Towards a Greener Manufacturing Environment

Green manufacturing strategies not only reduce the industry’s carbon footprint – they also make for more efficient processes from both a raw materials and waste perspective, resulting in a ‘win-win’ situation for both the environment and pharmaceutical companies.

There are many opportunities for investigating green manufacturing strategies in the pharmaceutical industry. Green engineering is defined as the design, commercialisation and use of processes and products that are feasible and economical, while reducing the risk to human health and the environment, and minimising the generation of pollution at the source. In this article, we look at the main causes of pharmaceutical waste and how they can be moderated, the approaches the industry can adopt to improve its environmental footprint, and the ways in which these green improvements can be measured.

CURRENT PRACTICES

While the pharmaceutical industry may not generate a large volume of waste in comparison with other sectors like steel manufacturing or petroleum refining, it has consistently generated one of the highest amounts of wastes per amount of finished product. This is due to the numerous process inefficiencies that exist from the synthesis of intermediates to the finished drug. The industry has traditionally used batch processes in which numerous organic synthesis reactions are conducted in sequential steps. Each of these steps requires its own isolation and purification train, which in turn typically requires different organic solvents (1). It has been estimated that solvent use can account for as much as 80-90 per cent of the total mass in a process, the majority of which are organic solvents (2). Since solvents are not part of the reaction stoichiometry, the spent solvent is either disposed of or recycled. Solvent usage and waste generation can thus be quite high when compared with the final API produced. The E-factor – the amount of waste generated per quantity of API – can typically range from 25 to over 100 kg/kg of API (3). Thus when a large volume API is produced in the 100-plus metric ton range, the variety and amount of solvents used can be significant.

The US Environmental Protection Agency (EPA) requires the pharmaceutical industry to report the disposition of chemicals to the Toxic Release Inventory (TRI). Although this list comprises only chemicals that meet certain pollutant criteria, it is still a good indicator of the waste profile. According to the TRI, the pharmaceutical industry in the US generated 128 million kg of waste in 2006. This waste included mainly organic solvents, the top three of which are methanol, 44.8 million kg/year; dichloromethane, 22.3 million kg/year; and toluene, 12.1 million kg/year. The top 10 solvents accounted for more than 80 per cent of the waste generated (see Figure 1, (4)). Over the last 10 years the industry has reduced solvent use and waste generation, but there is still a long way to go in improving productivity. According to the TRI 2006 report, the majority of solvent waste, approximately 70 per cent, was treated or recycled, and 30 per cent was used for energy recovery. Only a small percentage was still directly released into the environment (4). Since solvents are costly to purchase and dispose of, for a greener and more sustainable pharmaceutical industry it is imperative that
approaches to solvent reduction, recovery and substitution be more widely incorporated.

**GREENER PROCESSES**

The pharmaceutical industry is investigating many approaches to improve its environmental footprint. The goal is to make a better process in the early stages of clinical development when changes can more readily be made. As a drug moves further along the development timeline to final manufacturing, changes may be more difficult to implement. Even after a drug has been manufactured for a number of years, improvements to process efficiency can be made, as long as API quality is not affected.

A classic example of this is the award-winning improvements made by Pfizer in the sildenafil citrate process. They were able to reduce the solvent use from 1,540 to 5 kg/kg/API as the process was improved from the discovery stage through successive manufacturing campaigns. By improving the synthesis and incorporating solvent recovery methods, a significant reduction of highly hazardous solvents was achieved (5).

The optimisation of solvent use and reduction of waste generation have become key elements in improving the overall environmental footprint of the pharmaceutical industry. Solvent selection and solvent substitution practices, the elimination of hazardous solvents and opportunities for purification, re-use and recycling are all being explored as a means to reduce solvent use and waste generation. Solvent substitution practices – such as the replacement of chlorinated solvents (dichloromethane) with more benign alternatives – have yielded greener processes, while ionic liquids and supercritical carbon dioxide have potential as reaction media. The ‘plant of the future’ may use a limited number of ‘universal’ green solvents, the properties of which would also allow for easy recovery. The use of continuous processes, biosynthetic routes and greener solvents can all reduce the use of hazardous organic solvents. Therefore, a future manufacturing scheme would not only be greener but would be optimised to enable a more agile operation. A common method used to minimise both solvent use and waste generation can be achieved by reducing the number of chemical transformations or steps (telescoping) within a process. Process chemistry optimisation is typically practiced in the early development cycle and can yield significant improvements when scaled up to manufacturing. In addition, new approaches such as solid-state chemistry and microwave reactions are being explored for their potential in solvent reduction.

**SOLVENT RECOVERY**

Solvent recovery has increased at both pharmaceutical manufacturing and off-site recovery facilities. Distillation still dominates the processes used in solvent recovery operations, but this may not be perceived as being green by today’s standards. Energy-intensive operations – such as distillation – are coming under greater scrutiny at a time of volatile oil prices. Pharmaceutical wastes typically contain multiple solvents (in both homogenous and heterogeneous mixtures), unconverted reactants and other byproducts, requiring complex separation schemes to obtain high quality solvent for re-use. Although many manufacturers have a centralised solvent recovery facility, a new approach is to integrate separation processes at the point of use to perform the operation more easily. One of the challenges faced in solvent recovery is the separation of azeotropic mixtures. Traditionally, this has meant the use of entrainer-based distillation methods that are more energy-intensive and are associated with other environmental issues linked to the use of entrainers. One of the greener technologies that avoids this use of additional chemicals, energy and waste is membrane pervaporation.

Membrane pervaporation uses a highly selective semi-permeable barrier to facilitate the removal of selected chemicals from a liquid feed. Unlike equilibrium-based separations – such as distillation – that rely on the relative volatilities of the
substances to be separated, pervaporation relies on relative membrane permeabilities of the substances to accomplish the separation. A liquid feed is sent to the pervaporation unit, which is fitted with a hydrophilic membrane. The water selectively permeates the membrane leaving a retentate stream that now comprises the dehydrated solvent. Solvents that are good candidates for commercial-scale dehydration include isopropanol, ethanol, methanol, ethyl acetate, butyl acetate, acetone, acetonitrile, tetrahydrofuran, n-butanol and methylethylketone (6).

Current research shows that it is more efficient to use a hybrid process combining distillation and pervaporation to separate low water-content, azeotropic solvent waste streams (7). Distillation is used first to increase the solvent to the azeotropic concentration, and pervaporation is then used on the distillate stream to purify the solvent to the desired water content (see Figure 2). This optimises the capabilities of each process, since distillation is typically more effective in concentrating non-azeotropic dilute organic-water mixtures, and pervaporation is more effective in dehydrating high organic water concentration mixtures. Pervaporation is a suitable platform technology for the pharmaceutical industry; it is quite scalable to any operation from pilot plant to manufacturing campaigns and can run in a continuous or batch mode. In addition, a pervaporation system can have membranes changed over to optimise performance when handling different solvent mixtures for different drug campaigns. Current commercial types of membrane used in solvent dehydration are polyvinyl alcohol-based polymers and ceramics composed of silica or zeolites (8).

**MEASURING GREEN IMPROVEMENTS**

A simple process improvement metric based on waste reduced per API manufactured (E-factor) offers a straightforward analysis – but it may not necessarily indicate the ‘greenness’ of the improvements. This would be the case when, for example, more benign solvents are reduced instead of the more toxic ones. For this reason, solvent-scoring indices have been developed to quantify the greenness of solvents using factors that represent environmental health, safety and sustainability. GlaxoSmithKline (9), Pfizer (10) and Bristol-Myers Squibb (11) among others have developed their own methods to evaluate the greenness of solvents. The American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable is collaborating with its member companies to deliver a solvent selection guide in the near future (12). Slater and Savelski (1) have developed an approach to measure the overall greenness of a manufacturing process based on the amounts and environmental characteristics of the solvents used. This method uses a combination of health and safety parameters such as inhalation toxicity and ingestion toxicity, along with sustainability parameters like ozone depletion and global warming potential.

A thorough life-cycle inventory/assessment is the best approach when evaluating the greenness of a process as a whole. This can consider all of the inputs and outputs from a drug manufacturing process, or just focus on a particular step or alternative chemical used. The example in Figure 3 illustrates the environmental

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**Figure 2:** Integration of pervaporation and distillation in a solvent dehydration and recovery process

**Figure 3:** Life cycle assessment (LCA) system boundary for the solvent used in an API manufacturing process
impact of reducing solvent in an API manufacturing facility (see Figure 3). If the solvent used is either reduced or recycled, then fresh solvent does not need to be manufactured, and energy and raw materials are saved. This view beyond the plant boundary can also show the reduction in greenhouse gas emissions from the energy saved.

A typical life-cycle inventory can be generated using environmental software such as SimaPro (PRé Consultants). For example, to manufacture 1kg of IPA solvent requires 0.89kg raw materials and 61.9 MJ-Eq cumulative energy demand, and generates 2.19kg of emissions (including 1.63kg CO₂). This represents the ‘cradle’ of the solvent’s life cycle and the ‘grave’ would be its disposal. For waste disposal by thermal oxidation (incineration), the emissions produced can also be estimated with software such as EcoSolvent. Making the process greener, by reducing and recycling spent solvent, can lead to a significant reduction in emissions produced in the manufacture of virgin solvent and in the incineration process. Of course the cost, energy and emissions associated with the solvent recovery process must now be taken into account, but recent studies have shown that these are small when compared with overall solvent life-cycle emissions (7).

CONCLUSION

There are significant benefits that transcend carbon footprint reduction for the pharmaceutical industry to implement green design strategies. In general, a greener process is a more efficient process from both a raw materials and waste perspective. Energy and cost reductions will result from these design enhancements and the overall operation can be made more sustainable. The greener a process is, the better the process – resulting in a win-win situation for both the drug manufacturer and the environment.

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References