: goal definition and scoping, inventory analysis, impact assessment, and interpretation. Goal definition and scoping involves defining the product or process to be assessed, establishing the context of the assessment, and defining the boundaries of that assessment. Inventory analysis involves indentifying and quantifying all energy and materials used and all environmental emissions throughout the product or process's life cycle. Impact assessment involves assessing any potential human and ecological effects from the inventory. Interpretation involves evaluating the inventory analysis and impact assessment results to make an informed decision on which process or product is environmentally superior according to the goal definition.[1] The development of an LCA is not linear; throughout the process it is necessary to return to previous steps and interpret the results found and the relation of these results to other steps in the LCA process. This method of evaluating processes has proven successful in a variety of industries, including electronics, production of electricity, and transportation fuels. It has been applied to pharmaceuticals, although to a smaller extent. Applications have included catalyst selection for processing an intermediate, a comprehensive study on a pharmaceutical product by GlaxoSmithKline, and an analysis of Vitamin B12 production.[4] Because of wide scale use of LCA in the process industry, LCA was applied to three pharmaceutical case studies.

Application to pharmaceuticals

Through the life cycle assessment of a series of case studies, it will be demonstrated that implementing a solvent recovery or reduction system into pharmaceutical manufacturing processes can significantly reduce the emissions associated with the process. The importance of solvents and solvent use in the manufacture of complex drug products often comes as a surprise to analysts, as was reported by GlaxoSmithKline (GSK).[5] Although solvents rarely enter into reaction chemistry, their use constitutes a majority of the mass and energy demand in the pharmaceutical industry. 80–90% of reaction mass and approximately 60% of energy use in the production of an active pharmaceutical ingredient (API) is attributed to solvents.[6] These solvents are used in reactions for API synthesis, providing a medium for reactions to take place, as well as separation and washing steps used to purify the API produced during the reaction. It is common practice in the pharmaceutical industry to incinerate solvent waste that is disposed.[7] Two environmental

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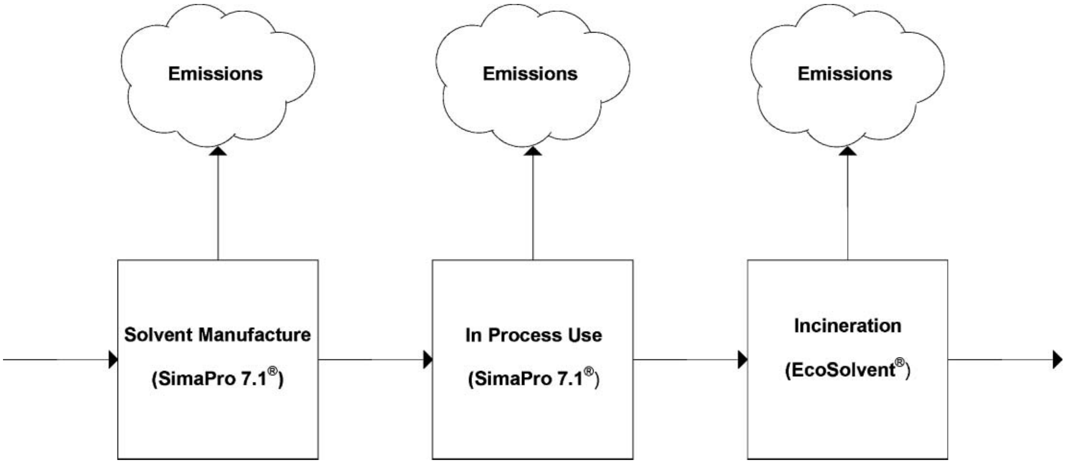


Fig. 1 Basic flow chart of solvent life cycle, associated emissions, and analysis software (shown in parentheses).

incentives for life cycle analysis of pharmaceutical solvent use and recovery exist due to the current practices of solvent use and incineration. The first incentive is that by recycling an increased proportion of solvent, less solvent must be produced for use as a virgin solvent feed. The second incentive is that the inventory of solvent waste to be treated is significantly decreased. Both solvent manufacture and disposal contribute significant proportions to the life cycle emissions of an API and will be further elaborated on in this article.

In 2008, the Toxic Release Inventory cited that the United States pharmaceutical industry generated 88 million kg of waste (categorized by the US EPA as either priority pollutants or hazardous air pollutants). 83% of this waste was attributed to the top ten solvents in use in the pharmaceutical sector.[8] By implementing an on-site solvent recovery system, this waste may be significantly decreased. A multitude of separation processes may be used to these ends, including traditional distillation and more novel approaches such as pervaporation and nanofiltration. This may be combined with a shift towards continuous rather than batch production processes for increased reductions in solvent waste.[6]

First, the necessity of performing an LCA on pharmaceutical solvent use will be demonstrated by displaying the large quantity of emissions produced outside of the battery limits of a pharmaceutical plant due to solvent production and waste treatment. Through the use of life cycle assessment in a series of case studies, it will be shown that solvent recovery in the pharmaceutical industry has a significant effect on the environmental impact of API manufacture.

Results and discussion

Comparison of solvent life cycle emission routes

The general life cycle of a solvent includes its production, in-process use, and waste treatment. The environmental effects of solvent production and waste treatment are often overlooked; however, these contribute significantly to the life cycle emissions for the production of an API. A basic flow chart of the life cycle emissions of a solvent and the associated analysis software can be found in Fig. 1.

A life cycle assessment has been performed on a variety of common solvents, using EcoSolvent® (Safety and Environmental Group, Zurich, Switzerland) and SimaPro 7.1® software packages. In order to demonstrate the environmental effect of solvent use on a broader scale, in-process emissions were neglected. In the preliminary analysis, these emissions were neglected based on the assumption that no solvent was to be consumed during use and that in-process emissions, such as fugitive emissions and emissions due to pumping, mixing, and heating, are negligible in comparison to the emissions from solvent production and waste treatment. In-process emissions will be discussed in further detail in the following case studies. It was assumed that no solvent was recovered and that all solvent waste was treated by incineration. It was also assumed that energy was recovered during incineration by recovering heat generated while incinerating waste by steam production. This was used to offset CO_2 waste and energy usage by decreasing the amount of energy required to manufacture solvents and to produce steam. Incineration was assumed to be carried out in-house. Each life cycle inventory was developed on a 1 kg of solvent basis. Table 1 displays a summary of the life cycle assessment results for the production of ten commonly used organic solvents. Included in Table 1 is an analysis for a "generic solvent," which is defined in SimaPro 7.1® and is an average of the solvents in the SimaPro 7.1® database. The number of solvents that this value is based upon changes as updates are added to the SimaPro database. The cumulative energy demand (CED) for the production of these ten solvents was calculated using SimaPro 7.1®. The CED is the overall energy requirement for the life cycle of a component as defined by the life cycle boundaries set by the analysis. This may include the energy from production, use, and disposal.[9] In this instance, the boundaries were defined as the cradle-to-gate life cycle for the manufacture of a solvent. The air, water, and soil emissions listed in Table 1 are defined as the mass of wastes released to air, water, or soil, respectively. The total emissions value is the sum of the air, water, and soil emissions. The CO_2 emissions are displayed because these emissions make up the greatest proportion of emissions to air. The mass of water in the raw materials is not included in the values listed in Table 1, as SimaPro 7.1® does not differentiate between process water and reaction water. Table 2 displays the

Table 1 Life cycle analysis for the production of 1 kg of various organic solvents

		Emissions					
	Raw[a] kg	Air kg	Water kg	Soil kg	CO_2 kg	Total kg	CED MJ-Eq
Acetone	1.53E+00	1.83E+00	2.56E-02	7.23E-07	1.80E+00	1.86E+00	6.73E+01
Acetonitrile	1.54E+00	1.97E+00	1.44E-01	6.80E-04	1.95E+00	2.12E+00	6.15E+01
Diethyl ether	1.17E+00	1.09E+00	1.66E-02	1.95E-04	1.08E+00	1.11E+00	4.80E+01
Ethanol	1.17E+00	1.09E+00	1.66E-02	2.00E-04	1.08E+00	1.11E+00	4.80E+01
Hexane	1.59E+00	8.84E-01	1.75E-01	5.93E-03	8.55E-01	1.06E+00	6.17E+01
IPA	1.55E+00	1.66E+00	5.42E-01	3.18E-04	1.63E+00	2.20E+00	6.32E+01
MeOH	8.34E-01	6.47E-01	6.39E-03	1.27E-04	6.44E-01	6.54E-01	3.78E+01
THF	4.01E+00	5.52E+00	2.31E-03	2.31E-03	5.46E+00	5.65E+00	1.28E+02
Toluene	1.36E+00	1.21E+00	3.87E-03	3.46E-07	1.19E+00	1.21E+00	6.34E+01
Generic solvent	1.74E+00	1.78E+00	1.22E-01	1.66E-04	1.75E+00	1.91E+00	6.51E+01

[a] Mass of raw materials consumed excluding water.

Table 2 Water requirements for the production of 1 kg of various organic solvents

	Cooling kg	Turbine kg	Fresh kg	Saline kg	Unspecified[a] kg
Acetone	7.86E+01	5.57E+00	1.11E-01	3.39E-01	3.11E+00
Acetonitrile	2.41E+02	1.61E+03	5.22E+00	5.92E-01	3.45E+00
Diethyl ether	3.17E+01	8.14E+02	1.31E+00	2.82E-01	1.46E+00
Ethanol	3.17E+01	8.15E+02	1.79E+00	2.82E-01	1.46E+00
Hexane	3.53E+01	1.68E+03	2.33E+00	1.50E+00	3.62E+00
IPA	4.91E+01	1.49E+03	4.09E+00	5.19E-01	1.35E+01
MeOH	1.03E+01	5.41E+02	1.62E+00	4.55E-01	2.34E-01
THF	7.09E+02	1.51E+04	1.67E+01	2.94E+00	4.41E+00
Toluene	8.97E+01	2.70E+00	2.05E-01	6.06E-01	8.25E-01
Generic solvent	8.13E+01	1.412E+03	1.94E+00	5.68E-01	9.69E+00

[a] Mass of water of unspecified origin.

Table 3 Life cycle analysis for the production of 1 kg of various commodity chemicals

		Emissions					
	Raw[a] kg	Air kg	Water kg	Soil kg	CO_2 kg	Total kg	CED MJ-Eq
Ammonia	6.24E-01	2.03E+00	4.55E-02	1.83E-03	2.02E+00	2.02E+00	4.23E+01
50 wt % Sulfuric acid	1.37E-01	1.54E-01	9.12E-03	1.54E-04	1.35E-01	1.35E-01	2.36E+00
TiO_2	5.01E+00	4.33E+00	4.33E-01	2.54E-03	4.26E+00	4.77E+00	8.86E+01

[a] Mass of raw materials consumed excluding water.

water usage associated with the production of 1 kg of each of the solvents in Table 1.

As it can be seen, the required process water, turbine water, and cooling water are nearly tenfold higher for THF than any other solvent listed. The organic solvent data was compared to the life cycle assessment for the production of 1 kg of a variety of non-organic solvent commodity chemicals.

A statistical analysis on production emissions comparing the two sets of data was performed using StatGraphics Plus 5.1® (StatPoint Technologies, Inc, Warrenton, Virginia). A sample of the results for the commodity chemicals is displayed in Table 3 and Table 4.

It was found that the only statistical difference between the production of 1 kg of an organic solvent and 1 kg of a commodity chemical was in the CED. This is supported by the notion that over half of organic chemicals require from 0 to 4 MJ of energy for manufacture as opposed to inorganic chemicals which range from −1 to 3 MJ of energy.[10] THF was also determined to have a significantly higher CED than the other organic solvents tested. This was attributed to the fact that the purification of THF poses unique difficulties, including a variety of severe azeotropes.[11] Although many of the other solvents tested also display azeotropes in a variety of mixtures, the azeotrope between THF and water is more energy intensive to overcome. This is supported by the fact that pressure swing distillation is typically employed in industry to separate THF and water mixtures.[12] The larger CED can also be associated with the smaller industrial demand and thus smaller production quantities of THF in comparison with other solvents. Considering the comparison of solvents to commodity chemicals, it may be concluded that there is no difference in the mass of waste attributed to the production of 1 kg of an

Table 4 Water requirements for the production of 1 kg of various commodity chemicals

	Cooling kg	Turbine kg	Fresh kg	Saline kg	Unspecified[a] kg
Ammonia	5.47E+00	1.34E+03	1.44E+00	9.70E-01	2.85E+00
50 wt% Sulfuric acid	2.26E+00	4.65E+02	5.64E-01	7.05E-02	4.92E+01
TiO_2	7.89E+01	1.15E+04	1.19E+01	2.64E+00	5.94E+01

[a] Mass of water of unspecified origin.

organic solvent or 1 kg of commodity chemical; however, there is a significantly larger energy demand for the production of organic solvents.

The significant effect of solvent reduction is, therefore, attributed to both the larger CED and the difference in use of the chemicals. Commodity chemicals are commonly used to adjust pH, catalyze reactions, and serve as the reactants in chemical processes. In the modern pharmaceutical industry, multiple steps are employed to produce an API. During each of these steps, large quantities of organic solvents are in use but do not enter into reaction stoichiometry. As a result, 80% to 90% of the total mass used in the production of an API may be attributed to solvents.[6] These solvents are disposed of rather than recycled, creating a massive environmental deficit from solvent production and disposal. For many commodity chemicals, the chemical inventory cannot be reduced without changing reaction pathways, stoichiometries, and catalysis. For solvents, however, implementation of a solvent recovery system can significantly decrease the chemical inventory and required raw materials thus decreasing the environmental footprint.

The life cycle inventories for the production of organic solvents display similar distributions of emissions. Since the subsequent case studies involve the solvents IPA, MeOH, and THF, the life cycle inventories of these solvents will be presented and discussed. Fig. 2 displays the distribution of emissions to air and water, the compositions of the air emissions, the total mass of emissions, and the mass of CO_2 emitted for the manufacture of each of these solvents. None of the solvents display an appreciable amount of emissions to soil in comparison to air and water. Emissions to soil are too low to be appreciated in Fig. 2 and are thus omitted. The mass of total emissions for each solvent is displayed below each graph. As it can be seen, emissions to air constitute the majority in each case. IPA is the only solvent to display a significant amount of emissions to water, approximately 25% compared to 2.2% for THF and 1.0% for MeOH. This may be attributed to the process used to produce IPA. Currently, IPA is commercially produced through the hydration of propylene in the presence of a highly concentrated sulfuric acid solution. This requires large amounts of reaction water, often employing propylene as the limiting reagent. It is also notable that a solution of 50 wt% sulfuric acid and water has 6.8% of total emissions to water, contributing to the elevated emissions to water for the production of IPA. The emissions values for a 50 wt% solution of sulfuric acid were calculated specifically for the production of sulfuric acid at a 50 wt% grade in SimaPro 7.1®. Other commercial methods for the production of IPA include hydration in gas/liquid mixed phase using strongly acidic ion exchange resins, gas phase hydration using strongly acidic solid acid catalysts, and gas phase hydration by catalysts carrying hetero-poly or inorganic acids.[13] All of these methods display similar issues with elevated emissions to water. Fig. 2 also demonstrates that carbon dioxide constitutes the vast majority of emissions for each of these solvents, between 74% and 98% of total emissions (96 to 99% of air emissions). This is attributed to combustion reactions within the production processes and transportation to and from the manufacturing plant. This is in agreement with a study done in the Netherlands that found that the majority of CO_2 emissions came from a

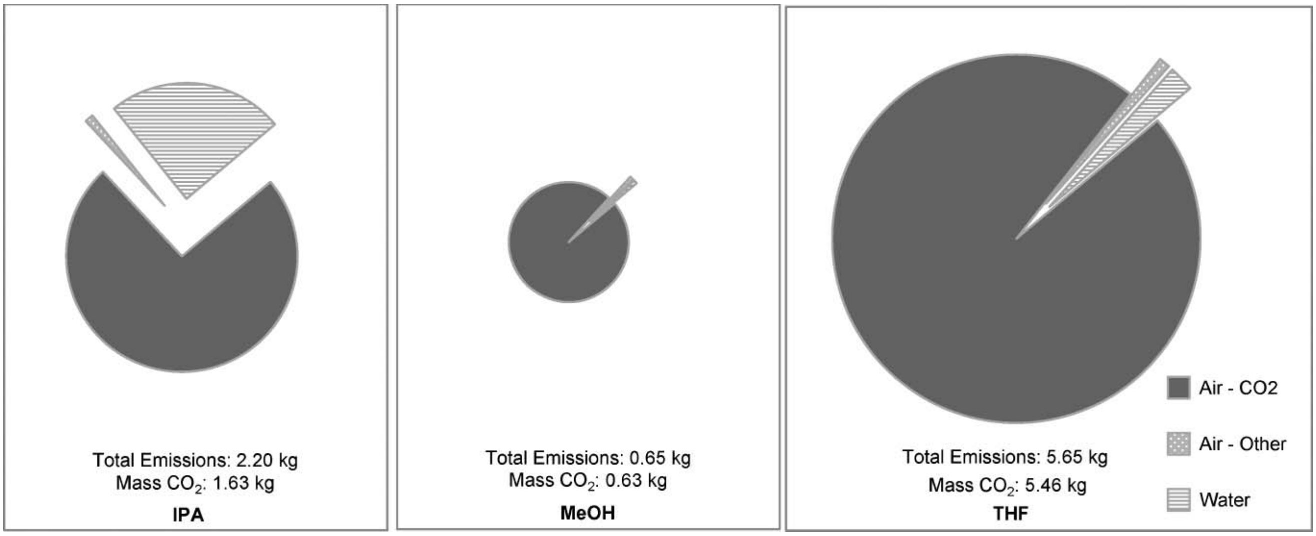


Fig. 2 Distribution of emissions for production of 1 kg of IPA, MeOH, and THF.

small number of manufacturing plants. Among these plants, the refining, petrochemical production and chemical production sectors were the first, second, and third largest offenders, respectively. These emissions were directly attributed to combustion reactions.[14] A study conducted in the United States associates approximately 97% of air emissions from transportation to CO_2.[5] This exemplifies the high proportion of CO_2 emissions that occur in chemical manufacture as a direct result of combustion reactions. Fig. 2 displays that the largest portion of emissions from the production of 1 kg of solvent is attributed to carbon dioxide. This large proportion of carbon dioxide is attributed to the energy for raw material acquisition, production, and transportation of the solvent. Therefore, reducing the amount of fresh solvent required to run a process can significantly reduce the carbon footprint of that process. It has also been determined that there are specific anomalies in the pollution profiles of particular solvents. IPA displays a significant amount of emissions to water as a result of industrial production practices specific to that solvent. Similarly, the production of THF displays a statistically larger CED than other solvents studied. THF also displays a significantly larger associated waste, resulting from the increased energy requirements. Thus, it may be concluded that the emissions from the manufacture of organic solvents is unique only in the CED, although anomalies specific to production of particular organic solvents do exist.

The carbon dioxide and greenhouse gas (GHG) emissions associated with incinerating each of these solvents also plays a crucial role in the life cycle emissions of these solvents. Studies have shown that roughly half of the GHG emissions and 40% of the energy requirements of the life cycle of an API can be attributed to the incineration of solvent waste.[5] In order to demonstrate the impact on pollution from the incineration of solvent waste, two environmental metrics will be employed. These metrics are the total carbon emissions directly released from the incineration of a solvent (CO_2 Incin.) and the CED resulting from solvent production (CED Solv. Prod.). Heat energy, converted into steam and electricity, may be recovered from the incineration process. This thereby reduces the total amount of energy required to produce the API, as well as reducing the associated carbon dioxide emissions. Therefore, an additional two metrics will be employed, the adjusted amount of CO_2 emissions released by the incineration of a solvent (CO_2 Offset) and the adjusted CED for the production of a solvent (Total CED Offset). These two metrics take into consideration the CO_2 released and the energy required with recovery of all energy released during solvent incineration. These metrics are given in units of CO_2-Eq and MJ-Eq, respectively. These units represent the equivalent amount of CO_2 and the equivalent amount of energy released and required, respectively. Table 5 displays these metrics for the previously discussed solvents. As can be seen, the Total CED Offset is always lower than the CED for solvent production because energy is recovered in the incineration process. The same is true for the CO_2 Offset. It is always lower than the CO_2 released from incineration because energy is recovered, therefore less energy must be produced. This CO_2 reduction is attributed to the reduction in energy that must be produced. Table 5 demonstrates that there is a significant amount of CO_2 released and energy consumed during the incineration of 1 kg of solvent, even when considering the use of steam generation for heating and energy production to offset life cycle CO_2 emissions. This is most notable for the life cycle of THF, displaying over double the CO_2 emissions and nearly double the energy demand of other solvents. However, much of this energy is recovered during incineration, thereby reducing the emissions from the incineration of THF to levels comparable to other solvents. This can be seen in the CO_2 Offset and Total CED Offset values for THF.

Table 5 CO_2 and energy demands/credits associated with the incineration of 1 kg of various solvents

	CO_2 Incin. kg CO_2	CO_2 Offset kg CO_2-Eq	CED Solv. Prod. MJ-Eq	Total CED Offset MJ-Eq
Acetone	2.55E+00	5.74E-01	6.73E+01	3.43E+01
Acetonitrile	3.31E+00	5.18E-01	6.15E+01	3.27E+01
Diethyl ether	1.47E+00	3.63E-01	4.80E+01	8.56E+00
Ethanol	1.40E+00	2.90E-01	4.80E+01	1.69E+01
Hexane	1.17E+00	3.46E-01	6.17E+01	7.89E+00
IPA	2.00E+00	3.40E-01	6.32E+01	2.68E+01
MeOH	9.40E-01	3.40E-01	3.76E+01	1.57E+01
THF	8.36E+00	5.44E-01	1.28E+02	9.08E+01
Toluene	2.43E+00	9.10E-01	6.34E+01	1.50E+01

This analysis shows that large quantities of emissions are released during manufacture and incineration of organic solvents. Although commodity chemicals produce a similar quantity and distribution of emissions during manufacture, in-process consumption of the chemical limits the quantity of the chemical that may be recycled. The mass intensity of solvents *versus* that of reagents within the pharmaceutical industry also makes solvent recovery an environmentally valuable pathway. As previously stated, solvents account for approximately 80% to 90% of the total mass involved in a pharmaceutical production process.[6] It has also been determined that there is a larger CED for organic solvents than there is for commodity chemicals. Less widely used chemicals were also determined to produce a potentially larger amount of emissions, as in the case of THF. This may be attributed to comparatively smaller production quantities, as well as particularly problematic azeotropes in the case of THF. Although many solvents display azeotropes, the azeotrope encountered when separating THF and water is particularly energy intensive. It was also determined that the majority of emissions are released to air, mostly as CO_2. Through solvent recovery, the amount of required fresh solvent, solvent production emissions, and incineration emissions may all be significantly reduced. This in turn will decrease the environmental and economic burden of the process.[7]

Three case studies will be used to demonstrate how solvent recovery may reduce the environmental impact of a process as well as how the use of LCA can clarify life cycle emissions for pharmaceutical solvent use. This may in turn be employed to determine greener options for solvent use involving solvent recovery or reduction.

Description of case studies

Three case studies were examined in which the use of solvents in the production of an API was reduced by implementation of greener processes. Focus was directed specifically to the implications of adding solvent recovery and reduction systems to reduce the overall environmental footprint of the pharmaceutical process. A cradle-to-grave approach was used to determine the amount of waste generated by solvent production, in-process emissions, and disposal of process wastes. The first case study considers the effects of recovering solvents within a pilot scale facility for the production of a new oncology drug being developed by Bristol-Myers Squibb (BMS). The second case study considers the effects of recovering solvents within a commercial facility for the production of celecoxib, the active ingredient in Pfizer's Celebrex®, a non-steroidal anti-inflammatory drug (NSAID).[15] The third case study considers the effects of recovering solvents within a process for the production of a synthetic pharmaceutical intermediate. The final API is to be used for the treatment of hypertension. Following is a more detailed description of each case study. Details of the design of the greener solvent recovery and/or reduction systems are not presented in this paper and are available elsewhere.[16–21]

Oncology drug in clinical trials – Bristol-Myers Squibb

The process examined by this case study is for the pilot scale production of an oncology drug in clinical trials. During one step, a mixture of THF, water, and a pharmaceutical intermediate must be dehydrated. As discussed previously, THF displays an azeotrope with water (95.7 : 4.3 THF–water) at standard temperature and pressure (STP). In order to dehydrate the mixture, the current process employs a constant volume distillation (CVD). CVD requires a large amount of an entrainer to be added to the separation. The entrainer used in this process is THF, resulting in an increased amount of THF waste. A proposal was made for the addition of a pervaporation (PV) system to the current CVD. The PV system would dehydrate the THF to the desired level and allow it to be recycled back into the process. The addition would decrease the amount of entrainer required thereby reducing the amount of virgin THF necessary and the amount of THF waste to be incinerated.[16,17,19,20]

Celecoxib – Pfizer

The commercial scale production of celecoxib, the API in Pfizer's arthritis drug Celebrex™, was studied to determine a green alternative for the handling of solvent waste. During the final crystallization and production step, large quantities of IPA and water are employed and constitute the majority of the waste stream. Separation of the IPA and water mixture is complicated by a multitude of impurities in the waste stream, including dissolved solids (or total dissolved solids, TDS), methanol, and ethanol. In addition, a variety of azeotropes arise between the IPA, methanol, ethanol, and water. Currently, wastes are incinerated at an off-site disposal facility. Pfizer suggested improving the process by employing existing capital assets. The goal of the case study was to configure equipment already existing at the facility to recover and recycle the IPA from the waste stream. An analysis on an array of designs demonstrated that it was necessary to employ distillation and PV to produce IPA at a high enough purity to be recycled. Based upon production flow rates and the available equipment sizes, a distillation-PV-distillation system was deemed necessary to achieve the required 99% pure IPA. Although several of the waste streams could be treated by the PV system, one waste stream containing IPA and the highest concentration of TDS was distilled once to concentrate the stream and then sold as a "generic solvent" to a third party. The remaining IPA waste mixture was sent to the distillation-PV-distillation system. This would allow an in-line recycle of the IPA at the celecoxib production facility. This recycle of IPA and sale of the "generic solvent" would reduce the total amount of virgin solvents required at the celecoxib production facility and at the third party facility. In addition, the need to incinerate solvent waste from the crystallization and production step would be eliminated.[16–18]

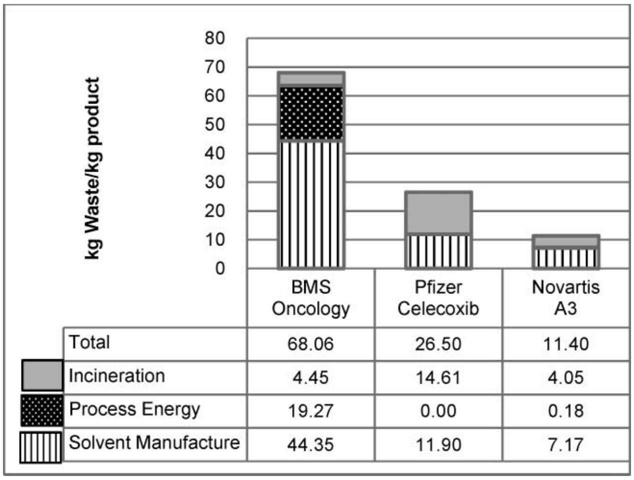
Synthetic intermediate – Novartis

During the commercial production of a synthetic pharmaceutical intermediate, the crude reaction mixture is produced in a Heck coupling reaction. This mixture contains a significant concentration of Pd. This concentration must be reduced before the intermediate may undergo further isolation. In order to achieve this, the current process employs a batch adsorption with activated carbon as the main adsorbent. Previous research indicated that an adsorbent which is more suitable for fixed bed operation would decrease process wastes. In addition, the vessel must be thoroughly rinsed with organic solvents and aqueous detergent after each adsorption. This produces a large mass of solvent waste, containing mostly MeOH, and solid waste, activated carbon. These wastes must be treated by incineration and disposal, respectively, increasing the environmental footprint of the process. A proposal was made to replace the batch adsorption with a fixed bed adsorber (FBA), in which a synthetic resin would be used as the adsorbent. This would allow for a reduction in the mass of virgin solvent and adsorbent required as well as a reduction in the emissions from disposing of the associated wastes.[21]

Analysis of case studies

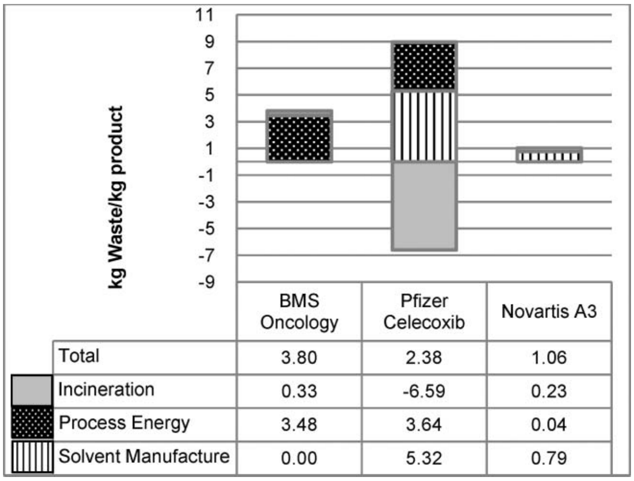
The three case studies were analyzed and compared using a cradle-to-grave life cycle analysis. For each case study, the current in-place process was considered the "base case" for that study. Environmental impacts were calculated considering only the differences between the base case and greener process design alternative in each case study, therefore, emissions from the manufacture of raw materials, unit processes, waste disposal, and other factors which were not affected by the green improvements were not included in the results. Results were calculated in terms of kg of waste per kg of API produced (kg of waste per kg of intermediate produced in the Novartis case study). This was done to simplify the comparison of the processes, as total production amounts varied from pilot to production scale. The total emissions and the distribution of their origins for the three base case scenarios and the three green alternatives are displayed in Fig. 3 and Fig. 4, respectively. These emissions take into account emissions avoided by selling waste as a generic solvent and from steam and electricity generation during incineration. These values were used to offset the emissions from incineration and disposal of solvent and solid wastes.[16–21]

The energy used to operate the solvent recovery and reduction systems was analyzed and the resultant life cycle emissions for its generation were determined. The difference in emissions for the energy of the processes is listed as an emissions source in Fig. 3



	BMS Oncology	Pfizer Celecoxib	Novartis A3
Total	68.06	26.50	11.40
▒ Incineration	4.45	14.61	4.05
▩ Process Energy	19.27	0.00	0.18
▥ Solvent Manufacture	44.35	11.90	7.17

Fig. 3 Total emissions for each base case scenario and the origins of those emissions.

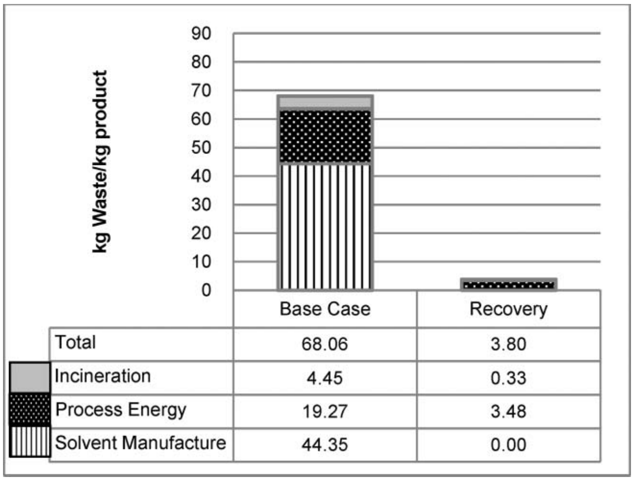


	BMS Oncology	Pfizer Celecoxib	Novartis A3
Total	3.80	2.38	1.06
▒ Incineration	0.33	-6.59	0.23
▩ Process Energy	3.48	3.64	0.04
▥ Solvent Manufacture	0.00	5.32	0.79

Fig. 4 Total emissions for each green alternative and the origins of those emissions.

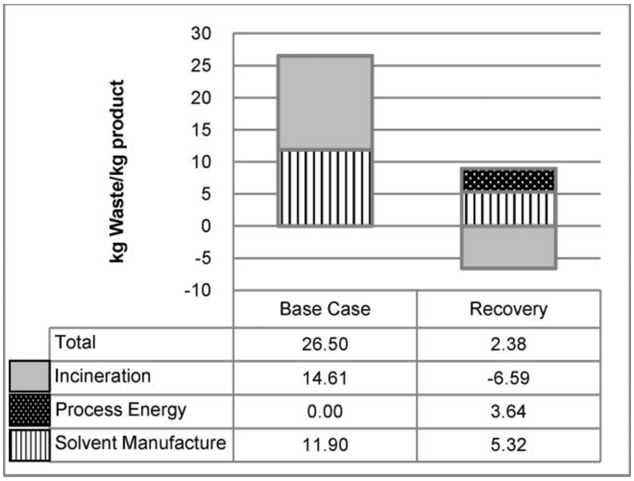
and Fig. 4 and includes the difference in energy requirements for steam and electricity within the API/intermediate production processes with incorporation of the solvent recovery or reduction system. Fig. 3 and Fig. 4 display the effect of solvent use on emissions within the pharmaceutical manufacturing processes. Emissions are associated with heating, pumping, and recovering solvents and entrainers used in the process. In some instances, the implementation of a solvent recovery system will not affect other process emissions. However, it may actually reduce emissions within the manufacturing process as there is less solvent to be heated and pumped. As stated, all values are calculated comparing the greener alternative process with the base case. For this reason, the Pfizer base case displays no emissions from the energy of the process as there was no change in the Celecoxib process, only in adding the solvent recovery system, which is shown in Fig. 4.[16–18] For the BMS case study, the allocation of wastes from the energy of the process was altered significantly. The heat duty required to run the CVD was decreased with the addition of the PV system, reducing the amount of steam required. This was because the need to add and heat an entrainer was avoided. However, the PV system has an associated electrical requirement so there is an increase in the emissions from electricity usage. In essence, the PV system reduces the amount of steam required for the CVD but increases the total amount of electricity required.[16,17,19,20] Similar differences are observed in the energy of the process for the Novartis case study, resulting from allocation of process electricity. The replacement of batch adsorption with an FBA system actually decreases the amount of energy required, as less adsorbent may be used and fewer vessel rinses are required. This difference in energy, however, is insignificant as it represents only 1.38% of the total life cycle emission reduction for the Novartis case study.[21] Pollution credits are given to the Pfizer proposal for sale of the mother liquor waste. This is displayed as a negative value in Fig. 4 and is used to offset the total pollution attributed with the Pfizer case study.[16–18] For these case studies, it is apparent that the reduction in emissions due to solvent manufacture is the most significant source of emission reductions, as can be seen in Fig. 3 and Fig. 4. It represents 69% of the emission reductions for the BMS case study, 44.4 kg of waste per kg of API produced, and 62% of the emission reductions for the Novartis case study, 6.38 kg of waste per kg intermediate produced. Excluding the emissions avoided by sale of IPA, solvent manufacture accounts for 37% of the emission reductions, 6.58 kg of waste per kg API produced for the Pfizer case study. If the emissions avoided by the sale of IPA are included, the total emissions are less than the emissions from solvent manufacture.[16–21] When these emission reductions are coupled with the reduction in emissions due to avoidance of excess solvent waste that must be incinerated, the effect is comparatively more significant. Fig. 3 and Fig. 4 demonstrate that a considerable proportion of the life cycle emissions for an API are attributed to solvent manufacture and incineration. This accounts for 75%, >100% (attributed to negative emissions from sale of IPA), and 99% of the emission reductions in the BMS, Pfizer, and Novartis case studies, respectively. This is attributed to the large amount of emissions resulting from solvent manufacture and incineration, as opposed to the energy of the process. These proportions are displayed in Fig. 3.[16–21] By implementing a solvent recovery or reduction system, over 90% of life cycle emissions from solvent use may be avoided. When considered with the mass intensity of solvents within the pharmaceutical industry, as discussed previously, this is a significant reduction in overall process emissions for the production of an API. Generally, greater than 80% of the raw materials that are employed in the production of an API are solvents. If 90% of the associated emissions from the solvents may be avoided, an overall reduction of over 70% of the total emissions for the production of an API may be expected (80% of total mass x 90% emissions reduction). The overall reduction in emissions for each case study may best be displayed by a direct comparison of each base case with the associated greener process case. This comparison is displayed in Fig. 5, Fig. 6, and Fig. 7.[16–21]

Fig. 5, Fig. 6 and Fig. 7 display that there is a large reduction in emissions with the addition of a solvent recovery or reduction system. The BMS case study displays a 94% reduction in overall emissions, equating to a reduction of 64.3 kg waste per kg API. Similarly, there is a 91% reduction in overall emissions for both the Pfizer and Novartis case studies. This equates to a



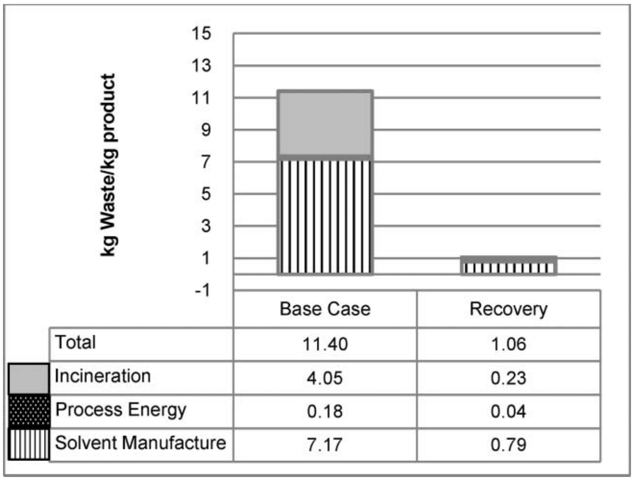
		Base Case	Recovery
	Total	68.06	3.80
░	Incineration	4.45	0.33
▓	Process Energy	19.27	3.48
▥	Solvent Manufacture	44.35	0.00

Fig. 5 Comparison of the base case and green process for the BMS case study.



		Base Case	Recovery
	Total	26.50	2.38
░	Incineration	14.61	-6.59
▓	Process Energy	0.00	3.64
▥	Solvent Manufacture	11.90	5.32

Fig. 6 Comparison of the base case and green process for the Pfizer case study.



		Base Case	Recovery
	Total	11.40	1.06
░	Incineration	4.05	0.23
▓	Process Energy	0.18	0.04
▥	Solvent Manufacture	7.17	0.79

Fig. 7 Comparison of the base case and green process for the Novartis case study.

24.1 and 10.34 kg of waste per kg of API reduction for the Pfizer and Novartis case studies, respectively.[16–21]

As it can be seen, the majority of the total emissions are attributed to processes outside of the battery limits of a pharmaceutical production facility. Solvent manufacture and disposal account for the majority of emissions in all three base case scenarios. If one were to view the environmental implications of solvent recovery within the gate-to-gate perspective, restricting emissions to those within the battery limits of the pharmaceutical manufacturing facility, there is little environmental incentive to implementing a solvent recovery system. However, when the entire life cycle analysis is taken into account, the environmental implications become much more significant.

Conclusions

Three aspects of solvent recovery and reduction are made apparent by these case studies. The first is that solvent manufacture and incineration play a significant role in the life cycle emissions of a pharmaceutical API. By implementing a solvent recovery or reduction system, these emissions can be considerably decreased. The second is that energy of the process and the associated emissions are trivial compared to the emissions from manufacture and incineration of solvents. From this it is apparent that the increased energy and associated emissions resulting from the addition of a solvent recovery or reduction system are minor in comparison to the emission reductions resulting from the reduced amount of virgin solvent and solvent waste. In some instances, the addition of a solvent recovery system may actually decrease overall energy requirements of a process, as seen in the BMS case study. The final and most significant aspect of solvent recovery and reduction is that the resultant process emission reductions become apparent only when viewing the process from the perspective of the entire life cycle. The gate-to-gate approach associated with the emissions within an API manufacturing facility overlooks the global implications of solvent recovery and reduction. When a life cycle analysis at a cradle-to-grave perspective is considered, these emission reductions become evident. From such an analysis, one may make a more complete decision on the greenest process for the manufacture of an API.

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